Henning Boecker · Charles H. Hillman
Lukas Scheef · Heiko K. Strüder *Editors*

Functional Neuroimaging in Exercise and Sport Sciences

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This book is dedicated to our families

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Preface

Regular physical exercise is associated with substantial health benefits. Recent evidence holds not only for cardiovascular effects promoting "physical health", but also for the central nervous system believed to promote "brain health". Moderate physical exercise has been found to improve learning, memory, and attentional processing, with recent research indicating that neuroprotective mechanisms and associated plasticity in brain structure and function also benefit. Physical exercise is also known to induce a range of acute or sustained psychophysiological effects; among these are mood elevation, stress reduction, anxiolysis, and hypoalgesia. To date, there is an important body of literature from animal exercise research that has allowed unraveling neurobiological mechanisms at the behavioral (e.g., water maze-type tests), cellular (e.g., neurogenesis, neuroangiogenesis), and humoral (e.g., neurotrophic factors, inflammatory cytokines) levels. For obvious reasons, the majority of the human literature in exercise research has been based on behavioral and indirect assessments of neurotrophic factors and released neurotransmitters in the blood.

Today, modern functional neuroimaging techniques afford direct measurement of the acute and chronic relation of physical exercise on the human brain, as well as the correlation of the derived physiological in vivo signals with behavioral outcomes recorded during and after exercise. A wide range of imaging techniques have been applied to human exercise research, ranging from electroencephalography (EEG), magnetoencephalography (MEG), near-infrared spectroscopy (NIRS), and magnetic resonance imaging (MRI) to positron emission tomography (PET). All of these imaging methods provide distinct information, and they differ considerably in terms of spatial and temporal resolution, availability, cost, and associated risks. However, from a "multimodal imaging" perspective, neuroimaging provides an unprecedented potential to unravel the neurobiology of human exercise, covering a wide spectrum ranging from structural plasticity in gray and white matter, network dynamics, global and regional perfusion, and evoked neuronal responses to the quantification of neurotransmitter release.

Accordingly, the scope of this book is to provide the current state of the human neuroimaging literature in the emerging field of the neurobiological exercise sciences and to outline future applications and directions of research, including clinical imaging studies in patients, which are as yet still in their infancy. The introductory Part I (Chaps. 1–4) provides an overview of mechanisms by which "brain health" is promoted through exercise, as derived from basic animal research. In Part II (Chaps. 5–13), the relevant methodological background is summarized for brain imaging applications in the exercise sciences; notably, this section encompasses detailed introductions to imaging methods, fitness evaluations, exercise training recommendations, as well as fitness-associated parameters (from neuropsychological tests indices to neurohumeral factors) that should be considered in imaging analyses of exercise studies. The subsequent part of the book will cover the current state of imaging applications in the following principal fields of research: the relation of exercise on brain perfusion, metabolism, and structure (Part III, Chaps. 14–17), the relation of exercise on cognitive processing (Part IV, Chaps. 18–20), and, finally, the relation of exercise on affective processing (Part V; Chaps. 21 and 22).

The editors of this book are very grateful to all authors for contributing their valuable expertise to this book. Deep thanks also go to Ms. Ann Avouris from Springer Publishing Co. who launched this project after attending a workshop by H. Boecker & C. Hillman entitled "Imaging the Effects of Physical Exercise on Brain Function" at the Organization for Human Brain Mapping (OHBM) Annual Meeting 2009 in San Francisco. "Functional Neuroimaging in Exercise and Sport Sciences" was developed with the understanding that neuroimaging will play a fundamental role for unraveling the impact of physical exercise on the human brain in the future and, on these grounds, hopefully for fostering further research into the prevention and treatment of brain disorders. While several other books are aimed at the neurobiological underpinnings of exercise, we believe that a unique feature of this book is that it is focused specifically on the important role of neuroimaging in the field of exercise and body–brain interactions. The book sheds light on the relation of exercise to various domains, for instance, structural plasticity, as measured with MRI-based morphometry methods; functional coherence and connectivity, as measured with EEG and resting state fMRI; "executive control" and other cognitive functions, as measured with task-related fMRI and event-related brain potentials (ERPs); neuroangiogenesis, as determined with MRI-based cerebral blood volume measurements; or neurotransmitter trafficking, as quantified by PET ligand activation studies, etc. Most importantly, this book makes the point that the exercise sciences should – in the future – be a joint research initiative of exercise scientists, neurobiologists, neuropsychologists, neuroimagers, and experts from other related disciplines.

We hope that "Functional Neuroimaging in Exercise Sciences" will be of interest to researchers working in the various fields subsumed by the term "exercise sciences", but also to a wider readership interested in this emerging field, including

doctoral students, post-doc scientists, exercise and health prevention specialists, or simply people who have (or want to have) a deeper understanding in how exercise promotes “brain health”.

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Part I
Theoretical Background, Animal Models, and Basic Sciences

Chapter 1
Exercise and the Brain: Neurogenesis, Synaptic Plasticity, Spine Density, and Angiogenesis

Zejun Wang and Henriette van Praag

Abstract This chapter focuses on the mechanisms underlying the effects of exercise on brain structural and synaptic plasticity as well as cognitive function in rodents. In normal young and aged mice wheel running increases neurotrophin, neurotransmitter, and angiogenesis levels, and enhances fine neuronal morphology such as dendritic branching and spine density. Specific to the dentate gyrus of the hippocampus is the increase in the production of new neurons with running, which may mediate at least in part the observed improvements in learning and memory. The role of exercise in mouse models of neurodegeneration such as Alzheimer's, Parkinson's disease and Huntington's disease is also evaluated and found to be generally beneficial with the potential exception of Huntington's disease. Furthermore, possible peripheral triggers elicited with exercise, such as muscle activation, that lead to improvements in brain structure and function are discussed.

1.1 Introduction

A sedentary lifestyle is accompanied by increased risk for cardiovascular, metabolic, and metastatic diseases (Allison et al. 1999; Powell and Blair 1994). In contrast, physical activity is known to benefit nearly every system in the body. Regular exercise results in improved cardiovascular health, greater bone mineral density, and decreased risk for cancer, stroke, and diabetes (Booth et al. 2002; Steinmetz and Potter 1996). More recently, human and animal studies have demonstrated that

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exercise targets many aspects of brain function and has broad effects on overall brain health. The benefits of exercise have been best defined for upregulation of cognition (Rogers et al. 1990; Suominen-Troyer et al. 1986; van Praag et al. 1999b), counteraction of age-related memory decline (Adlard et al. 2011; Erickson et al. 2011; Kramer et al. 1999; Laurin et al. 2001; van Praag et al. 2005; Voss et al. 2011), and depression (Babyak et al. 2000; Duman et al. 2008; Hunsberger et al. 2007; Lawlor and Hopker 2001).

Research pertaining to mechanisms underlying the effects of exercise on brain function has focused on changes in neuroplasticity such as neurogenesis, synaptic plasticity, spine density, and angiogenesis (Black et al. 1990; van Praag et al. 2005). Unique to the hippocampus, a brain area important for learning and memory, is the robust increase in new neurons associated with exercise in the dentate gyrus (DG) of the hippocampus (Clark et al. 2011; van der Borght et al. 2007; van Praag et al. 1999a, b). It has been hypothesized that the beneficial effects of physical exercise on cognition may be mediated at least in part by enhanced structural and synaptic plasticity in the hippocampus.

1.2 Exercise and Cognition in Rodents

1.2.1 Normal Young and Aged Rodents

In recent years many exercise and cognition studies have been carried out in adult rodents. This research strongly supports the benefit of exercise for brain function and has provided insight into the underlying cellular mechanisms. Both voluntary and forced exercise paradigms enhanced spatial memory in the Morris water maze, Y-maze, T-maze, and radial arm maze tests (Fordyce and Farrar 1991; van Praag 2008). The T-maze and Y-maze are typically used to test spontaneous alternation and (short-term) working memory, whereas the radial arm maze and water maze tasks are more prolonged and demanding. In particular the water maze can be used to test acquisition, i.e., learning of the task with repeated trials over days as well as retention, i.e., the search pattern in the pool when the platform is removed. Exercise enhances both learning and retention of the task (van Praag et al. 2005). Running also improved performance in hippocampus-dependent tasks that require limited movement, such as contextual fear conditioning, passive avoidance learning, and novel object recognition (Falls et al. 2010; Liu et al. 2008; Mello et al. 2009; O'Callaghan et al. 2007). Further evidence that exercise has specific cognitive benefits comes from a recent study in which a touchscreen method was used which has minimal motor requirements (Creer et al. 2010; Morton et al. 2006). The touchscreen system was used to investigate whether exercise can influence spatial pattern separation, a memory function that is attributed to the DG of the hippocampus (Leutgeb et al. 2007; McHugh et al. 2007). Sedentary and running mice were tested on a spatial discrimination task where stimuli were presented in close or distal proximity. There was no difference

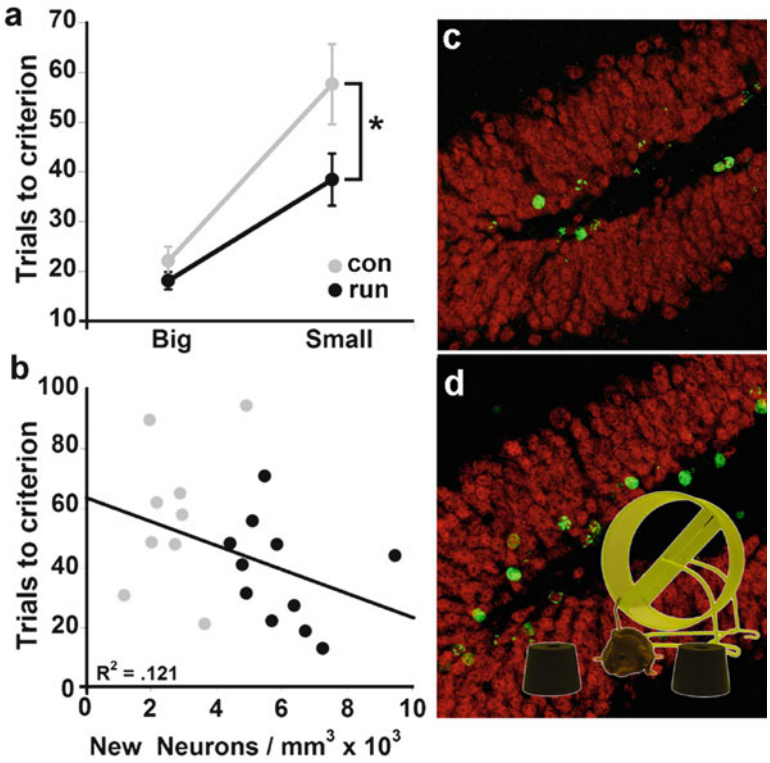

Fig. 1.1 Adult hippocampal neurogenesis is enhanced by exercise and may be linked to the ability to discriminate between objects and events that are closely linked in time and space. Specifically, a mouse learns to choose between two similar objects in a touch screen in close proximity to one another. Only one of the icons on the touch screen is reinforced with a food reward. (**a**) Probe trials were used to test acquisition of big and small separation between stimuli on the touch screen. Mice were trained to reach a criterion of seven out of eight trials correct. Runners performed better than controls when the task became more difficult, in acquisition of the small separation ($*p<0.05$), but not the big separation condition ($p>0.24$). (**b**) A trend toward a correlation between trials to acquisition of the small separation and new neuron density was observed ($p=0.13$). (**c**, **d**) Confocal images of BrdU-positive cells in the dentate gyrus of sections derived from control (**c**) and runner (**d**) mice, 10 weeks after the last injection. Sections were immunofluorescent double-labeled for BrdU (*green*) and NeuN (*red*) (Creer et al. 2010)

between the groups when the separation between locations to be discriminated was large. However, runners outperformed sedentary mice in fine pattern separation (Creer et al. 2010; Fig. 1.1).

The ability to learn new tasks decreases with age in rodents. On the cellular level, the number of synaptic contacts, synaptic strength, and plasticity is reduced in the hippocampus (Barnes 1994) and cortex (Chen et al. 1995). Recent research has shown that physical activity benefits spatial memory in aging rodents, even upon late-life onset. Housing aged C57Bl/6 male mice with a running wheel improved their acquisition and retention of the water maze task (van Praag et al. 2005)

and in another study, conditioned avoidance (Adlard et al. 2011). Furthermore, treadmill training improved learning in the Morris water maze (Albeck et al. 2006) and radial arm maze (Kim et al. 2010) in aged rats. In a more cognitively challenging task very old (26 months) mice could no longer learn to distinguish between closely spaced similar stimuli in the touchscreen system, but had a modest exercise-induced benefit when icons were spaced further apart (Creer et al. 2010). Overall, it appears that exercise continues to be beneficial for function throughout the course of normal aging.

1.2.2 Models of Neurodegenerative Disease

Exercise has been suggested to delay the onset of neurodegenerative diseases (Adlard et al. 2005; Friedland et al. 2001; Kaspar et al. 2005; Tillerson et al. 2003) and enhance recovery from brain injury (Bohannon 1993; Gobbo and O'Mara 2005; Grealy et al. 1999). While there is increasing evidence for benefits of physical activity for mouse models of Alzheimer's disease (AD) this may not be the case for Huntington's disease (HD) and ischemia/stroke (Komitova et al. 2005). For example, there is evidence from studies in gerbils that wheel running before ischemia is neuroprotective (Stummer et al. 1994). However, after stroke exercise has been shown to worsen outcome (Komitova et al. 2005). Thus, the effects of exercise should be evaluated carefully and separately for each pathological condition.

1.2.2.1 Alzheimer's Disease

The studies pertaining to the effects of exercise on cognition in mouse models of AD have reported beneficial effects of this intervention both before and after the onset of symptoms in several mouse models of the disease. Long-term exercise, started 5 months before disease onset, improved water maze learning. In addition, running reduced the load of β-amyloid plaques in both hippocampus and cortex (Adlard et al. 2005). Moreover, short-term running (3 weeks), initiated after disease onset (Nichol et al. 2007), improved both working and reference memory in aged AD Tg2576 mice and altered markers of inflammation (Parachikova et al. 2008). Running also enhanced water maze learning, increased brain-derived neurotrophic factor (BDNF) levels, and reduced apoptosis in Tg-NSE/PS2 mice (Um et al. 2011). Furthermore, in transgenic epsilon 4 allele of the apolipoprotein E gene (APOE e4) mice, a causative factor implicated in AD (Mahley et al. 2006), cognitive performance, and synaptic plasticity was improved (Nichol et al. 2009). Similarly, in AD triple transgenic mice (3xTg) running reduced pathology and improved behavior (Giménez-Llort et al. 2010). Thus, exercise is beneficial for cognition in normal rodents and in transgenic mouse models of dementia, even if started late in life or after the onset of disease symptoms.

1.2.2.2 Parkinson's Disease

The most well-studied models of Parkinson's disease (PD) involve the use of a neurotoxin, 6-hydroxydopamine (6-OHDA) or 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP), which can selectively destroy the dopamine neurons (Smith and Zigmond 2003). An early study found that motorized treadmill running following nigrostriatal damage ameliorated related motor symptoms and the vulnerability of dopamine neurons in both the 6-OHDA rat model and bilateral MPTP model in aged mice (Tillerson et al. 2003). Subsequently, it was demonstrated that treadmill running enhanced the survival of dopaminergic neurons in the substantia nigra and their fibers projecting into the striatum in the 6-OHDA-lesioned PD model of rats (Yoon et al. 2007). On the other hand, it has been reported voluntary running can improve motor outcome in 6-OHDA-infused rats, but does so without evident sparing of dopamine nerve terminals (O'Dell et al. 2007). Using the MPTP-lesioned mouse model of PD, Petzinger et al. (2007) suggested that the benefits of treadmill exercise on motor performance may be accompanied by changes in dopaminergic neurotransmission. However, in another study treadmill exercise improved overall rotarod performance and reduced anxiety in this model of PD, without changes in catecholamine neurochemistry (Gorton et al. 2010). In addition, in a mouse model of advanced PD, induced by injecting MPTP and probenecid, 4 weeks of treadmill exercise promoted physical endurance, cardiorespiratory, and metabolic adaptations, albeit without restoring nigrostriatal dopaminergic function (Al-Jarrah et al. 2007). It was also demonstrated that treadmill exercise can bring anomalous movement, balance, and gait pattern back to the state of normalcy in this PD model (Pothakos et al. 2009). Recent studies found that treadmill exercise can exert neuroprotective effects by BDNF or migration of neuroprogenitor cells in the 6-OHDA-lesioned PD model of rats with subsequent improvement in motor function (Tajiri et al. 2010). Physical activity also increased GluR2 subunit expression within the dorsolateral striatum of MPTP mice, a finding that is supported by neurophysiological studies (VanLeeuwen et al. 2010). Thus, the protective effects of forced exercise for dopaminergic neurons to 6-OHDA might be due in part to an increase in the availability of certain trophic factors and signaling cascades (Smith and Zigmond 2003) that may mediate the beneficial effects of exercise on neuroplasticity in rodent models of PD. Further studies are needed to demonstrate if exercise can ameliorate cognitive deficits in rodent models of PD.

1.2.2.3 Huntington's Disease

It remains unclear whether exercise delays or prevents HD. Initial research showed that environmental enrichment delays symptom onset in R6/1 transgenic mice (van Dellen et al. 2000). An important component of enrichment is physical activity. Indeed, in R6/1 mice, running normalized rearing behavior and delayed the onset of deficits in rear-paw clasping, motor coordination, and spatial working memory. However, rotarod performance, evaluating balance and coordination of the subjects,

ubiquitinated protein aggregates and hippocampal BDNF protein levels (Pang et al. 2006; van Dellen et al. 2008), and hippocampal neurogenesis in R6/2 mice (Kohl et al. 2007) were unchanged by exercise. In addition, running conferred some positive changes to electrophysiological properties of medium-sized spiny neurons in the striatum of R6/2 mice (Cepeda et al. 2010). However, our research indicates that exercise is not beneficial, and may be detrimental to a vulnerable nervous system in the N171-82Q mouse model of HD. Specifically, running started in presymptomatic 6-week-old male HD mice, did not improve function, and appeared to accelerate disease onset (shaking, hunched back, and poor grooming), reduced striatal volume, and impaired motor behavior, including a shorter latency to fall from the rotarod (a motorized cylinder that can rotate at a set or accelerating speed as designated by the experimenter) compared to sedentary controls. Furthermore, weight loss, reduced life span, hyperglycemia, Morris water maze learning deficits, diminished hippocampal neurogenesis, deficits in immature neuronal morphology, intranuclear inclusions, and decreased DG volume were refractory to physical activity (Potter et al. 2010). It remains to be determined what mechanisms are underlying the detrimental effects of exercise in this mouse model and also whether similar observations will be made in other models of the disease. Interestingly, a case study in humans also has indicated that physical exercise may not prevent or delay disease onset or progression. A HD marathon runner presented with myopathy 20 years before the predicted disease onset for 41 CAG repeats, indicating that daily exercise (running about 6 miles every day) certainly did not delay the disease development, but actually the onset was sooner than expected based on the number of CAG repeats (Altschuler 2006; Kosinski et al. 2007).

1.3 Mechanisms Underlying Effects of Exercise on Cognitive Function

Physical activity has many cognitive functional benefits and is accompanied by changes in the cytoarchitecture of the hippocampus and cortex, including synaptic plasticity, spine density, and angiogenesis. Neurogenic effects of exercise are only observed in the DG of the hippocampus (Fig. 1.2).

1.3.1 Neurogenesis

Although the initial description of neurogenesis in the adult brain in the early 1960s (Altman 1962) was met with skepticism, it has become well established that the adult mammalian brain can produce new neurons (Curtis et al. 2007; Eriksson et al. 1998). The existence of newborn neurons in the subgranular zone (SGZ) of the DG in the hippocampus, a brain region that is important for learning and memory, has

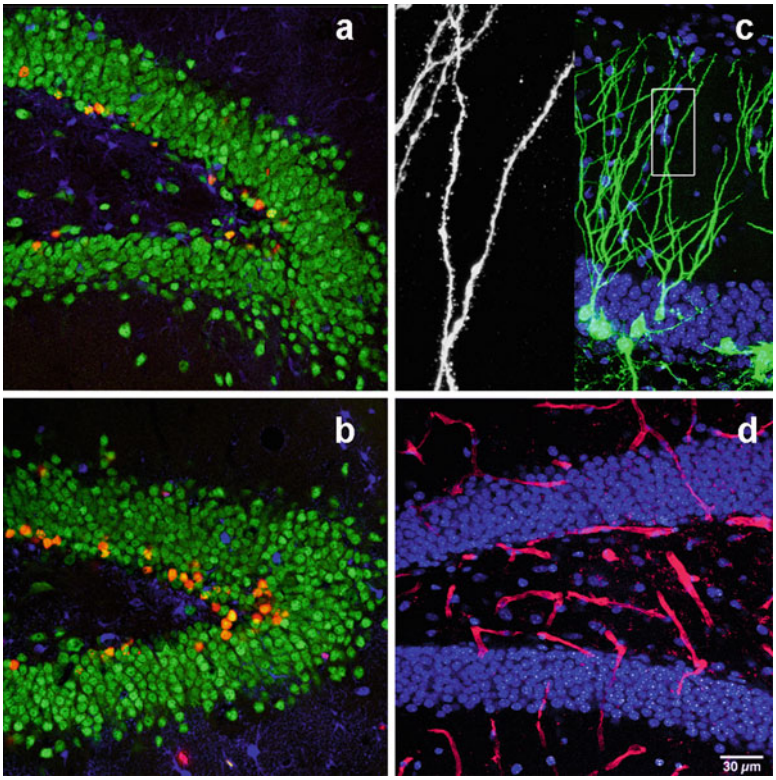

Fig. 1.2 Running improves adult hippocampal neurogenesis, spine density, and angiogenesis. (**a**, **b**) Confocal images of BrdU-positive cells in the dentate gyrus of sections derived from control (**a**) and runner (**b**) mice. Sections were immunofluorescent triple-labeled for BrdU (*red*), the neuronal marker NeuN (*green*), and the glial marker S100beta (*blue*). (**c**) Retrovirus expressing green fluorescent protein was used to label new dentate granule neurons in young running mice shown 4 weeks after injection, with insert of fine spine morphology. (**d**) Blood vessels in the dentate gyrus with tomato Lectin-stained vessels (*red*) and nuclei with DAPI (*blue*) (van Praag et al. 2005)

been confirmed using bromodeoxyuridine (BrdU; Kuhn et al. 1996) and retroviral labeling in conjunction with specific neuronal markers (van Praag et al. 2002). In a word, the term "adult neurogenesis" is used to describe the observation that new neurons are born from stem cells residing in discrete locations and that these new neurons migrate, differentiate, and mature into newly integrated, functioning cells in the adult mammalian brain (Zhao et al. 2008).

Further, research over the past decade has shown that adult neurogenesis is highly regulatable. Adult neurogenesis may be modified by a variety of extrinsic factors, including stress (Gould et al. 1990), aging (Kuhn et al. 1996), antidepressants (Santarelli et al. 2003), environmental enrichment (EE) (Kempermann et al. 1997), and physical activity (van Praag et al. 1999a, b). It was first shown that an EE, in which animals live in larger cages with several objects that are changed and

moved often, enhances the survival of neural stem cells (Kempermann et al. 1997). In parallel with increased neurogenesis, the animals performed better in a hippocampal-dependent spatial learning task, the Morris water maze.

However, as EE has many aspects, it was not known which of these variables may mediate the beneficial effect of enrichment on the number of newborn neurons. Thus, van Praag et al. (1999a) exposed mice to numerous conditions, including the full EE, as well as focused training on a spatial learning task (water maze), a non-learning swimming control condition, and voluntary exercise (running wheel), and for the first time included mice that only exercised in the attempt to elucidate the neurogenic factor. Similar to EE, voluntary exercise in a running wheel enhanced the survival of newborn neurons in the DG, whereas none of the other conditions had any effect on cell genesis. In addition, wheel running increased cell division as compared to all the other groups. The total number of surviving cells was similar between the enriched and running condition in this initial study. In this regard, a possible confounding variable could have been that EE also contained a running wheel. Indeed, in experiments in which running and enrichment without a wheel were compared, there were more BrdU-positive cells in the running than in the enriched condition (Ehninger and Kempermann 2003) or a nonsignificant trend of EE only (Fabel et al. 2009). It should also be noted that new evidence is emerging, suggesting that it may be the exercise component of EE which is the critical factor in enhancement of neurogenesis.

In a recent study, we aimed to dissociate effects of physical activity and enrichment in young female C57Bl/6 mice that were housed under control, running, enrichment, or enrichment plus running conditions, and injected with bromodeoxyuridine. Cell genesis was assessed after 12 days and differentiation was analyzed 1 month later. In addition, hippocampal BDNF protein levels were measured. New cell proliferation, survival, neuron number, and neurotrophin levels were enhanced only when running was accessible. We conclude that exercise is the critical factor mediating increased BDNF levels and adult hippocampal neurogenesis (Kobilo et al. 2011b; Fig. 1.3). In terms of neuroplasticity EE only has distinct effects on brain function and behavior (Black et al. 1990; Hendriksen et al. 2010; Meshi et al. 2006) that may differ from or could be complementary to physical activity; however, EE only does not increase neurogenesis or BDNF (see also Chaps. 2 and 8) levels in the hippocampus (Kobilo et al. 2011b).

In another study, we investigated whether there is an association between the amount of running and the number of new cells produced. In the studies with individually housed C57Bl/6 mice where there was little variation in distance run between animals (van Praag et al. 1999b), there was no obvious correlation. Interestingly, in this same strain there was an association between the number of new cells and performance on a spatial pattern separation task that became evident with running (Creer et al. 2010; Fig. 1.1). A different strain, 129SvEv, does show a wide range of wheel revolutions between individuals. There was a significant positive correlation between cell proliferation/survival and distance run in these mice (Allen et al. 2001). The correlation between wheel running and neurogenesis was also studied in mice bred for high levels of voluntary exercise over 26 generations

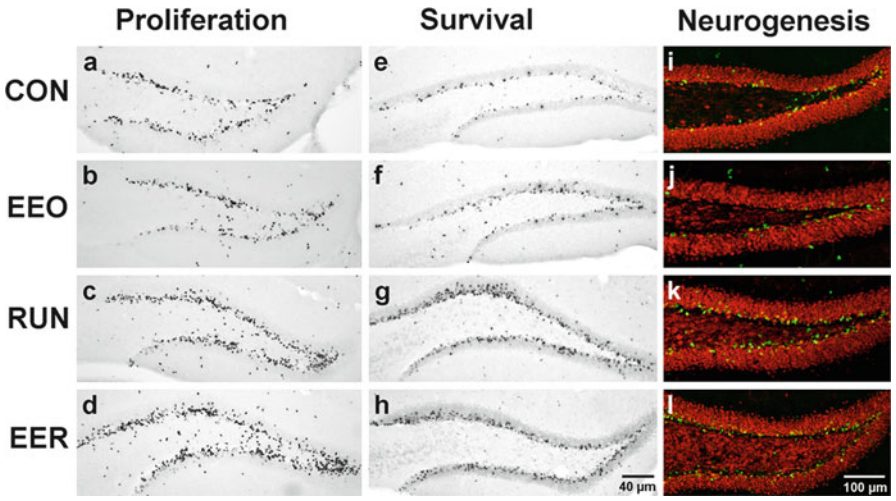

Fig. 1.3 Exercise is the neurogenic component of the enriched environment. Photomicrographs (**a**–**l**) of BrdU-positive cells 1 day to measure cell proliferation (**a**–**d**) and 4 weeks, to assess new cell survival (**e**–**h**) after the last BrdU injection in Control, CON (**a**, **e**, **i**), Enrichment only, EEO (**b**, **f**, **j**), running, RUN (**c**, **g**, **k**), and enrichment + running, EER (**d**, **h**, **l**) mice. (**i**–**l**) Confocal images of BrdU-positive cells in CON (**i**), EEO (**j**), RUN (**k**) and EER (**l**) 4 weeks after the last injection. Sections were immunofluorescent double-labeled for BrdU (*green*) and NeuN (*red*) indicating neuronal phenotype and showing the extent of adult neurogenesis in the different conditions (Kobilo et al. 2011b)

(Rhodes et al. 2003). In these mice, a lack of association between distance run and cell number and also no effect on spatial learning was observed, suggesting that selective breeding for hyperactivity is associated with neurological deficits that affect brain function and behavior (Rhodes et al. 2001).

A number of studies have investigated the kinetics of the effects of exercise on cell proliferation and neurogenesis. Research has shown that 10 days of wheel running increased cell genesis in individually as well as group-housed young and aged rodents (Allen et al. 2001; Kannangara et al. 2009, 2011; Persson et al. 2004; van der Borght et al. 2006). The onset of the effect of running on cell genesis, however, occurs sooner. Indeed, Kronenberg et al. (2006) using a BrdU labeling paradigm in which group-housed mice were injected once after the onset of running, 1 day before killing, reported that cell proliferation peaks after 3 days of running, and is still significantly enhanced at 10 days. After 32 days of running the pro-proliferative effect has returned to baseline. Interestingly, the number of immature neurons continues to increase at this time point (Kronenberg et al. 2006). Furthermore, circadian rhythm studies in which single-housed mice were allowed to run 1 or 3 h/day for 7 days, and injected with BrdU at different times during the day–night cycle, have indicated that the greatest amount of cell genesis is the middle of the dark cycle (Holmes et al. 2004). Another study, however, using Ki67 labeling suggests that the onset of the active cycle is optimal for the effect of physical activity on cell genesis (van der Borght et al. 2006).

Although most studies of exercise-induced neurogenesis in rodents have been performed using voluntary exercise in a running wheel paradigm, the forced treadmill training, interestingly, also had a similar cell genesis enhancing effect (Kim et al. 2003; Uda et al. 2006). In addition, exercise increases hippocampal neurogenesis not only in young mice (van Praag et al. 1999a, b), but also in aged mice (Kronenberg et al. 2006; van Praag et al. 2005), although in the latter the levels attained are not as high. Furthermore, whereas in 18-month-old mice exercise enhanced cell division in the DG as measured by BrdU labeling cell (Kannangara et al. 2011) and neurogenesis (van Praag et al. 2005), in the oldest mice (26 months) new cell number was no longer increased despite daily running wheel activity (Creer et al. 2010). These findings suggest that exercise might prevent age-dependent decline of neurogenesis when it is applied before or during the course of the aging process, and may delay loss of cognition with aging, by increasing the potential for new cell genesis and supporting the function of existing cells.

In summary, running causes a robust increase in neurogenesis in the DG of the hippocampus, a brain area important for learning and memory, with no effect on olfactory bulb neurogenesis (Brown et al. 2003). A possible mechanism underlying the exercise-induced increase in neurogenesis is the growth factor BDNF (see also Chaps. 2 and 8), which is strongly elevated as a result of running in rodents (Neeper et al. 1995; Kobilo et al. 2011b). In mice lacking the receptor tyrosine kinase TrkB in hippocampal progenitor cells, no increase in proliferation or neurogenesis is observed in response to wheel running (Li et al. 2008). Similarly, in conditional BDNF knockout mice, the neurogenic response to exercise was impaired (Choi et al. 2009), consistent with research that BDNF gene expression is elevated in the dentate gyrus (Farmer et al. 2004). It has been suggested that running wheel exercise may activate NMDA receptors in the hippocampus and that in turn may enhance mature BDNF production and secretion. Indeed, the running-induced enhancement of BDNF levels and hippocampal neurogenesis is suppressed in mice lacking the NMDA receptor β1 (Kitamura et al. 2003). Thus, the positive correlation between running, neurotrophins, and neurogenesis has raised the hypothesis that the production of new hippocampal neurons may mediate, in part, improved cognition associated with exercise.

1.3.2 Synaptic Plasticity

The exercise-induced increase in cell genesis is associated with enhanced hippocampal synaptic plasticity. In particular, long-term potentiation (LTP)—a possible physiological model of certain forms of learning and memory (Bliss and Collingridge 1993)—is influenced by physical activity. In our initial study, field excitatory postsynaptic potential (fEPSP) amplitudes, as well as LTP, were compared in hippocampal slices from running and control mice. fEPSPs were unchanged in both groups. However, LTP amplitude was enhanced in the DG in slices from running mice as compared to controls. Recordings from another hippocampal

subfield, area CA1, showed no change in LTP in response to running (van Praag et al. 1999b). In subsequent studies, DG LTP was studied in vivo in urethane anesthetized rats that have been housed with a running wheel (Farmer et al. 2004) or given forced treadmill exercise (O'Callaghan et al. 2007). In both the voluntary and forced exercise condition LTP in the DG was increased. Interestingly, in a recent study, upon ablation of adult neurogenesis using a genetic model in which a majority of adult-born neurons can be selectively ablated in the DG, both LTP and long-term depression (LTD) were compromised, probably as a result of an increased induction threshold (Massa et al. 2011).

Changes in synaptic plasticity associated with exercise occurred in the same region where neurogenesis was stimulated by running, suggesting that newborn cells have a functional role in this process. Although the new cells are a small percentage of the granule cell layer, several studies have indicated that they have greater plasticity than do mature cells. Indeed, in immature rats, DG LTP lasts longer than in adults (Bronzino et al. 1994). In another study, it was found that putative young cells had a lower threshold for LTP and were unaffected by GABA inhibition, indicating enhanced plasticity in the young cells (Wang et al. 2000). In a subsequent investigation, recordings were made from young neurons identified by electrophysiological criteria established during early postnatal development of DG neurons, immunoreactivity for immature neuronal markers, and developing dendritic morphology. It was shown that LTP can be induced more easily in young neurons than in mature neurons under identical conditions (Schmidt-Hieber et al. 2004). Recently, using retroviral labeling by which dividing cells can be labeled and visualized in live tissue using a fluorescent reporter gene (van Praag et al. 2002), it was reported that individual new neurons have increased LTP amplitude and a decreased induction threshold between 1 and 1.5 months of newborn neuron age. A proposed mechanism is increased dependence of LTP on *N*-methyl-D-aspartate (NMDA) NR2B receptors during this critical developmental period (Ge et al. 2007). Thus, exercise will enhance the number of cells with increased excitability and plasticity in the DG.

1.3.3 Spine Density

Apart from effects on production of new neurons in the DG of the hippocampus, exercise results in additional morphological changes. Donald Hebb suggested that changes in synaptic strength might be accompanied by alterations in neuronal morphology. Total dendritic length, as well as the complexity of the dendritic tree, can be altered by exercise (Eadie et al. 2005; Redila and Christie 2006; Stranahan et al. 2007). These features influence the conductance properties of the neuron, thereby regulating its function (Fig. 1.2).

Structural plasticity among dendritic spines has become accepted as an important mechanism for learning and memory (Lang et al. 2004; Zhou et al. 2004). The spatial and temporal pattern of spine formation closely follows that of

LTP; moreover, pharmacological treatments and genetic manipulations that block LTP also block spinogenesis (Engert and Bonhoeffer 1999). If one considers LTP as an underlying mechanism for learning and memory, then one must also accept a role for alterations in the number and structure of spines—because while the exact mechanisms of functional alterations in spine structure are still being elucidated, it is clear that these two processes are dependent on one another.

Importantly, exercise enhances dendritic spine density in the entorhinal cortex and hippocampus. Exercise was associated with increased dendritic spine density not only in granule neurons of the DG, but also in CA1 pyramidal neurons, and in layer III pyramidal neurons of the entorhinal cortex. In the CA1 region, wheel running induces a bias toward longer, thinner spines (Stranahan et al. 2007). In addition, both dendritic length and complexity are significantly increased in the DG of animals that exercise, and spine density is significantly greater on dendrites in the DG following voluntary physical activity (Eadie et al. 2005). It is of interest that running did not influence the development of individual newborn neurons in the adult brain other than accelerating the process of mushroom spine maturation (Zhao et al. 2006). The changes in the cytoarchitecture of the DG, both in terms of the addition of new neurons and the changes in fine morphology of individual neurons induced by voluntary exercise might underlie at least in part the enhancement of hippocampal LTP and hippocampal-dependent cognition.

1.3.4 Angiogenesis

Increased cerebral blood flow to various regions of the brain as a result of exercise may improve neuronal activity (Lange-Asschenfeldt and Kojda 2008). Indeed, alterations in cerebral blood flow, and its associated processes, could be a key mitigating factor between exercise, increased synaptic plasticity in the hippocampus, and enhanced learning and memory (Christie et al. 2008). Stummer et al. (1994) reported that providing animals with free access to a running wheel before brain injury increased the probability of survival and decreased damage to the DG following ischemia. Thus, it seems that exercise-induced changes in the cerebral vascular system might improve synaptic plasticity, and this protection might be in part conferred by an increase in the number (angiogenesis) and diameter of vessels (vasodilation) following exercise (Christie et al. 2008; Fig. 1.2).

Exercise enhances angiogenesis and vascular function in several regions of the brain including the motor cortex (McCloskey et al. 2001), cerebellum (Black et al. 1990; Isaacs et al. 1992), and hippocampus (Carro et al. 2001; Llorens-Martin et al. 2006; Trejo et al. 2001; van Praag et al. 2005). In recent years, there has been a growing interest in the relationship between angiogenic factors and neurogenesis. In the DG new cells are clustered close to blood vessels (Palmer et al. 2000) and proliferate in response to vascular growth factors (Cao et al. 2004; Jin et al. 2002). This had led to the hypothesis that neural progenitors cells are associated with a vascular niche and that neurogenesis and angiogenesis are closely correlated (Palmer et al. 2000;

Pereira et al. 2007; Shen et al. 2004; Thored et al. 2007; van der Borght et al. 2009). In particular, hippocampal gene transfer of vascular endothelial growth factor (VEGF; see also Chap. 8) in adult rats resulted in approximately double the number of new neurons in the DG and improved cognition (Cao et al. 2004). Peripheral infusion of insulin-like growth factor I (IGF-1, see also Chap. 8) also increased adult neurogenesis (Aberg et al. 2000), and reversed the aging-related reduction in new neuron production (Lichtenwalner et al. 2001).

Vasculature changes associated with exercise have been shown to occur in the brain and may be mediated by IGF-1 and VEGF. Physical activity increases the proliferation of brain endothelial cells (Lopez-Lopez et al. 2004) and angiogenesis (Anderson et al. 2002; Black et al. 1990; Kleim et al. 2002; Swain et al. 2003) throughout the brain. Running enhances IGF-1 gene expression (Ding et al. 2006a, b) and protein levels in the hippocampus (Carro et al. 2000). In addition, physical activity increases serum levels of both IGF-1 (Carro et al. 2000) and VEGF (Fabel et al. 2003), and blockade of peripheral VEGF and IGF-1 inhibited the increase in neurogenesis observed with running (Fabel et al. 2003; Trejo et al. 2001).

In the DG, unlimited voluntary exercise enhanced the perimeter and surface area of blood vessels in the DG of young, but not aged mice (van Praag et al. 2005). Recently, using MRI imaging in mice and humans a correlation between blood flow in the DG and neurogenesis was reported, suggesting that changes in blood flow in humans may be an indirect measure for levels of neurogenesis in humans (Pereira et al. 2007; see also Chap. 16). Interestingly, in a study in which we aimed to determine whether the plant-derived flavanol (−)epicatechin could enhance neurogenesis, we found that this compound caused a robust expansion of the vasculature but did not enhance cell genesis (van Praag et al. 2007), suggesting that there is not always a direct correlation between angiogenesis and neurogenesis. Even so, it should be noted that in very aged mice that no longer show an exercise-induced neurogenesis, the vascular response to exercise is also absent (Creer et al. 2010).

1.4 Running, Neurotransmission and Pharmacology

1.4.1 Antidepressants and Running

Physical activity influences many neurotransmitter systems in the brain including the glutamatergic (Farmer et al. 2004; Kitamura et al. 2003; Lou et al. 2008; Vasuta et al. 2007), endocannabinoid (Hill et al. 2010), opioidergic (Sforzo et al. 1986), and monoaminergic systems (Chaouloff 1989; see also Chaps. 3, 4, and 22). The latter is of particular interest as physical activity has been shown to lead to recovery from depression (Lawlor and Hopker 2001). Indeed, the antidepressant effect of exercise in humans (Ernst et al. 2006) has been shown to be just as potent as that of serotonergic medications (Babyak et al. 2000). Therefore, it is of interest that serotonergic agonists, including antidepressants such as fluoxetine (Encinas et al. 2006; Malberg et al. 2000), have been suggested to enhance cell

genesis, whereas administration of the serotonin 5-HT_{1A} receptor antagonists decreases cell proliferation in the DG (Radley and Jacobs 2002).

In a recent study, we aimed to evaluate to what extent the effects of antidepressants on neurogenesis are comparable to those of voluntary wheel running. Specifically, the selective serotonin reuptake inhibitor (SSRI) fluoxetine, which had been previously shown to enhance neurogenesis (Santarelli et al. 2003), and the new dual serotonergic–noradrenergic reuptake inhibitor (SNRI) duloxetine, which had not been evaluated in this context, were both tested. In this study, neurogenesis was evaluated in 2-month-old female C57Bl/6 mice after 28 days of treatment with fluoxetine (18 mg/kg), duloxetine (2, 6 or, 18 mg/kg), or exercise. Interestingly, BrdU-positive cell survival was enhanced by 200% in the running group only. In addition, only fluoxetine and running resulted in a phenotype shift with a greater percentage of BrdU-positive cells becoming new neurons. Thus, the neurogenic response to exercise is much stronger than to antidepressants and it is not very likely that anxiolytic effects of these drugs are mediated by adult neurogenesis (Marlatt et al. 2010). Recent research by others supports our findings in this regard (Hanson et al. 2011).

1.4.2 Endurance Factors

Another logical approach toward identifying pharmacological ways to enhance neurogenesis is the investigation whether skeletal muscle activation as a result of exercise or pharmacological agents underlies neurogenic and cognitive effects of aerobic activity. Indeed, much research pertaining to the effects of exercise on brain function has focused on cellular, structural, and biochemical changes in the brain without much consideration for the peripheral factors that may elicit changes in synaptic plasticity, angiogenesis, neurogenesis, and cognition (Cotman et al. 2007; Gomez-Pinilla 2008; Hillman et al. 2008; van Praag 2008). However, the possibility that skeletal muscle activation as a result of exercise or pharmacological agents underlies cognitive effects of aerobic activity has just begun to be explored (Kobilo et al. 2011a).

Recently, transcriptional factors regulating muscle fiber contractile and metabolic genes have been identified (Wang et al. 2004) and led to the identification of compounds that can increase the ability of cells to burn fat and enhance exercise endurance (Narkar et al. 2008). The peroxisome proliferator activated receptor delta (PPARdelta) is a transcription factor that regulates fast-twitch muscle fiber contraction and metabolism. Overexpression of this factor increased oxidative muscle fiber number. In addition, administration of the selective agonist GW501516 increased exercise stamina when combined with training (Narkar et al. 2008). PPARdelta is controlled by AMP-activated protein kinase (AMPK), a master metabolic regulator important for glucose homeostasis, appetite, and exercise physiology (Hardie 2004). Treatment with AMPK agonist AICAR enhanced running endurance by 45% in sedentary mice (Narkar et al. 2008).

Subsequently, we investigated the effects of endurance factors, PPARdelta agonist GW501516 and AICAR, activator of AMPK on memory and neurogenesis.

Mice were injected with GW or AICAR for 7 days and concurrently with BrdU to label dividing cells. Two weeks thereafter mice were tested in the Morris water maze. Both AICAR and GW improved retention of spatial memory. Moreover, AICAR significantly and GW modestly elevated DG neurogenesis. Thus, pharmacological activation of skeletal muscle may mediate cognitive effects of aerobic exercise (Kobilo et al. 2011a) and provide a possible therapeutic approach for conditions in which exercise is limited. Interestingly, although these compounds mimic some of the results of exercise their effects are not identical to physical activity itself. Prolonged administration of AICAR (14 days) no longer enhances spatial memory function or neurogenesis (Kobilo et al. 2011a). Similarly, short-term AICAR treatment promoted sirtuin 1 protein expression in skeletal muscle, whereas 14 days of treatment did not (Suwa et al. 2011).

1.5 Conclusions and Perspectives

Exercise is a quantifiable activity that improves cognition in young and aged animals and humans. The beneficial effects of exercise are mediated at least in part by regulation and changes in hippocampal function mediated by enhanced neurogenesis, synaptic plasticity, spine density, and angiogenesis. However, we also suggest that caution should be used when applying exercise to conditions of brain injury and neurodegenerative disease as the consequences could be detrimental (Potter et al. 2010). Furthermore, our current data have shown that the neurogenic response to exercise is much stronger than to antidepressants, fluoxetine and duloxetine, in adult mice (Marlatt et al. 2010). Moreover, we found that there is improved spatial memory in the Morris water maze test and enhanced neurogenesis after mice were injected with "exercise mimetics" (Kobilo et al. 2011a), suggesting that to some extent the beneficial effects of exercise can be elicited pharmacologically. Further research is needed to understand the cellular mechanisms underlying effects of aerobic activity on brain function.

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References

Aberg MA, Aberg ND, Hedbacker H, Oscarsson J, Eriksson PS (2000) Peripheral infusion of IGF-I selectively induces neurogenesis in the adult rat hippocampus. J Neurosci 20:2896–2903

Adlard PA, Perreau VM, Pop V, Cotman CW (2005) Voluntary exercise decreases amyloid load in a transgenic model of Alzheimer's disease. J Neurosci 25:4217–4221

Adlard PA, Engesser-Cesar C, Cotman CW (2011) Mild stress facilitates learning and exercise improves retention in aged mice. Exp Gerontol 46:53–59

Albeck DS, Sano K, Prewitt GE, Dalton L (2006) Mild forced treadmill exercise enhances spatial learning in the aged rat. Behav Brain Res 168:345–348

Al-Jarrah M, Pothakos K, Novikova L, Smirnova IV, Kurz MJ, Stehno-Bittel L, Lau YS (2007) Endurance exercise promotes cardiorespiratory rehabilitation without neurorestoration in the chronic mouse model of parkinsonism with severe neurodegeneration. Neuroscience 149:28–37

Allen DM, van Praag H, Ray J, Weaver Z, Winrow CJ, Carter TA, Braquet R, Harrington E, Ried T, Brown KD, Gage FH, Barlow C (2001) Ataxia telangiectasia mutated is essential during adult neurogenesis. Genes Dev 15:554–566

Allison DB, Fontaine KR, Manson JE, Stevens J, VanItallie TB (1999) Annual deaths attributable to obesity in the United States. JAMA 282:1530–1538

Altman J (1962) Are new neurons formed in the brains of adult mammals? Science 135:1127–1128

Altschuler EL (2006) Strenuous, intensive, long-term exercise does not prevent or delay the onset of Huntington's disease. Med Hypotheses 67:1429–1430

Anderson BJ, Eckburg PB, Relucio KI (2002) Alterations in the thickness of motor cortical subregions after motor-skill learning and exercise. Learn Mem 9:1–9

Babyak M, Blumenthal JA, Herman S, Khatri P, Doriaswamy M, Moore K, Craighead WE, Baldewicz TT, Krishnan KR (2000) Exercise treatment for major depression: maintenance of therapeutic benefit at 10 months. Psychosom Med 62:633–638

Barnes CA (1994) Normal aging: regionally specific changes in hippocampal synaptic transmission. Trends Neurosci 17:13–18

Black JE, Isaacs KR, Anderson BJ, Alcantara AA, Greenough WT (1990) Learning causes synaptogenesis, whereas motor activity causes angiogenesis, in cerebellar cortex of adult rats. Proc Natl Acad Sci USA 87:5568–5572

Bliss TV, Collingridge GL (1993) A synaptic model of memory: long-term potentiation in the hippocampus. Nature 361:31–39

Bohannon RW (1993) Physical rehabilitation in neurologic diseases. Curr Opin Neurol 6:765–772

Booth FW, Chakravarthy MV, Gordon SE, Spangenburg EE (2002) Waging war on physical inactivity: using modern molecular ammunition against an ancient enemy. J Appl Physiol 93:3–30

Bronzino JD, Abu-Hasaballah K, Austin-LaFrance RJ, Morgane PJ (1994) Maturation of long-term potentiation in the hippocampal dentate gyrus of the freely moving rat. Hippocampus 4:439–446

Brown J, Cooper-Kuhn CM, Kempermann G, van Praag H, Winkler J, Gage FH, Kuhn HG (2003) Enriched environment and physical activity stimulate hippocampal but not olfactory bulb neurogenesis. Eur J Neurosci 17:2042–2046

Cao L, Jiao X, Zuzga DS, Liu Y, Fong DM, Young D, During MJ (2004) VEGF links hippocampal activity with neurogenesis, learning and memory. Nat Genet 36:827–835

Carro E, Nunez A, Busiguina S, Torres-Aleman I (2000) Circulating insulin-like growth factor I mediates effects of exercise on the brain. J Neurosci 20:2926–2933

Carro E, Trejo JL, Busiguina S, Torres-Aleman I (2001) Circulating insulin-like growth factor I mediates the protective effects of physical exercise against brain insults of different etiology and anatomy. J Neurosci 21:5678–5684

Cepeda C, Cummings DM, Hickey MA, Kleiman-Weiner M, Chen JY, Watson JB, Levine MS (2010) Rescuing the corticostriatal synaptic disconnection in the R6/2 mouse model of Huntington's disease: exercise, adenosine receptors and ampakines. PLoS Curr 2:RRN1182

Chaouloff F (1989) Physical exercise and brain monoamines: a review. Acta Physiol Scand 137:1–13

Chen KS, Masliah E, Mallory M, Gage FH (1995) Synaptic loss in cognitively impaired aged rats is ameliorated by chronic human growth factor infusion. Neuroscience 68:19–27

Choi SH, Li Y, Parada LF, Sisodia SS (2009) Regulation of hippocampal progenitor cell survival, proliferation and dendritic development by BDNF. Mol Neurodegener 4:52

Christie BR, Eadie BD, Kannangara TS, Robillard JM, Shin J, Titterness AK (2008) Exercising our brains: how physical activity impacts synaptic plasticity in the dentate gyrus. Neuromolecular Med 10:47–58

Clark PJ, Kohman RA, Miller DS, Bhattacharya TK, Brzezinska WJ, Rhodes JS (2011) Genetic influences on exercise-induced adult hippocampal neurogenesis across 12 divergent mouse strains. Genes Brain Behav 10:345–353

Cotman CW, Berchtold NC, Christie LA (2007) Exercise builds brain health: key roles of growth factor cascades and inflammation. Trends Neurosci 30:464–472

Creer DJ, Romberg C, Saksida LM, van Praag H, Bussey TJ (2010) Running enhances spatial pattern separation in mice. Proc Natl Acad Sci USA 107:2367–2372

Curtis MA, Kam M, Nannmark U, Anderson MF, Axell MZ, Wikkelso C, Holtås S, van Roon-Mom WM, Björk-Eriksson T, Nordborg C, Frisén J, Dragunow M, Faull RL, Eriksson PS (2007) Human neuroblasts migrate to the olfactory bulb via a lateral ventricular extension. Science 315:1243–1249

Ding Q, Vaynman S, Akhavan M, Ying Z, Gomez-Pinilla F (2006a) Insulin-like growth factor I interfaces with brain-derived neurotrophic factor-mediated synaptic plasticity to modulate aspects of exercise-induced cognitive function. Neuroscience 140:823–833

Ding YH, Li J, Zhou Y, Rafols JA, Clark JC, Ding Y (2006b) Cerebral angiogenesis and expression of angiogenic factors in aging rats after exercise. Curr Neurovasc Res 3:15–23

Duman CH, Schlesinger L, Russell DS, Duman RS (2008) Voluntary exercise produces antidepressant and anxiolytic behavioral effects in mice. Brain Res 1199:148–158

Eadie BD, Redila VA, Christie BR (2005) Voluntary exercise alters the cytoarchitecture of the adult dentate gyrus by increasing cellular proliferation, dendritic complexity, and spine density. J Comp Neurol 486:39–47

Ehninger D, Kempermann G (2003) Regional effects of wheel running and environmental enrichment on cell genesis and microglia proliferation in the adult murine neocortex. Cereb Cortex 13:845–851

Encinas JM, Vaahtokari A, Enikolopov G (2006) Fluoxetine targets early progenitor cells in the adult brain. Proc Natl Acad Sci USA 103:8233–8238

Engert F, Bonhoeffer T (1999) Dendritic spine changes associated with hippocampal long-term synaptic plasticity. Nature 399:66–70

Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, Chaddock L, Kim JS, Heo S, Alves H, White SM, Wojcicki TR, Mailey E, Vieira VJ, Martin SA, Pence BD, Woods JA, McAuley E, Kramer AF (2011) Exercise training increases size of hippocampus and improves memory. Proc Natl Acad Sci USA 108:3017–3022

Eriksson PS, Perfilieva E, Björk-Eriksson T, Alborn AM, Nordborg C, Peterson DA, Gage FH (1998) Neurogenesis in the adult human hippocampus. Nat Med 4:1313–1317

Ernst C, Olson AK, Pinel JP, Lam RW, Christie BR (2006) Antidepressant effects of exercise: evidence for an adult-neurogenesis hypothesis? J Psychiatry Neurosci 31:84–92

Fabel K, Tam B, Kaufer D, Baiker A, Simmons N, Kuo CJ, Palmer TD (2003) VEGF is necessary for exercise-induced adult hippocampal neurogenesis. Eur J Neurosci 18:2803–2812

Fabel K, Wolf SA, Ehninger D, Babu H, Leal-Galicia P, Kempermann G (2009) Additive effects of physical exercise and environmental enrichment on adult hippocampal neurogenesis in mice. Front Neurosci 3:50

Falls WA, Fox JH, MacAulay CM (2010) Voluntary exercise improves both learning and consolidation of cued conditioned fear in C57 mice. Behav Brain Res 207:321–331

Farmer J, Zhao X, van Praag H, Wodtke K, Gage FH, Christie BR (2004) Effects of voluntary exercise on synaptic plasticity and gene expression in the dentate gyrus of adult male Sprague-Dawley rats in vivo. Neuroscience 124:71–79

Fordyce DE, Farrar RP (1991) Physical activity effects on hippocampal and parietal cortical cholinergic function and spatial learning in F344 rats. Behav Brain Res 43:115–123

Friedland RP, Fritsch T, Smyth KA, Koss E, Lerner AJ, Chen CH, Petot GJ, Debanne SM (2001) Patients with Alzheimer's disease have reduced activities in midlife compared with healthy control-group members. Proc Natl Acad Sci USA 98:3440–3445

Ge S, Yang CH, Hsu KS, Ming GL, Song H (2007) A critical period for enhanced synaptic plasticity in newly generated neurons of the adult brain. Neuron 54:559–566

Giménez-Llort L, García Y, Buccieri K, Revilla S, Suñol C, Cristofol R, Sanfeliu C (2010) Gender-specific neuroimmunoendocrine response to treadmill exercise in 3xTg-ADMice. Int J Alzheimers Dis 2010:128354

Gobbo OL, O'Mara SM (2005) Exercise, but not environmental enrichment, improves learning after kainic acid-induced hippocampal neurodegeneration in association with an increase in brain-derived neurotrophic factor. Behav Brain Res 159:21–26

Gomez-Pinilla F (2008) Brain foods: the effects of nutrients on brain function. Nat Rev Neurosci 9:568–578

Gorton LM, Vuckovic MG, Vertelkina N, Petzinger GM, Jakowec MW, Wood RI (2010) Exercise effects on motor and affective behavior and catecholamine neurochemistry in the MPTP-lesioned mouse. Behav Brain Res 213:253–262

Gould E, Woolley CS, McEwen BS (1990) Short-term glucocorticoid manipulations affect neuronal morphology and survival in the adult dentate gyrus. Neuroscience 37:367–375

Grealy MA, Johnson DA, Rushton SK (1999) Improving cognitive function after brain injury: the use of exercise and virtual reality. Arch Phys Med Rehabil 80:661–667

Hanson ND, Nemeroff CB, Owens MJ (2011) Lithium, but not fluoxetine or the corticotropin-releasing factor receptor 1 receptor antagonist R121919, increases cell proliferation in the adult dentate gyrus. J Pharmacol Exp Ther 337:180–186

Hardie DG (2004) The AMP-activated protein kinase pathway – new players upstream and downstream. J Cell Sci 117:5479–5487

Hendriksen H, Prins J, Olivier B, Oosting RS (2010) Environmental enrichment induces behavioral recovery and enhanced hippocampal cell proliferation in an antidepressant-resistant animal model for PTSD. PLoS One 5:e11943

Hill MN, Titterness AK, Morrish AC, Carrier EJ, Lee TT, Gil-Mohapel J, Gorzalka BB, Hillard CJ, Christie BR (2010) Endogenous cannabinoid signaling is required for voluntary exercise-induced enhancement of progenitor cell proliferation in the hippocampus. Hippocampus 20:513–523

Hillman CH, Erickson KI, Kramer AF (2008) Be smart, exercise your heart: exercise effects on brain and cognition. Nat Rev Neurosci 9:58–65

Holmes MM, Galea LA, Mistlberger RE, Kempermann G (2004) Adult hippocampal neurogenesis and voluntary running activity: circadian and dose-dependent effects. J Neurosci Res 76:216–222

Hunsberger JG, Newton SS, Bennett AH, Duman CH, Russell DS, Salton SR, Duman RS (2007) Antidepressant actions of the exercise-regulated gene VGF. Nat Med 13:1476–1482

Isaacs KR, Anderson BJ, Alcantara AA, Black JE, Greenough WT (1992) Exercise and the brain: angiogenesis in the adult rat cerebellum after vigorous physical activity and motor skill learning. J Cereb Blood Flow Metab 12:110–119

Jin K, Zhu K, Sun Y, Mao XO, Xie L, Greenberg DA (2002) Vascular endothelial growth factor (VEGF) stimulates neurogenesis in vitro and in vivo. Proc Natl Acad Sci USA 99:11946–11950

Kannangara TS, Webber A, Gil-Mohapel J, Christie BR (2009) Stress differentially regulates the effects of voluntary exercise on cell proliferation in the dentate gyrus of mice. Hippocampus 19:889–897

Kannangara TS, Lucero MJ, Gil-Mohapel J, Drapala RJ, Simpson JM, Christie BR, van Praag H (2011) Running reduces stress and enhances cell genesis in aged mice. Neurobiol Aging 32:2279–2286

Kaspar BK, Frost LM, Christian L, Umapathi P, Gage FH (2005) Synergy of insulin-like growth factor-1 and exercise in amyotrophic lateral sclerosis. Ann Neurol 57:649–655

Kempermann G, Kuhn HG, Gage FH (1997) More hippocampal neurons in adult mice living in an enriched environment. Nature 386:493–495

Kim YP, Kim HB, Kim MH, Jang BV, Lim YJ, Kim H, Kim SS, Kim EH, Kim CJ (2003) Magnitude- and time-dependence of the effect of treadmill exercise on cell proliferation in the dentate gyrus of rats. Int J Sports Med 24:114–117

Kim SE, Ko IG, Kim BK, Shin MS, Cho S, Kim CJ, Kim SH, Baek SS, Lee EK, Jee YS (2010) Treadmill exercise prevents aging-induced failure of memory through an increase in neurogenesis and suppression of apoptosis in rat hippocampus. Exp Gerontol 45:357–365

Kitamura T, Mishina M, Sugiyama H (2003) Enhancement of neurogenesis by running wheel exercises is suppressed in mice lacking NMDA receptor epsilon 1 subunit. Neurosci Res 47:55–63

Kleim JA, Cooper NR, VandenBerg PM (2002) Exercise induces angiogenesis but does not alter movement representations within rat motor cortex. Brain Res 934:1–6

Kobilo T, Yuan C, van Praag H (2011a) Endurance factors improve hippocampal neurogenesis and spatial memory in mice. Learn Mem 18:103–107

Kobilo T, Liu Q, Gandhi K, Mohammed M, Shaham Y, van Praag H (2011b) Running is the neurogenic and neurotrophic stimulus in environmental enrichment. Learn Mem 18(9): 605–609

Kohl Z, Kandasamy M, Winner B, Aigner R, Gross C, Couillard-Despres S, Bogdahn U, Aigner L, Winkler J (2007) Physical activity fails to rescue hippocampal neurogenesis deficits in the R6/2 mouse model of Huntington's disease. Brain Res 1155:24–33

Komitova M, Zhao LR, Gido G, Johansson BB, Eriksson P (2005) Postischemic exercise attenuates whereas enriched environment has certain enhancing effects on lesion-induced subventricular zone activation in the adult rat. Eur J Neurosci 21:2397–2405

Kosinski CM, Schlangen C, Gellerich FN, Gizatullina Z, Deschauer M, Schiefer J, Young AB, Landwehrmeyer GB, Toyka KV, Sellhaus B, Lindenberg KS (2007) Myopathy as a first symptom of Huntington's disease in a Marathon runner. Mov Disord 22:1637–1640

Kramer AF, Hahn S, Cohen NJ, Banich MT, McAuley E, Harrison CR, Chason J, Vakil E, Bardell L, Boileau RA, Colcombe A (1999) Ageing, fitness and neurocognitive function. Nature 400:418–419

Kronenberg G, Bick-Sander A, Bunk E, Wolf E, Ehninger D, Kempermann G (2006) Physical exercise prevents age-related decline in precursor cell activity in the mouse dentate gyrus. Neurobiol Aging 27:1505–1513

Kuhn HG, Dickinson-Anson H, Gage FH (1996) Neurogenesis in the dentate gyrus of the adult rat: age-related decrease of neuronal progenitor proliferation. J Neurosci 16:2027–2033

Lang C, Barco A, Zablow L, Kandel ER, Siegelbaum SA, Zakharenko SS (2004) Transient expansion of synaptically connected dendritic spines upon induction of hippocampal long-term potentiation. Proc Natl Acad Sci USA 101:16665–16670

Lange-Asschenfeldt C, Kojda G (2008) Alzheimer's disease, cerebrovascular dysfunction and the benefits of exercise: from vessels to neurons. Exp Gerontol 43(6):499–504

Laurin D, Verreault R, Lindsay J, MacPherson K, Rockwood K (2001) Physical activity and risk of cognitive impairment and dementia in elderly persons. Arch Neurol 58:498–504

Lawlor DA, Hopker SW (2001) The effectiveness of exercise as an intervention in the management of depression: systematic review and meta-regression analysis of randomised controlled trials. BMJ 322:763–767

Leutgeb JK, Leutgeb S, Moser MB, Moser EI (2007) Pattern separation in the dentate gyrus and CA3 of the hippocampus. Science 315:961–966

Li Y, Luikart BW, Birnbaum S, Chen J, Kwon CH, Kernie SG, Bassel-Duby R, Parada LF (2008) TrkB regulates hippocampal neurogenesis and governs sensitivity to antidepressive treatment. Neuron 59:399–412

Lichtenwalner R, Forbes M, Bennett S, Lynch C, Sonntag W, Riddle D (2001) Intracerebroventricular infusion of insulin-like growth factor-1 ameliorates the age-related decline in hippocampal neurogenesis. Neuroscience 107:606–613

Liu YF, Chen HI, Lin LC, Yu L, Liu YF, Kuo YM, Huang AM, Chuang JI, Wu FS, Liao PC, Jen CJ (2008) Treadmill exercise enhances passive avoidance learning in rats: the role of down-regulated serotonin system in the limbic system. Neurobiol Learn Mem 89:489–496

Llorens-Martin M, Torres-Aleman I, Trejo JL (2006) Pronounced individual variation in the response to the stimulatory action of exercise on immature hippocampal neurons. Hippocampus 16:480–490

Lopez-Lopez C, LeRoith T, Torres-Aleman I (2004) Insulin-like growth factor I is required for vessel remodeling in the adult brain. Proc Natl Acad Sci USA 101:9833–9838

Lou SJ, Liu JY, Chang H, Chen PJ (2008) Hippocampal neurogenesis and gene expression depend on exercise intensity in juvenile rats. Brain Res 1210:48–55

Mahley RW, Weisgraber KH, Huang Y (2006) ApolipoproteinE4: a causative factor and therapeutic target in neuropathology, including Alzheimer's disease. Proc Natl Acad Sci USA 103:5644–5651

Malberg JE, Eisch AJ, Nestler EJ, Duman RS (2000) Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. J Neurosci 20:9104–9110

Marlatt MW, Lucassen PJ, van Praag H (2010) Comparison of neurogenic effects of fluoxetine, duloxetine and running in mice. Brain Res 1341:93–99

Massa F, Koelh M, Wiesner T, Grosjean N, Revest JM, Piazza PV, Abrous DN, Oliet SH (2011) Conditional reduction of adult neurogenesis impairs bidirectional hippocampal synaptic plasticity. Proc Natl Acad Sci USA 108:6644–6649

McCloskey DP, Adamo DS, Anderson BJ (2001) Exercise increases metabolic capacity in the motor cortex and striatum, but not in the hippocampus. Brain Res 891:168–175

McHugh TJ, Jones MW, Quinn JJ, Balthasar N, Coppari R, Elmquist JK, Lowell BB, Fanselow MS, Wilson MA, Tonegawa S (2007) Dentate gyrus NMDA receptors mediate rapid pattern separation in the hippocampal network. Science 317:94–99

Mello PB, Benetti F, Cammarota M, Izquierdo I (2009) Physical exercise can reverse the deficit in fear memory induced by maternal deprivation. Neurobiol Learn Mem 92:364–369

Meshi D, Drew MR, Saxe M, Ansorge MS, David D, Santarelli L, Malapani C, Moore H, Hen R (2006) Hippocampal neurogenesis is not required for behavioral effects of environmental enrichment. Nat Neurosci 9:729–731

Morton AJ, Skillings E, Bussey TJ, Saksida LM (2006) Measuring cognitive deficits in disabled mice using an automated interactive touchscreen system. Nat Methods 3:767

Narkar VA, Downes M, Yu RT, Embler E, Wang YX, Banayo E, Mihaylova MM, Nelson MC, Zou Y, Juguilon H, Kang H, Shaw RJ, Evans RM (2008) AMPK and PPARdelta agonists are exercise mimetics. Cell 134:405–415

Neeper SA, Gómez-Pinilla F, Choi J, Cotman C (1995) Exercise and brain neurotrophins. Nature 373:109

Nichol KE, Parachikova AI, Cotman CW (2007) Three weeks of running wheel exposure improves cognitive performance in the aged Tg2576 mouse. Behav Brain Res 184:124–132

Nichol K, Deeny SP, Seif J, Camaclang K, Cotman CW (2009) Exercise improves cognition and hippocampal plasticity in APOE epsilon4 mice. Alzheimers Dement 5:287–294

O'Callaghan RM, Ohle R, Kelly AM (2007) The effects of forced exercise on hippocampal plasticity in the rat: a comparison of LTP, spatial- and non-spatial learning. Behav Brain Res 176:362–366

O'Dell SJ, Gross NB, Fricks AN, Casiano BD, Nguyen TB, Marshall JF (2007) Running wheel exercise enhances recovery from nigrostriatal dopamine injury without inducing neuroprotection. Neuroscience 144:1141–1151

Palmer TD, Willhoite AR, Gage FH (2000) Vascular niche for adult hippocampal neurogenesis. J Comp Neurol 425:479–494

Pang TY, Stam NC, Nithianantharajah J, Howard ML, Hannan AJ (2006) Differential effects of voluntary physical exercise on behavioral and brain-derived neurotrophic factor expression deficits in Huntington's disease transgenic mice. Neuroscience 141:569–584

Parachikova A, Nichol KE, Cotman CW (2008) Short-term exercise in aged Tg2576 mice alters neuroinflammation and improves cognition. Neurobiol Dis 30:121–129

Pereira AC, Huddleston DE, Brickman AM, Susonov AA, Hen R, McKhann GM, Sloan R, Gage FH, Brown TR, Small SA (2007) An in vivo correlate of exercise-induced neurogenesis in the adult dentate gyrus. Proc Natl Acad Sci USA 104:5638–5643

Persson AI, Naylor AS, Jonsottir IH, Nyberg F, Eriksson PS, Thorlin T (2004) Differential regulation of hippocampal progenitor proliferation by opioid receptor antagonists in running and non-running spontaneously hypertensive rats. Eur J Neurosci 19:1847–1855

Petzinger GM, Walsh JP, Akopian G, Hogg E, Abernathy A, Arevalo P, Turnquist P, Vuckovic M, Fisher BE, Togasaki DM, Jakowec MW (2007) Effects of treadmill exercise on dopaminergic transmission in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned mouse model of basal ganglia injury. J Neurosci 27:5291–5300

Pothakos K, Kurz MJ, Lau YS (2009) Restorative effect of endurance exercise on behavioral deficits in the chronic mouse model of Parkinson's disease with severe neurodegeneration. BMC Neurosci 10:6

Potter M, Yuan C, Ottenritter C, Mughal M, van Praag H (2010) Exercise is not beneficial and may accelerate symptom onset in a mouse model of Huntington's disease. PLoS Curr 2:RRN1201

Powell KE, Blair SN (1994) The public health burdens of sedentary living habits: theoretical but realistic estimates. Med Sci Sports Exerc 26:851–856

Radley JJ, Jacobs BL (2002) 5-HT1A receptor antagonist administration decreases cell proliferation in the dentate gyrus. Brain Res 955:264–267

Redila VA, Christie BR (2006) Exercise-induced changes in dendritic structure and complexity in the adult hippocampal dentate gyrus. Neuroscience 137:1299–1307

Rhodes JS, Hosack GR, Girard I, Kelley AE, Mitchell GS, Garland T Jr (2001) Differential sensitivity to acute administration of cocaine, GBR 12909, & fluoxetine in mice selectively bred for hyperactive wheel-running behavior. Psychopharmacology 158:120–131

Rhodes JS, van Praag H, Jeffrey S, Girard I, Mitchell GS, Garland T Jr, Gage FH (2003) Exercise increases hippocampal neurogenesis to high levels but does not improve spatial learning in mice bred for increased voluntary wheel running. Behav Neurosci 117:1006–1016

Rogers RL, Meyer JS, Mortel KF (1990) After reaching retirement age physical activity sustains cerebral perfusion and cognition. J Am Geriatr Soc 38:123–128

Santarelli L, Saxe M, Gross C, Surget A, Battaglia F, Dulawa S, Weisstaub N, Lee J, Duman R, Arancio O, Belzung C, Hen R (2003) Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. Science 301:805–809

Schmidt-Hieber C, Jonas P, Bischofberger J (2004) Enhanced synaptic plasticity in newly generated granule cells of the adult hippocampus. Nature 429:184–187

Sforzo GA, Seeger TF, Pert CB, Pert A, Dotson CO (1986) In vivo opioid receptor occupation in the rat brain following exercise. Med Sci Sports Exerc 18:380–384

Shen Q, Goderie SK, Jin L, Karanth N, Sun Y, Abramova N, Vincent P, Pumiglia K, Temple S (2004) Endothelial cells stimulate self-renewal and expand neurogenesis of neural stem cells. Science 304:1338–1340

Smith AD, Zigmond MJ (2003) Can the brain be protected through exercise? Lessons from an animal model of parkinsonism. Exp Neurol 184:31–39

Steinmetz KA, Potter JD (1996) Vegetables, fruit, and cancer prevention: a review. J Am Diet Assoc 96:1027–1039

Stranahan AM, Khalil D, Gould E (2007) Running induces widespread structural alterations in the hippocampus and entorhinal cortex. Hippocampus 17:1017–1022

Stummer W, Weber K, Tranmer B, Baethmann A, Kempski O (1994) Reduced mortality and brain damage after locomotor activity in gerbil forebrain ischemia. Stroke 25:1862–1869

Suominen-Troyer S, Davis KJ, Ismail AH, Salvendy G (1986) Impact of physical fitness on strategy development in decision-making tasks. Percept Mot Skills 62:71–77

Suwa M, Nakano H, Radak Z, Kumagai S (2011) Short-term adenosine monophosphate-activated protein kinase activator 5-aminoimidazole-4-carboxamide-1-beta-d-ribofuranoside treatment increases the sirtuin 1 protein expression in skeletal muscle. Metabolism 60:394–403

Swain RA, Harris AB, Wiener EC, Dutka MV, Morris HD, Theien BE, Konda S, Engberg K, Lauterbur PC, Greenough WT (2003) Prolonged exercise induces angiogenesis and increases cerebral blood volume in primary motor cortex of the rat. Neuroscience 117:1037–1046

Tajiri N, Yasuhara T, Shingo T, Kondo A, Yuan W, Kadota T, Wang F, Baba T, Tayra JT, Morimoto T, Jing M, Kikuchi Y, Kuramoto S, Agari T, Miyoshi Y, Fujino H, Obata F, Takeda I, Furuta T, Date I (2010) Exercise exerts neuroprotective effects on Parkinson's disease model of rats. Brain Res 1310:200–207

Thored P, Wood J, Arvidsson A, Cammenga J, Kokaia Z, Lindvall O (2007) Long-term neuroblast migration along blood vessels in an area with transient angiogenesis and increased vascularization after stroke. Stroke 38:3032–3039

Tillerson JL, Caudle WM, Reveron ME, Miller GW (2003) Exercise induces behavioral recovery and attenuates neurochemical deficits in rodent models of Parkinson's disease. Neuroscience 119:899–911

Trejo JL, Carro E, Torres-Aleman I (2001) Circulating insulin-like growth factor I mediates exercise-induced increases in the number of new neurons in the adult hippocampus. J Neurosci 21:1628–1634

Uda M, Ishido M, Kami K, Masuhara M (2006) Effects of chronic treadmill running on neurogenesis in the dentate gyrus of the hippocampus of adult rat. Brain Res 1104:64–72

Um HS, Kang EB, Koo JH, Kim HT, Jin-Lee, Kim EJ, Yang CH, An GY, Cho IH, Cho JY (2011) Treadmill exercise represses neuronal cell death in an aged transgenic mouse model of Alzheimer's disease. Neurosci Res 69:161–173

van Dellen A, Blakemore C, Deacon R, York D, Hannan AJ (2000) Delaying the onset of Huntington's in mice. Nature 404:721–722

van Dellen A, Cordery PM, Spires TL, Blakemore C, Hannan AJ (2008) Wheel running from a juvenile age delays onset of specific motor deficits but does not alter protein aggregate density in a mouse model of Huntington's disease. BMC Neurosci 9:34

van der Borght K, Ferrari F, Klauke K, Roman V, Havekes R, Sgoifo A, van der Zee EA, Meerlo P (2006) Hippocampal cell proliferation across the day: increase by running wheel activity, but no effect of sleep and wakefulness. Behav Brain Res 167:36–41

van der Borght K, Havekes R, Bos T, Eggen BJ, van der Zee EA (2007) Exercise improves memory acquisition and retrieval in the Y-maze task: relationship with hippocampal neurogenesis. Behav Neurosci 121:324–334

van der Borght K, Kóbor-Nyakas DE, Klauke K, Eggen BJ, Nyakas C, van der Zee EA, Meerlo P (2009) Physical exercise leads to rapid adaptations in hippocampal vasculature: temporal dynamics and relationship to cell proliferation and neurogenesis. Hippocampus 19:928–936

van Praag H (2008) Neurogenesis and exercise: past and future directions. Neuromolecular Med 10:128–140

van Praag H, Christie BR, Sejnowski TJ, Gage FH (1999a) Running enhances neurogenesis, learning and long-term potentiation in mice. Proc Natl Acad Sci USA 96:13427–13431

van Praag H, Kempermann G, Gage FH (1999b) Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. Nat Neurosci 2:266–270

van Praag H, Schinder AF, Christie BR, Toni N, Palmer TD, Gage FH (2002) Functional neurogenesis in the adult hippocampus. Nature 415:1030–1034

van Praag H, Shubert T, Zhao C, Gage FH (2005) Exercise enhances learning and hippocampal neurogenesis in aged mice. J Neurosci 25:8680–8685

van Praag H, Lucero MJ, Yeo GW, Stecker K, Heivand N, Zhao C, Yip E, Afandor M, Schroeter H, Hammerstone J, Gage FH (2007) Plant-derived flavanol (-)epicatechin enhances angiogenesis and retention of spatial memory in mice. J Neurosci 27:5869–5878

VanLeeuwen JE, Petzinger GM, Walsh JP, Akopian GK, Vuckovic M, Jakowec MW (2010) Altered AMPA receptor expression with treadmill exercise in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned mouse model of basal ganglia injury. J Neurosci Res 88:650–668

Vasuta C, Caunt C, James R, Samadi S, Schibuk E, Kannangara T, Titterness AK, Christie BR (2007) Effects of exercise on NMDA receptor subunit contributions to bidirectional synaptic plasticity in the mouse dentate gyrus. Hippocampus 17:1201–1208

Voss MW, Nagamatsu LS, Liu-Ambrose T, Kramer AF (2011) Exercise, brain, and cognition across the lifespan. J Appl Physiol. doi:10.1152/japplphysiol.00210.2011

Wang S, Scott BW, Wojtowicz JM (2000) Heterogenous properties of dentate granule neurons in the adult rat. J Neurobiol 42:248–257

Wang YX, Zhang CL, Yu RT, Cho HK, Nelson MC, Bayuga-Ocampo CR, Ham J, Kang H, Evans RM (2004) Regulation of muscle fiber type and running endurance by PPARdelta. PLoS Biol 2:e294

Yoon MC, Shin MS, Kim TS, Kim BK, Ko IG, Sung YH, Kim SE, Lee HH, Kim YP, Kim CJ (2007) Treadmill exercise suppresses nigrostriatal dopaminergic neuronal loss in 6-hydroxydopamine-induced Parkinson's rats. Neurosci Lett 423:12–17

Zhao C, Teng EM, Summers RG Jr, Ming GL, Gage FH (2006) Distinct morphological stages of dentate granule neuron maturation in the adult mouse hippocampus. J Neurosci 26:3–11

Zhao C, Deng W, Gage FH (2008) Mechanisms and functional implications of adult neurogenesis. Cell 132:645–660

Zhou Q, Homma KJ, Poo MM (2004) Shrinkage of dendritic spines associated with long-term depression of hippocampal synapses. Neuron 44:749–757

Chapter 2
Molecular Mechanisms for the Ability of Exercise Supporting Cognitive Abilities and Counteracting Neurological Disorders

Fernando Gómez-Pinilla and Cameron Feng

Abstract New evidence indicates that exercise exerts its effects by affecting molecular events related to the management of energy metabolism and synaptic plasticity. An important instigator in the molecular machinery stimulated by exercise is brain-derived neurotrophic factor (BDNF), which acts at the interface of metabolism and plasticity. Recent studies show that select dietary factors share similar mechanisms with exercise, and in some cases, they can complement the action of exercise. Therefore, exercise and dietary management appear as a noninvasive and effective strategy to counteract neurological and cognitive disorders.

2.1 Introduction

Exercise has played an important role during the evolution of mankind, and abundant research indicates that exercise is an important, but often lacking, element to maintain a healthy brain in the modern age. There is a very well-defined link between exercise and cognitive function such that exercise influences behavior and learning and memory (Albeck et al. 2006; Baruch et al. 2004; Carek et al. 2011; Hopkins et al. 2011; Smith et al. 2010). For example, exercise can promote the production of hormones, such as growth hormone (GH) and corticotrophin-releasing hormone (CRH), in the hypothalamus (Mastorakos et al. 2005; Nedvidkova et al. 2011). These hormones have significant modulatory effects not just in the body, but in the brain, as is illustrated by downstream effectors of CRH that regulate the circadian

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rhythm via the suprachiasmatic nucleus (Gannon and Millan 2006). As discussed in other chapters of this book (e.g., Chaps. 1 and 20), exercise can reduce the risk and symptoms of neurological diseases such as Alzheimer's and Parkinson's (Ahlskog 2011; Belarbi et al. 2011; Foster et al. 2011). New research on rodents has focused to identify main molecular mechanisms for the supporting action of exercise on cognitive function and emotions. Now we know that exercise upregulates genes involved in synaptic plasticity (Vaynman and Gómez-Pinilla 2005) that underlie cognitive processing. This chapter focuses on these mechanisms, touching on the potential link between cellular metabolism and synaptic plasticity in the attempt to elucidate the connection between exercise and the central nervous system (CNS) function. Many factors contribute to each of the functions of the CNS, and trying to understand the precise effects of exercise on such a highly complex network of neurons is overwhelming. We will discuss these findings on synaptic plasticity, energy metabolism, brain development, neurogenesis, neuroprotection, and epigenetics and build a more complete picture of how exercise increases cognitive function, defined as the ability to learn, or adapt to change, and the ability to resist neurological disorders.

2.2 Exercise, Synaptic Plasticity, and Cognition

Neuronal connections may be created, lost, strengthened, or weakened. The term synaptic plasticity describes the flexibility in which these connections can be affected: the greater the plasticity, the greater the ability of the CNS to adapt, grow, and repair itself (Caroni 1998; Warraich and Kleim 2010). Learning and memory research has placed much emphasis on synaptic plasticity, looking at the mechanisms involved with the plasticity, growth, and degeneration of synapses.

When exercise is involved, significant changes have been found in the mechanisms that support synaptic plasticity, thus promoting brain growth and increased learning performance. To illustrate this statement, a recent study showed an increase in bilateral hippocampal volume in aerobically fit rats, which correlated with better spatial memory performance, when compared to non-exercised rats (Erickson et al. 2009) (see also Chap. 17). Studies on the hippocampus have been important in the understanding of synaptic plasticity and how exercise may have an effect. Its role in spatial memory (Smith and Mizumori 2006) allows behavioral analysis of changes in the hippocampus while its role in the consolidation of short-term memory into long-term memory (Guzowski et al. 2000; Winocur and Moscovitch 2011) gives implications on the mechanisms of synaptic plasticity.

Such studies on exercise and the hippocampus have pinpointed the role of exercise to that of modulating neurotrophic factors critical for brain function. Brain-derived neurotrophic factor (BDNF) has emerged as the most important of these factors as a large number of studies indicate that hippocampal BDNF is a significant mediator for the effects of exercise on learning and memory (see also Chaps. 1 and 8). The strong relationship of BDNF to the link between exercise and synaptic plasticity is evidenced

when hippocampal BDNF function is blocked. Improvements in performance on the spatial learning task Morris water maze (MWM) in exercised rats were abolished when the BDNF inhibitor TrkB-IgG was injected into the hippocampus. Where improvements were marked by increases in BDNF protein levels and its downstream effector, cyclic-AMP response-element-binding protein (CREB), exercised individuals with the inhibitor showed no such increases (Griesbach et al. 2009; Vaynman et al. 2004). Due to this strict correlation between exercise and BDNF levels and function, an understanding of the roles of BDNF in the CNS has proven valuable in understanding the effects of exercise on synaptic plasticity.

BDNF is largely involved with neuronal excitability and synaptic transmission. Mainly found in axons and dendrites, the majority of BDNF is found in and released by the postsynaptic terminal. However, similar mechanisms regulate the release at both sites (pre- and postsynapses). Sufficient depolarization and activation of gated channels, including gamma-aminobutyric acid (GABA) and glutamate receptors, are important. For example, Hartmann et al. (2001) discovered that the activation of postsynaptic AMPA receptors (AMPAR) induces the release of BDNF, providing evidence for the release of BDNF in response to synaptic depolarization. More specifically, the rise in intracellular calcium concentration and activation of calmodulin-dependent protein kinase II (CaMKII), both of which are grounds for neuronal excitation, seems to be critical for BDNF secretion (Wang et al. 2002). Consider the fact that persistent excitation, i.e., in the case of high-frequency stimulation, induces long-term potentiation (LTP—an underlying physiological substrate for memory), and the connection between BDNF and synaptic plasticity becomes promising.

The secretion of BDNF into the synapse is found to be important for the maintenance and function of synapses, with effects at both the pre- and postsynapse. Studies of BDNF on glutamatergic synapses found that the activation of TrkB channels by BDNF induced glutamate release at the presynaptic terminal and produced a multiplex of gene expression changes and protein synthesis at the postsynapse (Bramham and Messaoudi 2005) (Fig. 2.1). Indeed, BDNF knockout neurons show a disruption in glutamate-regulated neuronal plasticity in neocortical neurons (Walz et al. 2006). Tanaka et al. (2008) have shown that BDNF secretion is positively correlated with the modulation of dendritic spine-head morphology, specifically spine enlargement—a mechanism of synaptic growth.

Synaptic plasticity also includes regulation of the release of neurotransmitters and the changes in synapse morphology. Studies indicate that learning as a function of synaptic plasticity is divided into three major stages: neuronal excitation, early LTP, and late LTP (Abbott and Nelson 2000; Maren and Baudry 1995; Parvez et al. 2010). Interestingly, BDNF has not only been implicated in all three stages, but plays an essential role in each. Neuronal excitation begins the process of memory formation. This excitatory phase is characterized by the firing of the presynapse and the induction of an excitatory postsynaptic potential (EPSP) and is facilitated by BDNF. As mentioned above, BDNF induces glutamate release at the presynapse, but there is yet another role. Figurov et al. (1996) found that BDNF acts on the postsynapse to inhibit synaptic fatigue during neuronal excitation, effectively prolonging the induced EPSP and increasing the likelihood of the synapse entering

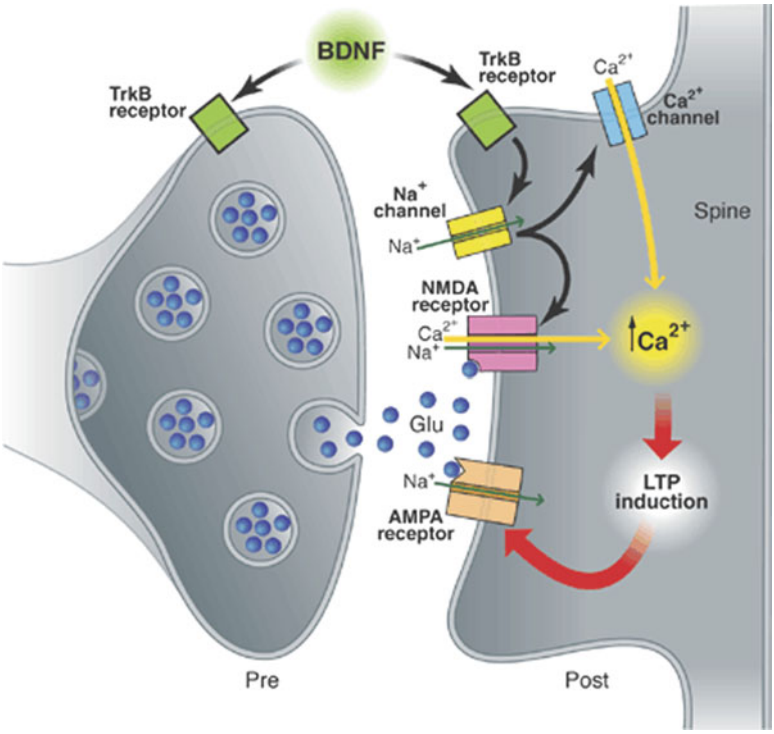

Fig. 2.1 BDNF has a central role in synaptic activity and LTP induction. BDNF-activated TrkB receptors induce glutamate release at the presynaptic terminal and increase activity at the postsynapse. TrkB receptors are associated with postsynaptic depolarization and the facilitation of calcium influx to drive LTP (Manabe 2002)

early phase LTP. Early LTP is characterized by high concentrations of intracellular calcium and an increase in AMPAR activity, with AMPARs added to the postsynaptic membrane. At this stage, rather than maintaining neuronal excitation, BDNF seems to intensify excitation by promoting the influx of calcium into the cell to enhance depolarization (Kovalchuk et al. 2002) (Fig. 2.1). The presence of BDNF allows the induction of early LTP in CA1 pyramidal cells of the hippocampus even with low-frequency stimulation (Kang et al. 1997). Late LTP is brought about by changes in gene expression and protein synthesis (Pittenger and Kandel 2003) to define the temporary changes invoked by the excitatory and early-LTP phases. These changes seem to be modulated by BDNF as the inhibition of BDNF activity (i.e., through the application of a TrkB antibody) blocks late LTP (Kang et al. 1997; Minichiello et al. 2002) (Fig. 2.1).

Exercise has the capacity to overcome several types of insults to the CNS by building some type of resilience at synaptic level, which we now know depends much on BDNF activity. Exercise has been consistently shown to increase BDNF protein and mRNA levels under a variety of conditions (Knaepen et al. 2010;

Zoladz and Pilc 2010), and it is thus through BDNF that exercise can affect cognitive processes. "Cognitive processes," however, is a general term, but we will soon see that this generality is quite fitting in the discussion of the roles of exercise on the CNS.

2.3 Exercise and Energy Metabolism

The brain requires high levels of oxygen and energy to function and new research indicates a strong association between neuronal energy metabolism and synaptic plasticity, such that metabolic signals are strong modulators of synaptic plasticity and cognitive function (Vaynman and Gómez-Pinilla 2006). Exercise and metabolism go hand in hand as exercise is an important metabolic activator, such that metabolic processes may be one mode in which exercise can affect the CNS.

We studied this possibility through the analysis of the role of BDNF on various molecules of energy management in the hippocampus, using voluntary exercise as an experimental factor. This study in rats examined the metabolic proteins AMPA-activated protein kinase (AMPK), ubiquitous mitochondrial creatine kinase (uMtCK), and mitochondrial uncoupling protein 2 (UCP-2), as well as the hormone ghrelin and trophic actor insulin-like growth factor 1 (IGF-1). The first three markers were chosen for their specific metabolic effects in neurons: AMPK acts as a "fuel gauge" by sensing low energy levels (Hardie 2004), uMtCK is involved with energy maintenance and transduction (Boero et al. 2003), and UCP-2 allows for the leakage of protons across mitochondrial membranes, uncoupling mitochondrial electron transport from ATP synthesis (Cheng et al. 2003; Kim-Han and Dugan 2005). Ghrelin is secreted by the empty stomach to promote hunger, and hippocampal injections of the hormone have shown to increase memory retention in rats (Carlini et al. 2002, 2004). IGF-1 functions similarly to BDNF in the nervous system by acting in similar ways on synaptic plasticity (Ramsey et al. 2005), neurotransmitter synthesis and release (Anlar et al. 1999), and cognitive behavior (Carro et al. 2001; Saatman et al. 1997). In our study, increases in AMPK, uMtCK, ghrelin, and IGF-1 mRNA levels all correlated with better performance in spatial learning. Exercise was shown to significantly increase the mRNA levels of all metabolic proteins, including ghrelin, and IGF-1 (Gómez-Pinilla et al. 2008). Interestingly, all five factors positively correlated with mRNA levels of BDNF, suggesting a possible relation between BDNF and neuronal metabolism (Fig. 2.2).

To determine if hippocampal BDNF has a direct link to energy metabolism in the form of AMPK, uMtCK, UCP-2, ghrelin, and IGF-1 activity, TrkB-IgG was administered in one group of rats to inhibit BDNF function. The blocking of BDNF action in exercised rats effectively abolished the effects of exercise on the mentioned proteins, returning them to sedentary control levels. No changes were found in the sedentary control rats with TrkB-IgG administered, suggesting that exercise promotes metabolic processes in the hippocampus through the functions of BDNF. The findings described in this section help define the role of cellular metabolism and synaptic plasticity through BDNF activity, and open the possibility for a holistic effect of exercise on CNS function.

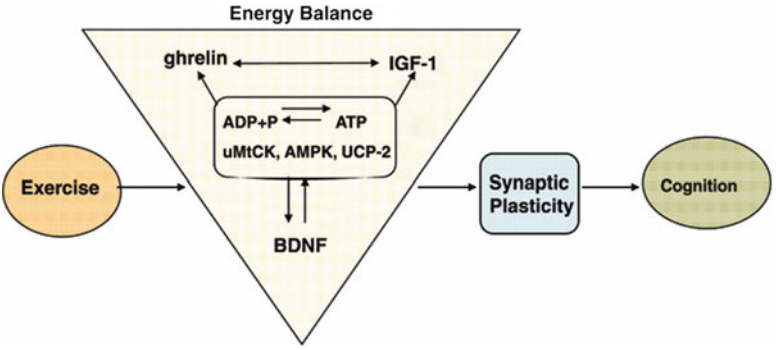

Fig. 2.2 Exercise affects cognition through metabolic processes. Exercise-induced BDNF contributes to modulate neuronal energy metabolism by regulating uMtCK, AMPK, and UCP-2. BDNF also interacts with ghrelin and IGF-1 to influence synaptic plasticity (Gómez-Pinilla et al. 2008)

2.4 Exercise During Brain Development

Exercise during development has beneficial effects on the brain. Parnpiansil et al. (2003) demonstrated that these effects begin as early as stages of fetal development in which mothers who exercise during pregnancy will produce offspring with greater learning ability. This may be due to the fact that maternally derived neurotrophic factors important for brain development may cross the placenta from the blood to influence the fetus (Gilmore et al. 2003; Uchida et al. 2000) (see also Chap. 8). Indeed, pregnant rats forced to undergo treadmill running (30 min/day, 20 m/min) for 5 consecutive days a week produced pups that performed better on spatial learning tasks than those whose mothers did not exercise (Parnpiansil et al. 2003). This was positively correlated with an increase in BDNF mRNA in the hippocampus of the pups, further supporting the notion of an increased benefit of maternally derived neurotrophic factors through exercise. In the paragraphs that follow, we will discuss other possible mechanisms through which exercise can positively influence the developing brain.

Exercise largely influences synaptic plasticity, and this capacity can be particularly important during brain development. The development of the brain is characterized by a peaking in synaptic density during the "critical period," followed by the weeding of synapses in a process called "pruning" to maintain only those that are important. Most neuroscientists agree that there is a positive relationship between the number of maintained synapses and cognitive ability (Bibb et al. 2010; Kasai et al. 2010; Sahay et al. 2011). It is previously explained that exercise modulates a number of neuronal mechanisms involved in synaptic plasticity. As such, exercise during brain development might significantly reduce pruning and instead strengthen the weaker synapses. Gomes da Silva et al. (2012) found this to be the case where rats aerobically exercised from postnatal 21 days (P21) to P60 showed an increased mossy-fiber density at the hippocampus at P96. Improved learning and memory were found in these rats, and not surprisingly, BDNF and BDNF receptor expression levels were also increased.

2.5 Exercise Induces Neurogenesis

Exercise also influences the generation of new neurons during development. This process of neuronal proliferation is called neurogenesis and is essential for the growth of the brain. In fact, it was previously assumed that neurogenesis was a process only for development and could not occur past brain maturation. Nevertheless, there is striking evidence that new neurons can be created in the adult stages from neural stem cells (NSCs). The olfactory bulb and the hippocampus contain high concentrations of NSCs and are two extensively studied regions in the mammalian brain for adult neurogenesis (Yoneyama et al. 2011). Abundant research in the last decade has focused on the contribution of exercise as one of the strongest promoters of NSC proliferation and neurogenesis in the adult rodent (Itoh et al. 2011a; Kernie and Parent 2010). Even in the aging mice, exercise is able to induce net hippocampal neurogenesis at 2 years of age as evidenced by immunohistochemistry study staining for markers of neuronal proliferation (Kronenberg et al. 2006). It is assumable that the mechanisms of adult neurogenesis induced by exercise are analogous to those during the stages of brain development.

Exercise appears to promote neurogenesis through increasing BDNF, IGF-1, and vascular endothelial growth factor (VEGF) levels (Wong-Goodrich et al. 2010) (see also Chaps. 1 and 8). BDNF and IGF-1 have been shown important for neurogenesis through their regulation of multiple neuronal mechanisms and neuronal growth and maintenance. Such mechanisms include those affecting metabolic function and synaptic plasticity, as explained above. VEGF is important for the growth of new blood vessels also known as angiogenesis. As with any cell in the body, increased blood flow is necessary for the survival and growth of new neurons (Namieci ska et al. 2005). The inhibition of IGF-1 and/or VEGF functions has been found to reverse the increases in neurogenesis observed from exercise (Carro et al. 2001; Fabel et al. 2003; Trejo et al. 2001). In addition to the effect of growth factors, exercise can affect the anti-apoptotic pathway of neurons to promote neurogenesis by increasing neuronal survival, especially of those recently formed. This was discovered when the phosphatidylinositol-3-kinase (PI3K)—anti-apoptotic kinase (Akt) pathway—was inhibited in the dentate gyrus of exercised rats, abolishing the increased survival of newly generated neurons without affecting cell proliferation (Bruel-Jungerman et al. 2009). The neuroprotective role of exercise, however, is important not only during development but as protecting the adult CNS against diseases and insults.

2.6 Neuroprotective Effects of Exercise

Several neurological and cognitive disorders are somehow related dysfunctions in the mechanisms of neuronal plasticity, metabolism, and survivability, and exercise is a candidate for the prevention and treatment of Alzheimer's disease (AD), Parkinson's disease (PD), major depression, traumatic brain injury (TBI), damage

from stroke, etc. Here we discuss the clinical implications of exercise-induced mechanisms on the CNS and the findings that support them. Despite weighing only about 2% of our total body weight, the brain consumes about 20% of the body's oxygen. This intense metabolic demand (Isaacs et al. 2006) induces high levels of oxidative stress that, if not moderated, can produce complications resulting in neuronal apoptosis and neurological disorder. One model of PD in which a mutation of the mitochondrial protein Parkin induces elevated reactive oxygen species (ROS), an agent of oxidative stress and toxic by-product of mitochondrial function, and eventual neuronal death (Palacino et al. 2004) illustrates this point. Given that exercise supports neuronal energy metabolism, exercise is a potential candidate reducing oxidative stress and protecting mitochondrial function in PD.

PD and AD have been in the forefront of neurodegenerative disease research, and in both, mitochondrial dysfunction plays a significant role in their pathogenesis (Han et al. 2011; Hoekstra et al. 2011). For example, neuronal apoptosis has been shown to be mediated by increased ROS due to an accumulation of α-synuclein, the hallmark protein of PD (Xu et al. 2002). In AD, mitochondrial dysfunction seems to precede cognitive functional impairment as documented by decreased brain metabolism (Blass 2000) and increased oxidative stress (Zhu et al. 2007). Interestingly, exercise has been evidenced to dramatically decrease disease severity and delay onset in PD and AD (Ahlskog 2011; Jak 2012). A recent study by Lau et al. (2011) found that moderate treadmill exercise of 5 days a week, 40 min a day, attenuates the loss of tyrosine hydroxylase (TH) and dopaminergic (DA) cells in the nigrostriatal pathway of induced chronic PD mice. These findings were correlated with an overall promotion of mitochondrial function as determined by increased (normalizing) levels of antioxidant enzymes Mn superoxide dismutase (SOD) and Cu–Zn SOD as well as decreased (normalizing) levels of stress-inducing striatal carbonylated proteins when compared to the sedentary chronic PD mice. In a similar study on AD, Um et al. (2011) found that treadmill running in transgenic AD mice significantly reduced AD pathology including amyloid-β deposition and Tau phosphorylation in the hippocampus. They also found a reduction in cyclooxygenase-2 expression, indicating healthier mitochondrial function. One mechanism for these findings in AD is that exercise increases neprilysin activity (Marx 2005), an enzyme that metabolizes the naturally occurring amyloid-β protein. Since amyloid-β has binding sites on the mitochondria that, when accumulated in AD, become toxic to mitochondrial function (Borger et al. 2011), exercise helps prevent mitochondrial dysfunction and general neurodegeneration.

TBI as a model to study functional impairments of the CNS has given details to the protective mechanisms produced by exercise. TBI-induced animals show disruptions in attention and learning and memory, and development of mood disorders and motor deficits (Mota et al. 2012; Wheaton et al. 2011; Wu et al. 2011). These disruptions are associated with decreased levels of synaptic plasticity markers and increased oxidative stress (Wu et al. 2006). Additionally, experimental models of TBI in rats exhibit an inability of their neurons to respond to physiological levels of stimulation, thus restricting functional recovery (Colle et al. 1986; Hovda et al. 1987). Exercise, both before (Mota et al. 2012) and after TBI, decreases the severity

of TBI symptoms and aids in recovery. Evidence shows the benefit of exercise on multiple domains of nervous system insult by promoting synaptic plasticity (Chytrova et al. 2008; Griesbach et al. 2009), counteracting metabolic dysfunction (Lima et al. 2009; Szabo et al. 2010), and preventing neuronal cell death (Itoh et al. 2011b; Kim et al. 2010). However, the timing of the application of exercise after the onset of injury is critical and depends on the metabolic stage of the brain (Griesbach et al. 2007). In fact, premature application of exercise post-injury may even exacerbate the symptoms of TBI by overstressing the system and disrupting the recovery process (Griesbach et al. 2004a, 2011).

Exercise seems to aid in the recovery of brain injury by supporting synaptic plasticity and neuronal growth. For example, 1 week of voluntary exercise in the form of wheel running after TBI increases levels of BDNF, CREB, and synapsin 1 in the hippocampus of rats 21 days post-injury. These increases correlate with improved spatial learning, suggesting a therapeutic potential of exercise following TBI (Griesbach et al. 2004b). Furthermore, exercise has been shown to counteract TBI-related increases in levels of the neurite outgrowth inhibitors myelin-associated glycoprotein (MAG) and (Nogo-A) as well as reductions in growth-associated protein 43 (GAP-43) and synaptophysin (SYP) (Chytrova et al. 2008). Interestingly, the inhibition of BDNF through the administration of TrkB-IgG disrupts these benefits, pinpointing a functional role of BDNF on synaptic plasticity after TBI (Chytrova et al. 2008; Griesbach et al. 2009).

Moderate to severe TBI produces lesions in the brain by promoting neuronal death or apoptosis (Zhang et al. 2005). Exercise can prevent this apoptosis as illustrated in the study by Itoh et al. (2011b) using single-stranded DNA (ssDNA) as a marker for apoptosis and neuronal specific nuclear protein (NeuN) as a marker for healthy cells. Immunohistochemistry staining of ssDNA showed that exercised TBI rats expressed lower levels of ssDNA and greater levels of NeuN in the injury area. As a result, apoptosis was significantly reduced and neuronal survival was maintained. Exercise seems to achieve this by stimulating the PI3K-Akt pathway and by activating TrkA and TrkB receptors through the upregulation and concerted efforts of neuronal growth factors, such as IGF-1 and BDNF (Chae and Kim 2009; Nguyen et al. 2010). In conclusion, exercise improves the outlook of the CNS after TBI, and other brain pathologies, by protecting neurons and promoting recovery.

2.7 Exercise and Diet Interaction

Studies on the effects of foods on the brain have revealed similar outcomes to those of exercise on the CNS. Our laboratory has focused on the yellow polyphenolic curry compound curcumin and fatty acid docosahexaenoic acid (DHA) due to their previously determined healthy effects on body function. Curcumin is a chemical compound of the turmeric plant (*Curcuma longa*). It has potential as a strong antioxidant with the ability to increase free radical scavengers and

reduce lipid peroxidation (Wei et al. 2006). DHA, on the other hand, is part of the anti-inflammatory omega-3 fatty acids (O3FAs) family largely found among cold-water fish, such as salmon, in nuts, and in flaxseeds, among other dietary sources. DHA makes up about 17% of total fatty acids in the neuronal membrane (Horrocks and Farooqui 2004), supporting synaptic membrane fluidity of neurons (Suzuki et al. 1998) and regulating gene signaling and expression (Salem et al. 2001). The significance of curcumin and DHA for neuronal function has implicated them as potential therapeutic agents against AD (Agrawal et al. 2010; Corrigan et al. 1998; Tully et al. 2003) and TBI (Wu et al. 2004, 2006), as much as exercise. Consequently, the actions of these dietary supplements on the CNS may prove useful in further elucidating their combined actions with exercise on the CNS.

It has been shown that diets high in curcumin, docosahexaenoic acid (DHA), or both have strong implications on supporting synaptic plasticity and counteracting oxidative stress (Gómez-Pinilla 2008; Saw et al. 2010; Sharma et al. 2010). Their actions are synonymous to those of exercise and, in fact, were complementary when both DHA supplementation and exercise were used as experimental factors (Gómez-Pinilla and Ying 2010; Wu et al. 2008). Chytrova et al. (2009) found that exercise further elevated levels of syntaxin-3, GAP-43, and the *N*-methyl-D-aspartate (NMDA) receptor subunit NR2B that were originally elevated with DHA supplementation alone. It is intriguing that exercise was selective only to these proteins that are affected by the DHA diet, suggesting a close link between exercise and DHA. Specifically, this indicates a possible action of exercise on neuronal DHA and possibly other O3FAs to promote synaptic plasticity. Potential roles are the growth and maintenance of dendrites and axons. Because DHA and other fatty acids of the plasma membrane are not sufficiently synthesized by the body and brain (Kim 2007), the potential of exercise to maintain and encourage DHA function (Fig. 2.3) within the nervous system is significant. The vulnerability of the plasma membrane to oxidative stress (Avery 2011), the antioxidative properties of curcumin, and the increased outcomes found when curcumin and DHA were combined (Saw et al. 2010) all point to the potential of exercise to work in combinations with dietary components to reduce oxidative stress (see Sect. 2.6).

As discussed above, exercise stimulates the PI3K-Akt pathway. Interestingly, DHA also influences this pathway (Akbar et al. 2005) through identical mechanisms found in exercise. Particularly, O3FAs interact with the energy metabolism of neurons to mediate IGF-1 and BDNF levels in the brain. IGF-1 and BDNF activities, in turn, converge into multiple systems of synaptic plasticity, including the PI3K-Akt and CaMKII systems (Fig. 2.3). These systems have been implicated in exercise to produce similar results on cognitive function, providing significant evidence that exercise and O3FAs are part of the same pathways (Gómez-Pinilla 2008). As such, these findings on O3FAs, specifically DHA, tremendously emphasize the interaction among exercise, neurotrophic factors, and synaptic plasticity, as is summarized in Fig. 2.3.

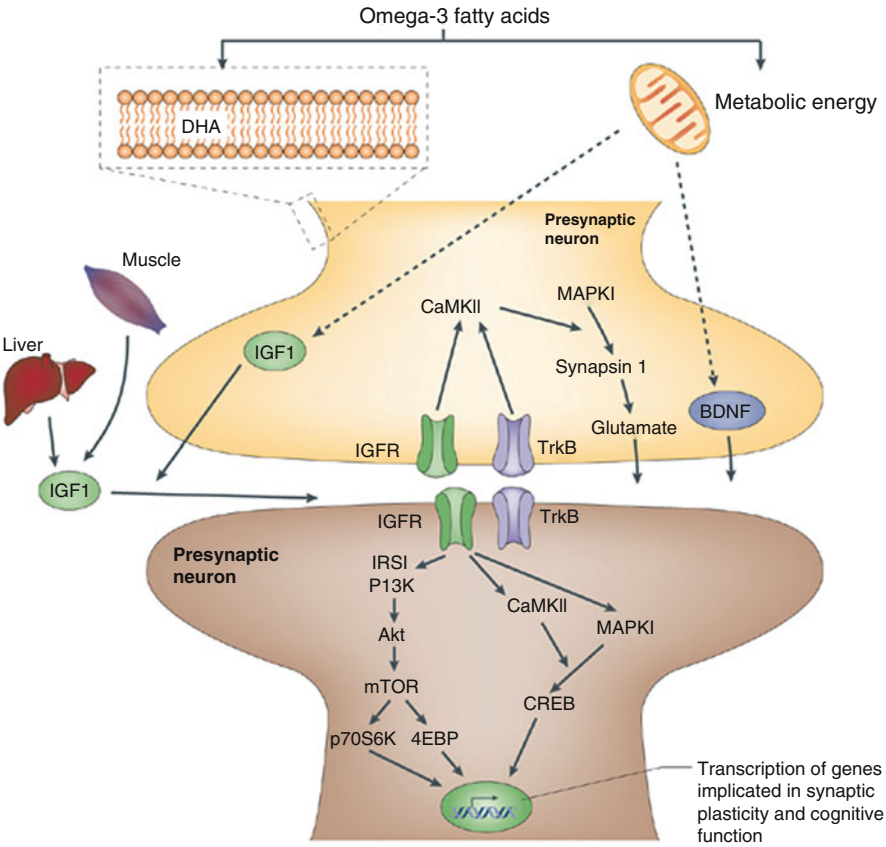

Fig. 2.3 Omega-3 fatty acids on synaptic plasticity. Exercise maintains DHA content and activity in the CNS. O3FAs are central in the regulation of neuronal metabolic energy, which mediates levels of IGF-1 and BDNF. Both can act on the presynapse to stimulate the CaMKII pathway to induce synaptic transmission. At the postsynaptic terminal, activated IGF-1 and BDNF receptors stimulate pathways involved with synaptic plasticity. Examples shown in the figure are that of the PI3K-Akt anti-apoptotic pathway and the CaMKII pathway associated with LTP (Gómez-Pinilla 2008)

2.8 Epigenetics of Exercise

Epigenetics is a relatively new direction of study concerning exercise and cognition. Most epigenetic mechanisms function through a change in transcript promoter activity through the methylation of DNA and histone deacetylation (Burzynski 2003). BDNF has been the focus of epigenetic studies, revealing that BDNF function

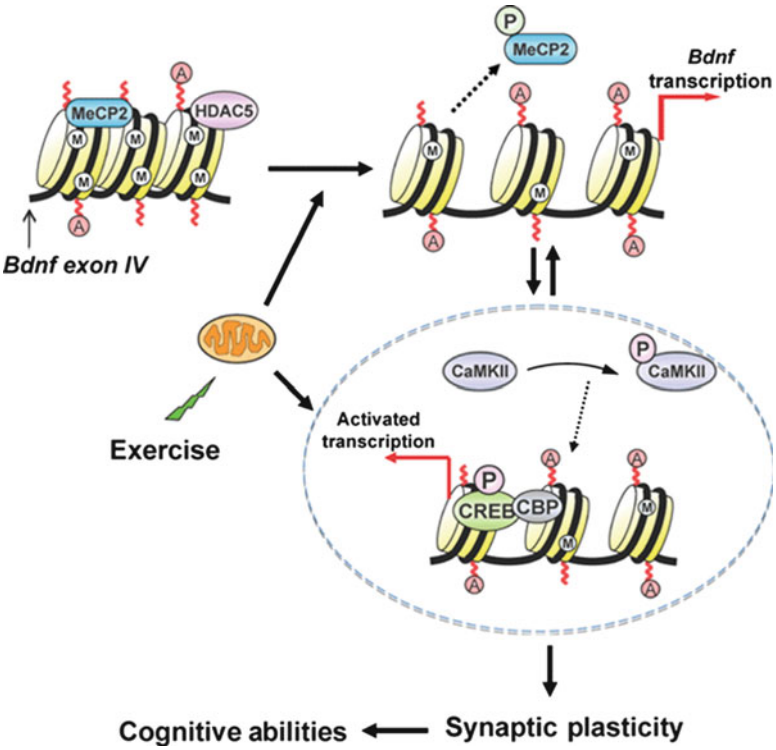

Fig. 2.4 Effect of exercise on the epigenetic modification of BDNF transcription. Recent studies suggest that exercise may affect BDNF transcription by regulation the epigenome, particularly influencing DNA methylation and histone H3 acetylation, with the involvement of MeCP2. Exercise also induces CaMKII and CREB phosphorylation that contribute BDNF transcription and BDNF action on synaptic plasticity. *A* histone acetylation, *CBP* CREB-binding protein, *M* CpG site methylation, *P* phosphorylation (Gómez-Pinilla et al. 2011)

is highly susceptible to epigenetic regulation. For example, synaptic depolarization influences the methylation of the BDNF gene promoter IV, effectively dissociating the transcript suppressor methyl-CpG-binding protein (MeCP2) from the promoter (Chao and Zoghbi 2009; Chen et al. 2003) and increasing BDNF gene expression. Additionally, Tsankova et al. (2006) have shown that epigenetic regulation of BDNF activity is involved in depressive behavior in mice.

Physical activity has been shown to increase BDNF levels (Ding et al. 2011) by interacting with epigenetic mechanisms (Gómez-Pinilla et al. 2011). Our recent study has shown that exercise affects BDNF transcription by influencing CpG methylation, MeCP2 levels, and histone H3 acetylation in rat hippocampus. Furthermore, exercise increased levels of phospho-CaMKII and phospho-CREB—two important elements in the pathways involved with epigenetic modulation of BDNF transcription through neuronal activity (Gómez-Pinilla et al. 2011) (Fig. 2.4). It is known that BDNF regulates synaptic plasticity and neuronal survival (Cohen-Cory et al. 2010;

Lee et al. 2001). The new studies emphasize the ability of exercise to promote synaptic plasticity and regulate behavior by influencing the epigenome. Information on the epigenetic influence of exercise has the added possibility to evaluate the potential of exercise to affect future generations.

2.9 Conclusion

The study of the effects of exercise on the brain has revealed a collage of important findings, particularly with regard to its effects on mechanisms of learning and memory. Exercise plays a supportive role on brain function acting through mechanisms of energy metabolism, synaptic plasticity, neurogenesis, and neuronal survival. Animal studies have provided strong evidence of BDNF as the main mediator between physical activity and cognitive function. These findings emphasize the importance of regular exercise in modern society, especially as a productive strategy to reduce the burden associated with increasing rates of neurodegenerative disorders such as Alzheimer's and Parkinson's diseases. Studies also emphasize the benefits of early exercise in developing children into adulthood. The effects of exercise are manifested in promoting cognitive ability at all ages and particularly in preventing cognitive decline during aging. New developments indicate the influence of exercise on the epigenome with the capacity to reduce psychiatric and cognitive disorders. These new studies also suggest the exciting possibility that the benefits of exercise are long-lasting and heritable. Humans have adapted an active lifestyle throughout the hunter-gatherer societies of ancient mankind, suggesting that the sedentary lifestyles of today's society are contributing to the modern prevalence of various metabolic diseases, such as obesity and diabetes. Based on new evidence about a close interaction between cellular metabolism and synaptic plasticity, exercise seems to influence cognition by utilizing metabolic processes. This also implies the values of exercise in attenuating metabolic disorders and preventing cognitive disorders and promoting mental health. In summary, exercise helps to keep a consistency between genetic makeup and health, ultimately promoting for a healthy body and healthy brain through mechanisms that humans have evolved to maintain.

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References

Abbott LF, Nelson SB (2000) Synaptic plasticity: taming the beast. Nat Neurosci 3(Suppl): 1178–1183

Agrawal R, Mishra B, Tyagi E, Nath C, Shukla R (2010) Effect of curcumin on brain insulin receptors and memory functions in STZ (ICV) induced dementia model of rat. Pharmacol Res 61:247–252

Ahlskog JE (2011) Does vigorous exercise have a neuroprotective effect in Parkinson disease? Neurology 77:288–294
Akbar M, Calderon F, Wen Z, Kim HY (2005) Docosahexaenoic acid: a positive modulator of Akt signaling in neuronal survival. Proc Natl Acad Sci USA 102:10858–10863
Albeck DS, Sano K, Prewitt GE, Dalton L (2006) Mild forced treadmill exercise enhances spatial learning in the aged rat. Behav Brain Res 168:345–348
Anlar B, Sullivan KA, Feldman EL (1999) Insulin-like growth factor-I and central nervous system development. Horm Metab Res 31:120–125
Avery SV (2011) Molecular targets of oxidative stress. Biochem J 434:201–210
Baruch DE, Swain RA, Helmstetter FJ (2004) Effects of exercise on Pavlovian fear conditioning. Behav Neurosci 118:1123–1127
Belarbi K, Burnouf S, Fernandez-Gomez FJ, Laurent C, Lestavel S, Figeac M, Sultan A, Troquier L, Leboucher A, Caillierez R, Grosjean ME, Demeyer D, Obriot H, Brion I, Barbot B, Galas MC, Staels B, Humez S, Sergeant N, Schraen-Maschke S, Muhr-Tailleux A, Hamdane M, Buée L, Blum D (2011) Beneficial effects of exercise in a transgenic mouse model of Alzheimer's disease-like Tau pathology. Neurobiol Dis 43:486–494
Bibb JA, Mayford MR, Tsien JZ, Alberini CM (2010) Cognition enhancement strategies. J Neurosci 30:14987–14992
Blass JP (2000) The mitochondrial spiral. An adequate cause of dementia in the Alzheimer's syndrome. Ann N Y Acad Sci 924:170–183
Boero J, Qin W, Cheng J, Woolsey TA, Strauss AW, Khuchua Z (2003) Restricted neuronal expression of ubiquitous mitochondrial creatine kinase: changing patterns in development and with increased activity. Mol Cell Biochem 244:69–76
Borger E, Aitken L, Muirhead KE, Allen ZE, Ainge JA, Conway SJ, Gunn-Moore FJ (2011) Mitochondrial β-amyloid in Alzheimer's disease. Biochem Soc Trans 39:868–873
Bramham CR, Messaoudi E (2005) BDNF function in adult synaptic plasticity: the synaptic consolidation hypothesis. Prog Neurobiol 76:99–125
Bruel-Jungerman E, Veyrac A, Dufour F, Horwood J, Laroche S, Davis S (2009) Inhibition of PI3K-Akt signaling blocks exercise-mediated enhancement of adult neurogenesis and synaptic plasticity in the dentate gyrus. PLoS One 4:e7901
Burzynski SR (2003) Gene silencing – a new theory of aging. Med Hypotheses 60:578–583
Carek PJ, Laibstain SE, Carek SM (2011) Exercise for the treatment of depression and anxiety. Int J Psychiatry Med 41:15–28
Carlini VP, Monzón ME, Varas MM, Cragnolini AB, Schiöth HB, Scimonelli TN, de Barioglio SR (2002) Ghrelin increases anxiety-like behavior and memory retention in rats. Biochem Biophys Res Commun 299:739–743
Carlini VP, Varas MM, Cragnolini AB, Schiöth HB, Scimonelli TN, de Barioglio SR (2004) Differential role of the hippocampus, amygdala, and dorsal raphe nucleus in regulating feeding, memory, and anxiety-like behavioral responses to ghrelin. Biochem Biophys Res Commun 313:635–641
Caroni P (1998) Neuro-regeneration: plasticity for repair and adaptation. Essays Biochem 33:53–64
Carro E, Trejo JL, Busiguina S, Torres-Aleman I (2001) Circulating insulin-like growth factor I mediates the protective effects of physical exercise against brain insults of different etiology and anatomy. J Neurosci 21:5678–5684
Chae CH, Kim HT (2009) Forced, moderate-intensity treadmill exercise suppresses apoptosis by increasing the level of NGF and stimulating phosphatidylinositol 3-kinase signaling in the hippocampus of induced aging rats. Neurochem Int 55:208–213
Chao HT, Zoghbi HY (2009) The yin and yang of MeCP2 phosphorylation. Proc Natl Acad Sci USA 106:4577–4578
Chen WG, Chang Q, Lin Y, Meissner A, West AE, Griffith EC, Jaenisch R, Greenberg ME (2003) Derepression of BDNF transcription involves calcium-dependent phosphorylation of MeCP2. Science 302:885–889
Cheng G, Polito CC, Haines JK, Shafizadeh SF, Fiorini RN, Zhou X, Schmidt MG, Chavin KD (2003) Decrease of intracellular ATP content downregulated UCP2 expression in mouse hepatocytes. Biochem Biophys Res Commun 308:573–580

Chytrova G, Ying Z, Gómez-Pinilla F (2008) Exercise normalizes levels of MAG and Nogo-A growth inhibitors after brain trauma. Eur J Neurosci 27:1–11
Chytrova G, Ying Z, Gómez-Pinilla F (2009) Exercise contributes to the effects of DHA dietary supplementation by acting on membrane-related synaptic systems. Brain Res 1341:32–40
Cohen-Cory S, Kidane AH, Shirkey NJ, Marshak S (2010) Brain-derived neurotrophic factor and the development of structural neuronal connectivity. Dev Neurobiol 70:271–288
Colle LM, Holmes LJ, Pappius HM (1986) Correlation between behavioral status and cerebral glucose utilization in rats following freezing lesion. Brain Res 397:27–36
Corrigan FM, Horrobin DF, Skinner ER, Besson JA, Cooper MB (1998) Abnormal content of n-6 and n-3 long-chain unsaturated fatty acids in the phosphoglycerides and cholesterol esters of parahippocampal cortex from Alzheimer's disease patients and its relationship to acetyl CoA content. Int J Biochem Cell Biol 30:197–207
Ding Q, Ying Z, Gómez-Pinilla F (2011) Exercise influences hippocampal plasticity by modulating brain-derived neurotrophic factor processing. Neuroscience 192:773–780
Erickson KI, Prakash RS, Voss MW, Chaddock L, Hu L, Morris KS, White SM, Wójcicki TR, McAuley E, Kramer AF (2009) Aerobic fitness is associated with hippocampal volume in elderly humans. Hippocampus 19:1030–1039
Fabel K, Tam B, Kaufer D, Baiker A, Simmons N, Kuo CJ, Palmer TD (2003) VEGF is necessary for exercise-induced adult hippocampal neurogenesis. Eur J Neurosci 18:2803–2812
Figurov A, Pozzo-Miller LD, Olafsson P, Wang T, Lu B (1996) Regulation of synaptic responses to high-frequency stimulation and LTP by neurotrophins in the hippocampus. Nature 381: 706–709
Foster PP, Rosenblatt KP, Kuljiš RO (2011) Exercise-induced cognitive plasticity, implications for mild cognitive impairment and Alzheimer's disease. Front Neurol 2:28
Gannon RL, Millan MJ (2006) The corticotropin-releasing factor (CRF)(1) receptor antagonists CP154,526 and DMP695 inhibit light-induced phase advances of hamster circadian activity rhythms. Brain Res 1083:96–102
Gilmore JH, Jarskog LF, Vadlamudi S (2003) Maternal infection regulates BDNF and NGF expression in fetal and neonatal brain and maternal-fetal unit of the rat. J Neuroimmunol 138:49–55
Gomes da Silva S, Unsain N, Mascó DH, Toscano-Silva M, de Amorim HA, Silva Araújo BH, Simões PS, da Graça Naffah-Mazzacoratti M, Mortara RA, Scorza FA, Cavalheiro EA, Arida RM (2012) Early exercise promotes positive hippocampal plasticity and improves spatial memory in the adult life of rats. Hippocampus 22(2):347–358
Gómez-Pinilla F (2008) Brain foods: the effects of nutrients on brain function. Nat Rev Neurosci 9:568–578
Gómez-Pinilla F, Ying Z (2010) Differential effects of exercise and dietary docosahexaenoic acid on molecular systems associated with control of allostasis in the hypothalamus and hippocampus. Neuroscience 168:130–137
Gómez-Pinilla F, Vaynman S, Ying Z (2008) Brain-derived neurotrophic factor functions as a metabotrophin to mediate the effects of exercise on cognition. Eur J Neurosci 28:2278–2287
Gómez-Pinilla F, Zhuang Y, Feng J, Ying Z, Fan G (2011) Exercise impacts brain-derived neurotrophic factor plasticity by engaging mechanisms of epigenetic regulation. Eur J Neurosci 33:383–390
Griesbach GS, Gómez-Pinilla F, Hovda DA (2004a) The upregulation of plasticity-related proteins following TBI is disrupted with acute voluntary exercise. Brain Res 1016:154–162
Griesbach GS, Hovda DA, Molteni R, Wu A, Gómez-Pinilla F (2004b) Voluntary exercise following traumatic brain injury: brain-derived neurotrophic factor upregulation and recovery of function. Neuroscience 125:129–139
Griesbach GS, Gómez-Pinilla F, Hovda DA (2007) Time window for voluntary exercise-induced increases in hippocampal neuroplasticity molecules after traumatic brain injury is severity dependent. J Neurotrauma 24:1161–1171
Griesbach GS, Hovda DA, Gómez-Pinilla F (2009) Exercise-induced improvement in cognitive performance after traumatic brain injury in rats is dependent on BDNF activation. Brain Res 1288:105–115

Griesbach GS, Hovda DA, Tio DL, Taylor AN (2011) Heightening of the stress response during the first weeks after a mild traumatic brain injury. Neuroscience 178:147–158

Guzowski JF, Lyford GL, Stevenson GD, Houston FP, McGaugh JL, Worley PF, Barnes CA (2000) Inhibition of activity-dependent arc protein expression in the rat hippocampus impairs the maintenance of long-term potentiation and the consolidation of long-term memory. J Neurosci 20:3993–4001

Han XJ, Tomizawa K, Fujimura A, Ohmori I, Nishiki T, Matsushita M, Matsui H (2011) Regulation of mitochondrial dynamics and neurodegenerative diseases. Acta Med Okayama 65:1–10

Hardie DG (2004) AMP-activated protein kinase: a key system mediating metabolic responses to exercise. Med Sci Sports Exerc 36:28–34

Hartmann M, Heumann R, Lessmann V (2001) Synaptic secretion of BDNF after high-frequency stimulation of glutamatergic synapses. EMBO J 20:5887–5897

Hoekstra JG, Montine KS, Zhang J, Montine TJ (2011) Mitochondrial therapeutics in Alzheimer's disease and Parkinson's disease. Alzheimers Res Ther 3:21

Hopkins ME, Nitecki R, Bucci DJ (2011) Physical exercise during adolescence versus adulthood: differential effects on object recognition memory and brain-derived neurotrophic factor levels. Neuroscience 194:84–94

Horrocks LA, Farooqui AA (2004) Docosahexaenoic acid in the diet: its importance in maintenance and restoration of neural membrane function. Prostaglandins Leukot Essent Fatty Acids 70:361–372

Hovda DA, Sutton RL, Feeney DM (1987) Recovery of tactile placing after visual cortex ablation in cat: a behavioral and metabolic study of diaschisis. Exp Neurol 97:391–402

Isaacs AM, Senn DB, Yuan M, Shine JP, Yankner BA (2006) Acceleration of amyloid beta-peptide aggregation by physiological concentrations of calcium. J Biol Chem 281:27916–27923

Itoh T, Imano M, Nishida S, Tsubaki M, Hashimoto S, Ito A, Satou T (2011a) Exercise increases neural stem cell proliferation surrounding the area of damage following rat traumatic brain injury. J Neural Transm 118:193–202

Itoh T, Imano M, Nishida S, Tsubaki M, Hashimoto S, Ito A, Satou T (2011b) Exercise inhibits neuronal apoptosis and improves cerebral function following rat traumatic brain injury. J Neural Transm 118(9):1263–1272

Jak AJ (2012) The impact of physical and mental activity on cognitive aging. Curr Top Behav Neurosci 10:273–291

Kang H, Welcher AA, Shelton D, Schuman EM (1997) Neurotrophins and time: different roles for TrkB signaling in hippocampal long-term potentiation. Neuron 19:653–664

Kasai H, Hayama T, Ishikawa M, Watanabe S, Yagishita S, Noguchi J (2010) Learning rules and persistence of dendritic spines. Eur J Neurosci 32:241–249

Kernie SG, Parent JM (2010) Forebrain neurogenesis after focal Ischemic and traumatic brain injury. Neurobiol Dis 37:267–274

Kim HY (2007) Novel metabolism of docosahexaenoic acid in neural cells. J Biol Chem 282:18661–18665

Kim DH, Ko IG, Kim BK, Kim TW, Kim SE, Shin MS, Kim CJ, Kim H, Kim KM, Baek SS (2010) Treadmill exercise inhibits traumatic brain injury-induced hippocampal apoptosis. Physiol Behav 101:660–665

Kim-Han JS, Dugan LL (2005) Mitochondrial uncoupling proteins in the central nervous system. Antioxid Redox Signal 7:1173–1181

Knaepen K, Goekint M, Heyman EM, Meeusen R (2010) Neuroplasticity – exercise-induced response of peripheral brain-derived neurotrophic factor: a systematic review of experimental studies in human subjects. Sports Med 40:765–801

Kovalchuk Y, Hanse E, Kafitz KW, Konnerth A (2002) Postsynaptic Induction of BDNF-Mediated Long-Term Potentiation. Science 295:1729–1734

Kronenberg G, Bick-Sander A, Bunk E, Wolf C, Ehninger D, Kempermann G (2006) Physical exercise prevents age-related decline in precursor cell activity in the mouse dentate gyrus. Neurobiol Aging 27:1505–1513

Lau YS, Patki G, Das-Panja K, Le WD, Ahmad SO (2011) Neuroprotective effects and mechanisms of exercise in a chronic mouse model of Parkinson's disease with moderate neurodegeneration. Eur J Neurosci 33:1264–1274

Lee R, Kermani P, Teng KK, Hempstead BL (2001) Regulation of cell survival by secreted proneurotrophins. Science 294:1945–1948

Lima FD, Oliveira MS, Furian AF, Souza MA, Rambo LM, Ribeiro LR, Silva LF, Retamoso LT, Hoffmann MS, Magni DV, Pereira L, Fighera MR, Mello CF, Royes LF (2009) Adaptation to oxidative challenge induced by chronic physical exercise prevents Na+, K+-ATPase activity inhibition after traumatic brain injury. Brain Res 1279:147–155

Manabe T (2002) Does BDNF have pre- or postsynaptic targets? Science 295:1651–1653

Maren S, Baudry M (1995) Properties and mechanisms of long-term synaptic plasticity in the mammalian brain: relationships to learning and memory. Neurobiol Learn Mem 63:1–18

Marx J (2005) Alzheimer's disease. Play and exercise protect mouse brain from amyloid buildup. Science 307:1547

Mastorakos G, Pavlatou M, Diamanti-Kandarakis E, Chrousos GP (2005) Exercise and the stress system. Hormones (Athens) 4:73–89

Minichiello L, Calella AM, Medina DL, Bonhoeffer T, Klein R, Korte M (2002) Mechanism of TrkB-mediated hippocampal long-term potentiation. Neuron 36:121–137

Mota BC, Pereira L, Souza MA, Silva LF, Magni DV, Ferreira AP, Oliveira MS, Furian AF, Mazzardo-Martins L, Silva MD, Santos AR, Ferreira J, Fighera MR, Royes LF (2012) Exercise pre-conditioning reduces brain inflammation and protects against toxicity induced by traumatic brain injury: behavioral and neurochemical approach. Neurotox Res 21(2):175–184

Namiecińska M, Marciniak K, Nowak JZ (2005) VEGF as an angiogenic, neurotrophic, and neuroprotective factor. Postepy Hig Med Dosw (Online) 59:573–583

Nedvidkova J, Smitka K, Papezova H, Vondra K, Hill M, Hainer V (2011) Acipimox during exercise points to an inhibitory feedback of GH on ghrelin secretion in bulimic and healthy women. Regul Pept 167:134–139

Nguyen TL, Kim CK, Cho JH, Lee KH, Ahn JY (2010) Neuroprotection signaling pathway of nerve growth factor and brain-derived neurotrophic factor against staurosporine induced apoptosis in hippocampal H19-7/IGF-IR [corrected]. Exp Mol Med 42:583–595

Palacino JJ, Sagi D, Goldberg MS, Krauss S, Motz C, Wacker M, Klose J, Shen J (2004) Mitochondrial dysfunction and oxidative damage in parkin-deficient mice. J Biol Chem 279:18614–18622

Parnpiansil P, Jutapakdeegul N, Chentanez T, Kotchabhakdi N (2003) Exercise during pregnancy increases hippocampal brain-derived neurotrophic factor mRNA expression and spatial learning in neonatal rat pup. Neurosci Lett 352:45–48

Parvez S, Ramachandran B, Frey JU (2010) Functional differences between and across different regions of the apical branch of hippocampal CA1 dendrites with respect to long-term depression induction and synaptic cross-tagging. J Neurosci 30:5118–5123

Pittenger C, Kandel ER (2003) In search of general mechanisms for long-lasting plasticity: aplysia and the hippocampus. Philos Trans R Soc Lond B Biol Sci 358:757–763

Ramsey MM, Adams MM, Ariwodola OJ, Sonntag WE, Weiner JL (2005) Functional characterization of des-IGF-1 action at excitatory synapses in the CA1 region of rat hippocampus. J Neurophysiol 94:247–254

Saatman KE, Contreras PC, Smith DH, Raghupathi R, McDermott KL, Fernandez SC, Sanderson KL, Voddi M, McIntosh TK (1997) Insulin-like growth factor-1 (IGF-1) improves both neurological motor and cognitive outcome following experimental brain injury. Exp Neurol 147:418–427

Sahay A, Scobie KN, Hill AS, O'Carroll CM, Kheirbek MA, Burghardt NS, Fenton AA, Dranovsky A, Hen R (2011) Increasing adult hippocampal neurogenesis is sufficient to improve pattern separation. Nature 472:466–470

Salem N Jr, Litman B, Kim HY, Gawrisch K (2001) Mechanisms of action of docosahexaenoic acid in the nervous system. Lipids 36:945–959

Saw CL, Huang Y, Kong AN (2010) Synergistic anti-inflammatory effects of low doses of curcumin in combination with polyunsaturated fatty acids: docosahexaenoic acid or eicosapentaenoic acid. Biochem Pharmacol 79:421–430

Sharma S, Ying Z, Gómez-Pinilla F (2010) A pyrazole curcumin derivative restores membrane homeostasis disrupted after brain trauma. Exp Neurol 226:191–199

Smith DM, Mizumori SJ (2006) Hippocampal place cells, context, and episodic memory. Hippocampus 16:716–729

Smith PJ, Blumenthal JA, Hoffman BM, Cooper H, Strauman TA, Welsh-Bohmer K, Browndyke JN, Sherwood A (2010) Aerobic exercise and neurocognitive performance: a meta-analytic review of randomized controlled trials. Psychosom Med 72:239–252

Suzuki H, Park SJ, Tamura M, Ando S (1998) Effect of the long-term feeding of dietary lipids on the learning ability, fatty acid composition of brain stem phospholipids and synaptic membrane fluidity in adult mice: a comparison of sardine oil diet with palm oil diet. Mech Ageing Dev 101:119–128

Szabo Z, Ying Z, Radak Z, Gómez-Pinilla F (2010) Voluntary exercise may engage proteasome function to benefit the brain after trauma. Brain Res 1341:25–31

Tanaka J, Horiike Y, Matsuzaki M, Miyazaki T, Ellis-Davies GC, Kasai H (2008) Protein synthesis and neurotrophin-dependent structural plasticity of single dendritic spines. Science 319:1683–1687

Trejo JL, Carro E, Torres-Aleman I (2001) Circulating insulin-like growth factor I mediates exercise-induced increases in the number of new neurons in the adult hippocampus. J Neurosci 21:1628–1634

Tsankova NM, Berton O, Renthal W, Kumar A, Neve RL, Nestler EJ (2006) Sustained hippocampal chromatin regulation in a mouse model of depression and antidepressant action. Nat Neurosci 9:519–525

Tully AM, Roche HM, Doyle R, Fallon C, Bruce I, Lawlor B, Coakley D, Gibney MJ (2003) Low serum cholesteryl ester-docosahexaenoic acid levels in Alzheimer's disease: a case-control study. Br J Nutr 89:483–489

Uchida S, Inanaga Y, Kobayashi M, Hurukawa S, Araie M, Sakuragawa N (2000) Neurotrophic function of conditioned medium from human amniotic epithelial cells. J Neurosci Res 62:585–590

Um HS, Kang EB, Koo JH, Kim HT, Jin-Lee, Kim EJ, Yang CH, An GY, Cho IH, Cho JY (2011) Treadmill exercise represses neuronal cell death in an aged transgenic mouse model of Alzheimer's disease. Neurosci Res 69:161–173

Vaynman S, Gómez-Pinilla F (2005) License to run: exercise impacts functional plasticity in the intact and injured central nervous system by using neurotrophins. Neurorehabil Neural Repair 19:283–295

Vaynman S, Gómez-Pinilla F (2006) Revenge of the "sit": how lifestyle impacts neuronal and cognitive health through molecular systems that interface energy metabolism with neuronal plasticity. J Neurosci Res 84:699–715

Vaynman S, Ying Z, Gómez-Pinilla F (2004) Hippocampal BDNF mediates the efficacy of exercise on synaptic plasticity and cognition. Eur J Neurosci 20:2580–2590

Walz C, Jüngling K, Lessmann V, Gottmann K (2006) Presynaptic plasticity in an immature neocortical network requires NMDA receptor activation and BDNF release. J Neurophysiol 96:3512–3516

Wang X, Butowt R, Vasko MR, von Bartheld CS (2002) Mechanisms of the release of anterogradely transported neurotrophin-3 from axon terminals. J Neurosci 22:931–945

Warraich Z, Kleim JA (2010) Neural plasticity: the biological substrate for neurorehabilitation. PM R 2:S208–S219

Wei QY, Chen WF, Zhou B, Yang L, Liu ZL (2006) Inhibition of lipid peroxidation and protein oxidation in rat liver mitochondria by curcumin and its analogues. Biochim Biophys Acta 1760:70–77

Wheaton P, Mathias JL, Vink R (2011) Impact of pharmacological treatments on outcome in adult rodents after traumatic brain injury: a meta-analysis. J Psychopharmacol 25(12):1581–1599

Winocur G, Moscovitch M (2011) Memory transformation and systems consolidation. J Int Neuropsychol Soc 17(5):766–780

Wong-Goodrich SJ, Pfau ML, Flores CT, Fraser JA, Williams CL, Jones LW (2010) Voluntary running prevents progressive memory decline and increases adult hippocampal neurogenesis and growth factor expression after whole-brain irradiation. Cancer Res 70:9329–9338

Wu A, Ying Z, Gómez-Pinilla F (2004) Dietary omega-3 fatty acids normalize BDNF levels, reduce oxidative damage, and counteract learning disability after traumatic brain injury in rats. J Neurotrauma 21:1457–1467

Wu A, Ying Z, Gómez-Pinilla F (2006) Dietary curcumin counteracts the outcome of traumatic brain injury on oxidative stress, synaptic plasticity, and cognition. Exp Neurol 197:309–317

Wu A, Ying Z, Gómez-Pinilla F (2008) Docosahexaenoic acid dietary supplementation enhances the effects of exercise on synaptic plasticity and cognition. Neuroscience 155:751–759

Wu A, Ying Z, Schubert D, Gómez-Pinilla F (2011) Brain and spinal cord interaction: a dietary curcumin derivative counteracts locomotor and cognitive deficits after brain trauma. Neurorehabil Neural Repair 25:332–342

Xu J, Kao SY, Lee FJ, Song W, Jin LW, Yankner BA (2002) Dopamine-dependent neurotoxicity of alpha-synuclein: a mechanism for selective neurodegeneration in Parkinson disease. Nat Med 8:600–606

Yoneyama M, Shiba T, Hasebe S, Ogita K (2011) Adult neurogenesis is regulated by endogenous factors produced during neurodegeneration. J Pharmacol Sci 115(4):425–432

Zhang X, Chen Y, Jenkins LW, Kochanek PM, Clark RS (2005) Bench-to-bedside review: apoptosis/programmed cell death triggered by traumatic brain injury. Crit Care 9:66–75

Zhu X, Lee HG, Perry G, Smith MA (2007) Alzheimer disease, the two-hit hypothesis: an update. Biochim Biophys Acta 1772:494–502

Zoladz JA, Pilc A (2010) The effect of physical activity on the brain derived neurotrophic factor: from animal to human studies. J Physiol Pharmacol 61:533–541

Chapter 3
Opioids and Exercise: Animal Models

Rod K. Dishman and Philip V. Holmes

Abstract This chapter provides an accounting of the study of endogenous opioids and exercise, focusing on animal studies. We describe the advantages and limitations of rodent models for the study of brain and behavior and give examples of how those models can be applied to investigate the role of opioids within brain neuromodulatory systems that may be useful for the study of the motivation to be physically active and the behavioral consequences of physical activity.

3.1 Introduction

The weight of the accumulated evidence supports the conclusion that physical activity is associated with positive mental health outcomes, including fewer symptoms of depression and anxiety, better sleep, feelings of increased energy, less pain, or distress, and better cognitive function (Dishman et al. 2013; Physical Activity Guidelines Advisory Committee 2008; http://www.health.gov/PAGuidelines/Report/G8_mentalhealth.aspx). Nonetheless, the circumstances in which physical

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activity causes these positive aspects of mental health remain unclear (De Moor et al. 2008; Morgan 1997). Biological mechanisms that explain the putative benefits of being physically active are poorly understood (Dishman et al. 2006). Likewise, the biology of motivation to be physically active has received very little study (Dishman 2008), despite substantial evidence that physical activity is strongly heritable (Bray et al. 2009; Stubbe et al. 2006). The idea that endogenous opioid peptides play a central role in modulating the antecedents and consequences of physical activity has been widely perpetuated for more than 30 years without much scientific evidence to support it (Dishman 1985; Dishman and O'Connor 2009).

Opioid peptides (e.g., β-endorphin and met- and leu-enkephalin) are reliably elevated in the plasma of humans during intense exercise. One recent review reported that 59 of 65 studies from 1982 to 2008 show significant increases in peripheral concentrations of β-endorphin as a result of exercise (Boecker et al. 2010). Whether plasma β-endorphin and its precursor molecule pro-opiomelanocortin (POMC) have a dose-gradient response to exercise is less clear (Goldfarb and Jamurtas 1997; Harbach and Hempelmann 2005; Nybo and Secher 2004). Research also suggests that these peripheral changes are not reflective of β-endorphin concentrations in the brain and that, while peripheral opioids help regulate physiological responses that support energy expenditure and modulate nociception during exercise, it is unlikely that they directly affect the brain (Boecker et al. 2010; Dishman 1985; Nybo and Secher 2004). Furthermore, a plausible link between peripheral opioid peptides and behavioral functions of the central nervous system (e.g., mood, cognitive function, or hypoalgesia) has not been established. It is more likely that the brain during exercise is affected by opioids other than those derived from pituitary POMC (Fallon and Leslie 1986). Studies with rats and mice show increased levels of endorphins or altered enkephalin receptor binding in the brain after acute exercise, but the effects of the levels on behavior, emotion, or physiology were not demonstrated (Hoffmann 1997). Only recently has evidence emerged to support that endogenous opioids are released in human brains after prolonged exercise (Boecker et al. 2008b).

Application of behavioral neuroscience to physical activity studies is necessary to elucidate, or eliminate, plausible opioidergic mechanisms, thereby advancing our understanding of the choice to be physically active and whether physical activity truly benefits mental health (Boecker et al. 2008a; Meeusen et al. 2001). Especially needed are studies that synergize human brain imaging (Boecker et al. 2008a) with behavioral neuroscience approaches that use animal models of human function or disease (e.g., Dishman 1997; Dishman et al. 2006; Holmes 2003).

3.2 Endogenous Opioids

Endogenous opioids are peptides that have pharmacological actions similar to exogenous opiates such as heroin and morphine. Endogenous opioids act by binding to mu (μ), kappa (κ), or delta (δ) receptors. Because of the widespread distribution of

these receptors throughout the peripheral and central nervous systems, endogenous opioids have diverse effects including hedonics, pain regulation, cardiovascular regulation, respiration, appetite and thirst, gastrointestinal activity, renal function, temperature regulation, metabolism, hormonal secretion, reproduction, immunity, learning, and memory (Akil et al. 1998; Evans et al. 1988).

The enkephalins (ENK), which include two forms, leu-ENK and met-ENK, are signaling ligands that modulate neural, endocrine, and immune systems, thereby influencing a wide range of functions including nociception, reward, and stress responses. Although ENK-expressing neurons are distributed throughout the brain, ENK is most abundant in the subpopulation of GABAergic medium spiny neurons of the striatum that predominantly express dopamine D2 receptors (Akil et al. 1998; Churchill et al. 1998; Heimer et al. 1991). ENK neurons of the ventral striatum project extensively to the ventral pallidum which is a critical neural circuit for the affective functions of endogenous opioids (Smith and Berridge 2007). ENK binds preferentially to δ-opioid receptors, though it exhibits appreciable affinity for μ and κ receptors as well (Akil et al. 1998). Desensitization of δ opioid receptors in the ventral striatum has been linked to anxiety and depression-like effects, and ENK may therefore maintain normal affective tone through its interaction with δ receptors (Perrine et al. 2008; Torregrossa et al. 2006). Other CNS systems where ENK mediates critical regulatory functions during affective experience, stress, and nociception include the amygdala, periaqueductal gray, and dorsal horn of the spinal cord (Akil et al. 1998; Jonsdottir 2000). Met-enkephalin and leu-enkephalin are also stored in the adrenal medulla where they are coreleased with catecholamines into the gastrointestinal tract, heart, and blood circulation during stress.

The distribution of dynorphin (DYN) generally overlaps with the distribution of ENK, but within the striatum, most DYN is found in medium spiny neurons that express the D1 receptor subtype (Akil et al. 1998; Jonsdottir 2000). In the ventral striatum, this population of medium spiny neurons projects to the ventral tegmental area (VTA). The behavioral functions of DYN are often opposite to functions of ENK. DYN, expressed in A and B forms, binds primarily to κ-opioid receptors which mediate the effects of DYN on stress-induced dysphoria and aversion via projections from the dorsal raphe nuclei to the nucleus accumbens (Land et al. 2009). Furthermore, there is strong evidence that DYN/κ-opioid receptor binding locally inhibits dopamine release in the VTA and nucleus accumbens, modulating the rewarding effects of opiates and food and possibly wheel running (Mansour et al. 1995; Nestler and Carlezon 2006; Shippenberg and Rea 1997). Endomorphins, more recently discovered endogenous substances with a different structure than the endorphins, dynorphins, and enkephalins, bind more tightly to the μ receptor than other opioid peptides and also have wide-ranging effects, many of which mimic the effects of other opioids (Fichna et al. 2007).

Investigators studying opioids and exercise have focused most of their research on β-endorphin which can act as a neurotransmitter, neuromodulator, and a hormone. Beta-endorphin is found in abundance peripherally in the eyes, heart, kidneys, gastrointestinal tract, and adrenal glands and centrally in the spinal cord and the brain (Imura and Yoshikatsu 1981). The highest concentration of β-endorphin-expressing

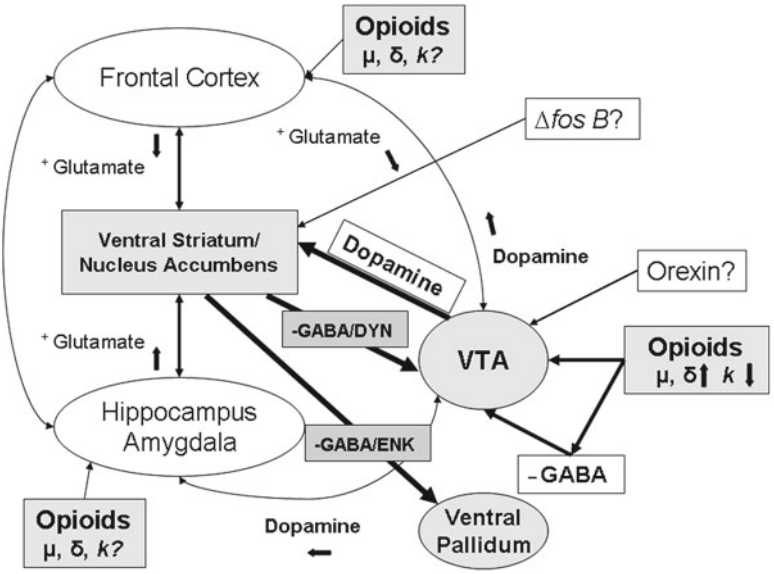

Fig. 3.1 Plausible opioid and early gene modulation in the mesolimbic dopamine system involved with motivation and pleasure (*VTA* ventral tegmental area, *ENK* enkephalin, *DYN* dynorphin)

neurons is found in the hypothalamus, with extensive projections throughout the brain (e.g., limbic system, the periaqueductal gray, brainstem; Hegadoren et al. 2009). Other significant populations of β-endorphin neurons are found in the nucleus tractus solitarius with projections to the ventrolateral medulla. POMC-expressing neurons are found in the VTA and the nucleus accumbens (Leriche et al. 2007) which modulate hedonics and appetitively motivated behaviors (Fig. 3.1). Beta-endorphin produces hypoalgesia, respiratory depression, bradycardia, contraction of the pupil, and hypothermia. Beta-endorphin is secreted into the blood from the anterior and intermediate regions of the pituitary during vigorous exercise depending in part on the intensity of the exercise. It is usually accompanied by increases in ACTH, which is derived along with β-endorphin and melanocortin from the common precursor POMC. Hence, peripheral levels of β-endorphin during and shortly after acute exercise may be viewed as an indication of the stress response to the exercise.

3.3 Animal Models: Motivation and Hedonics

Most research into the putative link between exercise, opioids, and affective responses has been conducted in the context of the hedonic and/or addictive properties of opioids. Theories of addiction derived from animal models are therefore informative for this line of inquiry, at least in terms of identifying meaningful behavioral measures in nonhuman subjects. However, before selecting dependent

variables related to hedonic or appetitively motivated behaviors in rodents, it is important to consider the theoretical rationale for these measures. The research therefore requires critical evaluation of evidence-based theories of the neurobiological mechanisms that mediate motivational and hedonic processes before proceeding with a particular paradigm. The following section will provide a brief overview of the extant evidence for the specific role of opioids and their interactions with dopamine in reward-related processes.

Although opioid peptides are the focus of this chapter, it is important to consider the functional interactions between opioid peptides and dopamine to understand the relative roles of motivational and hedonic processes in the antecedents and consequences of exercise. The actions of dopamine and opioids in ventral striatal reward systems are inextricably linked, and any understanding of the relationship between exercise effects on motivation and mood must take into account the interplay between these two neurotransmitter systems.

There is wide consensus concerning the role of mesolimbic dopamine in mediating behavioral responses to natural rewards, such as feeding, reproductive behaviors, play, etc. (Berridge and Robinson 1998; Lutter and Nestler 2009; Robbins and Everitt 1996; Wise 2004). However, accounts of the precise role of dopamine have rapidly evolved. Traditionally, dopamine function has been conceptualized in terms of the hedonic aspects of reward processes (Koob and Le Moal 1997; Wise 2008), but accumulating evidence consistently supports the conclusion that mesolimbic dopaminergic systems mediate the motivational aspects of reward rather than pleasure per se (Berridge and Robinson 1998; Flagel et al. 2011; Smith and Berridge 2007). This evidence has led to the development of the incentive salience hypothesis (and variants thereof), which, simply stated, emphasizes the importance of dopamine in the "wanting" that is triggered by reward-related conditioned stimuli. According to this model, the "liking" or pleasure associated with reward involves activation of other systems parallel to or downstream of the mesolimbic dopamine pathways. These other, hedonic-based systems involve GABA and opioid peptides in distinct yet integrated pathways within the ventral striatum and striatal pallidal circuits, among others (Smith and Berridge 2007).

The incentive salience hypothesis has posed serious challenges to addiction models centered on the role of hedonics rather than motivational processes in addiction. Widely accepted examples of these models, such as the hedonic allostasis theory (Koob and Le Moal 1997) conceptualize addictive behaviors as a response to hypoactivity in dopamine systems. This hypodopaminergic state is purported to induce compensatory behavioral activation (e.g., drug seeking, sensation seeking, compulsive exercise, etc.) as a means to restore normal hedonic tone. In stark contrast, application of the incentive salience model to addiction emphasizes the role of dopamine as the driver of the behavioral activation that ultimately leads to the outcomes that induce pleasure. Dopamine thus mediates the motivation that triggers the relevant behaviors, such as drug seeking, sensation seeking, exercise, etc.

These two models make diametrically different predictions about the roles of dopamine and opioid peptides in the motivation to exercise and the pleasure or "high" that may be derived from this activity. The hedonic allostasis theory, which

may also be interpreted as an "anhedonia model," predicts that dysphoria, presumably mediated by deficits in dopamine transmission, drives the organism to reexperience the euphoria that is a consequence of the relevant behavior. Accordingly, in some individuals, the desire to exercise would be linked to low baseline dopaminergic tone, and exercise may restore dopaminergic transmission to the levels necessary to achieve euphoria. Though the hedonic allostasis model emphasizes dopamine over other systems that may also mediate pleasure, one could easily incorporate exercise-induced opioid activation into this scheme as well in order to account for exercise-induced hedonia. Compulsive exercise or "addiction" to exercise thus would depend on correcting a dysphoric state caused by low dopaminergic (and presumably also opioidergic) tone, according to this account. By example, a test of this hypothesis could examine various indices of dopaminergic and/or opioid activity in rat strains selectively bred for differing levels of spontaneous exercise in an activity wheel. According to the hedonic allostasis model, one would expect to find lower functioning of these transmitters under resting conditions in rats predisposed to exhibit higher levels of wheel running.

In contrast to these hypotheses, the incentive salience model predicts that higher dopaminergic transmission would drive appetitively motivated behaviors such as exercise because the mesolimbic dopamine system plays precisely this role in the evolutionary success of the organism. Conversely, lower dopaminergic transmission would be expected to yield decreased incentive for behavioral activation. As a component of the neural system that identifies cues associated with enhanced survival, dopamine is purported to recruit attentional resources to identify these cues, adjust motivational levels accordingly, and activate the appropriate behavioral response. Whether this coordinated activation leads to a subjective experience in humans related to pleasure or dysphoria may depend on the constellation of cues predicting the outcome that was learned to be associated with that event (whether it is running toward a potential mate or running away from a potential predator). In either case, the primary cognitive state is motivation (i.e., craving, desire, impulse), the related behavioral state is activation, and dopamine mediates both of these functions. In the example of behavioral activation that leads to positive outcomes, such as the procurement of food or a mate, the consummatory cues associated with ingesting or copulating may trigger the GABAergic and/or opioid hedonic circuits (Smith and Berridge 2007). In the case of fleeing from or fighting off a predator, activation of the hedonic opioid circuits may depend on cues that signal successful escape or avoidance of the threat. Dopamine transmission is thus responsible for activating the behavior necessary to achieve the successful outcome in either case, whereas opioids may be more directly involved in the hedonic response associated with that outcome. The model thus predicts that higher basal dopamine transmission would be associated with greater exercise propensity and lower dopamine transmission associated with less (Fig. 3.2). The theoretical model illustrated in Fig. 3.2 also implicates differences in opioid function between individuals with high or low dopaminergic tone. The hypothesized decrease in ENK in the ventral striatum may produce a compensatory increase in opioid receptors, such as that previously observed in high-running rats (Greenwood et al. 2011). The impact of this opioid

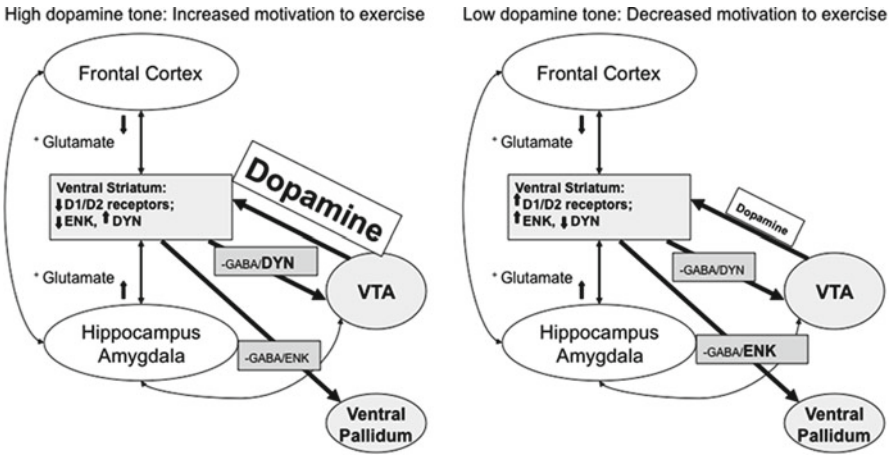

Fig. 3.2 Predicted relationships between high and low endogenous dopaminergic tone and their subsequent effects on opioids, dopamine receptors, and exercise

regulation on the hedonics associated with exercise is difficult to predict, as both decreased transmission (lower ENK) and increased transmission (upregulated receptors) may occur.

Though clear evidence of the phenomenon is still lacking, it is tempting to hypothesize that the "high" or euphoria associated with thrill seeking and extreme sports, including extreme exercise, fits the paradigm of opioid activation triggered by a fight or flight response. It should be noted that this interpretation is entirely consistent with the well-established role of endogenous opioids in stress-induced hypoalgesia (see below), though it emphasizes the function of opioids in hedonic systems of the ventral striatum and ventral pallidum rather than pain regulatory systems in the spinal cord and brainstem.

The specific test of the role of dopamine in exercise as predicted by the incentive salience hypothesis would be to examine the relationship between basal dopamine activity or that induced by exercise-related cues and individual or strain differences in spontaneous wheel running. According to the model, higher basal dopamine potential would predict higher rates of wheel running. Predictions concerning the role of opioids in postexercise hedonic activation are premature at this point since the generalizability of the phenomenon has yet to be convincingly established in humans or animal models, and operational measures of hedonics in animal models are difficult to validate (Holmes 2003).

Other popular accounts of the putative links between exercise and addictive behaviors focus on withdrawal states. The widely held notions of compulsive or addictive behavior that emphasize relief from withdrawal symptoms as a primary motivator are not well supported by experimental or clinical evidence. The major drawback of this kind of model is the evidence that craving and drug-seeking behavior are frequently not linked to a withdrawal syndrome (Erb 2010). Though this kind of model is still popularly accepted and is a predecessor of the hedonic allostasis

model, it is inconsistent with the extensive evidence that links craving or compulsive behavior to cue-induced activation of the mesolimbic dopamine system (Berridge and Robinson 1998; Flagel et al. 2011).

Based on this theoretical foundation, it is clear that behavioral measures of the effects of exercise on emotional states in rodent models should begin with a dissociation of motivational and hedonic variables. In comparing the strengths and weaknesses of a variety of measures of appetitive motivation, systematic measures of reproductive behaviors in rats provide distinct advantages (Holmes 2003). Operationalizing behavioral manifestations of hedonic variables continues to pose a serious challenge to behavioral neuroscience research. Though some "anhedonia" models, such as diminished preference for dilute sucrose solutions, show some validity, measures of hedonic activation assessed through increased palatable food consumption are hopelessly confounded with variables associated with motivation and energy balance. Nonetheless, the measures of affective taste reactions in rats described by Berridge and Robinson (1998) represent arguably the best alternative for quantifying hedonic responses.

3.4 Effects of Exercise on Dopamine

If opioids in the central nervous system do influence behavioral responses to exercise, the effects will result from complex interactions involving other neurotransmitter systems that govern hedonic states and reward-motivated behavior as described above. Little is known about the effects of physical activity on the brain mesolimbic dopamine (DA) system (mainly the neural circuit between the VTA, the nucleus accumbens of the ventral striatum, and the frontal cortex) (Dishman et al. 2006; Knab and Lightfoot 2010). Treadmill running acutely increases DA release (Meeusen et al. 2001) (see also Chap. 4) and turnover (Hattori et al. 1994) and chronically upregulates D2 receptors (MacRae et al. 1987) in the striatum of rats, but forced treadmill running by rats and mice likely confounds exertion with emotional stress and is thus a poor model of voluntary physical activity. For example, stress hormones can cause opioid release (Nikolarakis et al. 1987). In contrast to the effects of treadmill running, elevated striatal DA activity in rats selectively bred for high fitness was normalized after chronic wheel running (Waters et al. 2008), whereas gene expression for D2 receptors was unchanged in the nucleus of mice (Knab et al. 2009) but was decreased in the nucleus accumbens of rats (Greenwood et al. 2011). The influence of exercise on endomorphin activity has not yet been investigated; however, the injection of endomorphin-1 into the posterior VTA increases locomotor activity (Zangen et al. 2002).

Opioid modulation of brain dopamine is a central feature in models of motivated behavior and addiction. One study found that c-fos and delta fosB (early genes that induce the expression of other regulatory genes) in the nucleus accumbens were activated during wheel running in rats and that mice who overexpress delta fosB selectively in striatal dynorphin-containing neurons run more than control litter mates

(Werme et al. 2002). Delta fosB could plausibly facilitate wheel running by inhibiting the release by GABA neurons of colocalized dynorphin, which otherwise binds with κ-opioid receptors to inhibit DA release in the VTA or accumbens (Werme et al. 2002). In short, it is plausible that central opioids modulate dopamine and/or other neurotransmitter systems that control metabolic or hedonic drives that regulate physical activity.

3.5 Effects of Exercise on Opioids

A large volume of research, initiated nearly 30 years ago, linked the endorphin superfamily with disorders of mood and personality (Post and Ballenger 1984; Risch and Pickar 1983). About the same time, interest in opioid peptides and exercise was sparked by ligand-binding studies which showed that opiate receptor occupancy was altered in rat brain following acute exercise (Pert and Bowie 1979; Wardlaw and Frantz 1980), but subsequent studies produced conflicting results. Brain β-endorphin levels were higher in the nucleus accumbens and leu-enkephalin levels were higher in the VTA after 2 h of forced treadmill running (Blake et al. 1984). In contrast, opioid receptor binding was higher in several brain regions after 2 h of forced swimming, indicative of lower levels of endorphins (Sforzo et al. 1986). Because those studies used forced, stressful exercise and did not measure behavioral responses that mimic signs of euphoria, reduced anxiety, or hypoalgesia, the results neither supported nor refuted the hypothesis that exercise affects mood or pain by endorphin mechanisms. Also, chronic treadmill running did not alter basal levels of brain opioid peptides (Houghten et al. 1986). In short, there was no evidence for a direct link between exercise-induced changes in mood or hypoalgesia and opioid peptides measured in either the blood or the brain (Dishman 1985).

A particularly elegant way to determine whether an experimental manipulation activates a specific endogenous neurotransmitter system is to test whether repeated exposure to that manipulation produces a tolerance to drugs mimicking the endogenous neurotransmitter. Smith and Lyle (2006) thus demonstrated that voluntary exercise produces a cross-tolerance to the analgesic effects of morphine. In a similar vein, naloxone-precipitated withdrawal is exaggerated following chronic wheel running (Kanarek et al. 2009).

There is limited evidence demonstrating that physical activity has direct effects on gene expression of endogenous opioids: β-endorphin, ENK, and DYN (Bjørnebekk et al. 2006; Jonsdottir et al. 1997). One of the first seminal studies that found increased β-endorphin concentrations in the cerebrospinal fluid (CSF) not only used a voluntary running but also demonstrated elevated levels 48 h after cessation of exercise—46 h longer than previous research indicated changes (Hoffmann et al. 1990). A more recent study corroborated these earlier findings by showing that running, like cocaine, increases DYN mRNA levels in the caudate putamen of rats bred for running and drug preference. Additionally, the effect is blocked by opioid receptor antagonists indicating not only upregulation of mRNA but also μ-receptor activation (Werme et al. 2000).

DYN is released in the paraventricular nucleus (PVN) as a result of aerobic exercise and is associated with release of other neuropeptides associated with energy balance, such as NPY (Chen et al. 2007). Moreover, voluntary running directly increases DYN-converting enzyme activity in the cerebral spinal fluid, thereby converting DYN to leu-enkephalin and producing hypoalgesia (Persson et al. 1993). Furthermore, the early transcription factor delta fosB, which is upregulated by running, also inhibits DYN release suggesting a mechanism by which physical activity could be rewarding (Werme et al. 2002). Also, both cocaine and wheel running cause an increase in DYN-A mRNA in the caudate putamen, an area necessary in movement and learning, of rats bred for drug and running preference (Werme et al. 2000). There is strong evidence that DYN release in the paraventricular nucleus (PVN) as a result of aerobic exercise is associated with release of other neuropeptides associated with energy balance, such as NPY (Chen et al. 2007), and that the neuronal subpopulations expressing DYN receptors, μ opiate receptors, and DA receptors are also affected (Gerfen 2000).

Opioids also are involved in brain neurotrophic processes induced by voluntary physical activity (Koehl et al. 2008; Persson et al. 2004). Neurotrophic responses can influence a broad spectrum of brain-behavior systems, such as learning and neural plasticity after brain insults (Dishman et al. 2006; van Praag 2008) (see also Chaps. 1 and 2).

3.6 Opioids and Nociception After Exercise

Peripheral endogenous opioids are involved in the modulation of nociception and can act on peripheral afferents and spinal neurons. Thus, opioid entry into the brain would not be required for an antinociceptive effect. The available data do not strongly support the hypothesis that opioids alone cause hypoalgesia during or after high-intensity exercise (Dishman and O'Connor 2009). Although opioid-mediated hypoalgesia (Cook et al. 2000) could indirectly influence the CNS, peripheral opioid responses to acute exercise appear to mainly modulate catecholamine influences on cardiovascular, respiratory, and endocrine responses during exercise (Thoren et al. 1990).

3.7 Summary

It is important to remember that no single neurotransmitter or neuromodulator system will solely explain behaviors that are pertinent for understanding human motivation, emotion, nociception, and states of consciousness, which depend upon complex interactions of many neural circuits. Fluctuation in human affective experience undoubtedly depends upon regulation of many excitatory and inhibitory neurotransmitters (e.g., acetylcholine, GABA, and glutamate), neuromodulators (e.g., dopamine, norepinephrine, and serotonin), neurotrophic factors (e.g., BDNF and

NGF), neuropeptides besides opioid peptides (e.g., cholecystokinin, CRF, galanin, NPY, and VGF), membrane lipids (e.g., endocannabinoids), gases (e.g., nitric oxide), and intracellular signaling that controls gene transcription and translation, as well as posttranslational regulation of neurons. Pleasure and pain systems, and their associated memories, are fundamental to biological drives that sustain and perpetuate life and that provide the basis for acquired motivation and avoidance of danger. Although exogenous pharmaceuticals such as opiates, amphetamines, benzodiazepines, and tetrahydrocannabinol have strong, direct effects on mood and pain, equally strong effects by endogenous systems that mimic those responses would not be biologically adaptive in the absence of trauma. Hence, it is unusual for people to have euphoric, addictive, or analgesic experiences simply by engaging in physical activity and exercise. Why and how physical exertion alters brain neural systems in mentally healthy and unhealthy ways among most people, or in special populations, are important experimental questions that warrant behavioral neuroscience investigation using animal models.

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References

Akil H, Owens C, Glutstein H, Taylor L, Curran E, Watson S (1998) Endogenous opioids: overview and current issues. Drug Alcohol Depend 51:127–140

Berridge KC, Robinson TE (1998) What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? Brain Res Brain Res Rev 28:309–369

Bjørnebekk A, Mathé AA, Brené S (2006) Running has differential effects on NPY, opiates, and cell proliferation in an animal model of depression and controls. Neuropsychopharmacology 31:256–264

Blake MJ, Stein EA, Vomachka AJ (1984) Effects of exercise training on brain opioid peptides and serum LH in female rats. Peptides 5:953–958

Boecker H, Henriksen G, Sprenger T, Miederer I, Willoch F, Valet M, Berthele A, Tölle TR (2008a) Positron emission tomography ligand activation studies in the sports sciences: measuring neurochemistry in vivo. Methods 45:307–318

Boecker H, Sprenger T, Spilker ME, Henriksen G, Koppenhoefer M, Wagner KJ, Valet M, Berthele A, Tolle TR (2008b) The runner's high: opioidergic mechanisms in the human brain. Cereb Cortex 18:2523–2531

Boecker H, Othman A, Mueckter S, Scheef L, Pensel M, Daamen M, Jankowski J, Schild HH, Tölle TR, Schreckenberger M (2010) Advocating neuroimaging studies of transmitter release in human physical exercise challenges studies. Open Access J Sports Med 1:167–175

Bray MS, Hagberg JM, Parousse L, Rankinen T, Roth SM, Wolfarth B, Bouchard C (2009) The human gene map for performance and health-related fitness phenotypes: the 2006-2007 update. Med Sci Sports Exerc 41:35–73

Chen J-X, Zhao X, Yue G-X, Wang ZF (2007) Influence of acute and chronic treadmill exercise on rat plasma lactate and brain NPY, L-ENK, DYN A1-13 cell. Mol Neurobiol 27:1–10

Churchill L, Klitenick MA, Kalivas PW (1998) Dopamine depletion reorganizes projections from the nucleus accumbens and ventral pallidum that mediate opioid-induced motor activity. J Neurosci 18:80774–80785

Cook DB, O'Connor PJ, Ray CA (2000) Muscle pain perception and sympathetic nerve activity to exercise during opoid modulation. Am J Physiol Regul Integr Comp Physiol 279:R1565–R1573

De Moor MH, Boomsma DI, Stubbe JH, Willemsen G, de Geus EJ (2008) Testing causality in the association between regular exercise and symptoms of anxiety and depression. Arch Gen Psychiatry 65:897–905

Dishman RK (1985) Medical psychology in exercise and sport. Med Clin North Am 69:123–143

Dishman RK (1997) Brain monoamines, exercise, and behavioral stress: animal models. Med Sci Sports Exerc 29:63–74

Dishman RK (2008) Gene-physical activity interactions in the etiology of obesity: behavioral considerations. Obesity 16(Suppl 3s):S60–S65

Dishman RK, O'Connor PJ (2009) Lessons in exercise neurobiology: the case of endorphins. Ment Health Phys Act 2:4–9

Dishman RK, Berthoud HR, Booth FW, Cotman CW, Edgerton VR, Fleshner MR, Gandevia SC, Gomez-Pinilla F, Greenwood BN, Hillman CH, Kramer AF, Levin BE, Moran TH, Russo-Neustadt AA, Salamone JD, Van Hoomissen JD, Wade CE, York DA, Zigmond MJ (2006) Neurobiology of exercise. Obesity (Silver Spring) 14:345–356

Dishman RK, Heath G, Lee IM (2013) Physical activity epidemiology, 2nd edn. Human Kinetics, Champaign, IL, pp 1–640

Erb S (2010) Evaluation of the relationship between anxiety during withdrawal and stress-induced reinstatement of cocaine seeking. Prog Neuropsychopharmacol Biol Psychiatry 34:798–807

Evans CJ, Hammond DL, Fredrickson RCA (1988) The opioid peptides. In: Pasternak GW (ed) The opiate receptors. Humana, Clifton, NJ, pp 23–74

Fallon JH, Leslie FM (1986) Distribution of dynorphin and enkephalin peptides in the rat brain. J Comp Neurol 249:293–336

Fichna J, Janecka A, Costentin J, DoRego JC (2007) The endomorphin system and its evolving neurophysiological role. Pharmacol Rev 59:88–123

Flagel SB, Clark JJ, Robinson TE, Mayo L, Czuj A, Willuhn I, Akers CA, Clinton SM, Phillips PEM, Akil H (2011) A selective role for dopamine in stimulus-reward learning. Nature 469:53–59

Gerfen CR (2000) Molecular effects of dopamine on striatal-projection pathways. Trends Neurosci 23(Suppl 1):S64–S70

Goldfarb AH, Jamurtas AZ (1997) Beta-endorphin response to exercise. An update. Sports Med 24:8–16

Greenwood BN, Foley TE, Le TV, Strong PV, Loughridge AB, Day HE, Fleshner M (2011) Long-term voluntary wheel running is rewarding and produces plasticity in the mesolimbic reward pathway. Behav Brain Res 217:354–362

Harbach HW, Hempelmann G (2005) Proopiomelanocortin and exercise. In: Kraemer WJ, Rogol AD (eds) The endocrine system and exercise. Blackwell, Malden, MA, pp 134–155

Hattori S, Naoi M, Nishino H (1994) Striatal dopamine turnover during treadmill running in the rat: relation to the speed of running. Brain Res Bull 35:41–49

Hegadoren KM, O'Donnell T, Lanius R, Coupland NJ, Lacaze-Masmonteil N (2009) The role of beta-endorphin in the pathophysiology of major depression. Neuropeptides 43:241–253

Heimer L, Zahm DS, Churchill L, Kalivas PW, Wohltmann C (1991) Specificity in the projection patterns of accumbal core and shell in the rat. Neuroscience 41:89–125

Hoffmann P (1997) The endorphin hypothesis. In: Morgan WP (ed) Physical activity and mental health. Taylor & Francis, Washington, DC, pp 163–177

Hoffmann P, Terenius L, Thorén P (1990) Cerebrospinal fluid immunoreactive beta-endorphin concentration is increased by voluntary exercise in the spontaneously hypertensive rat. Regul Pept 28:233–239

Holmes PV (2003) Rodent models of depression: reexamining validity without anthropomorphic inference. Crit Rev Neurobiol 15:143–174

Houghten RA, Pratt SM, Young EA, Brown H, Spann DR (1986) Effect of chronic exercise on beta-endorphin receptor levels in rats. NIDA Res Monogr 75:505–508

Imura H, Yoshikatsu N (1981) "Endorphins" in pituitary and other tissues. Ann Rev Physiol 43:265–278

Jonsdottir IH (2000) Neuropeptides and their interaction with exercise and immune function. Immunol Cell Biol 78:562–570

Jonsdottir IH, Hoffmann P, Thorèn P (1997) Physical exercise, endogenous opioids and immune function. Acta Physiol Scand 640(suppl):47–50
Kanarek RB, D'Anci KE, Jurdak N, Mathes WF (2009) Running and addiction: precipitated withdrawal in a rat model of activity-based anorexia. Behav Neurosci 123:905–912
Knab AM, Lightfoot JT (2010) Does the difference between physically active and couch potato lie in the dopamine system? Int J Biol Sci 6:133–150
Knab AM, Bowen RS, Hamilton AT, Gulledge AA, Lightfoot JT (2009) Altered dopaminergic profiles: implications for the regulation of voluntary physical activity. Behav Brain Res 204:147–152
Koehl M, Meerlo P, Gonzales D, Rontal A, Turek FW, Abrous DN (2008) Exercise-induced promotion of hippocampal cell proliferation requires beta-endorphin. FASEB J 22:2253–2262
Koob GF, Le Moal M (1997) Drug abuse: hedonic homeostatic dysregulation. Science 278:52–58
Land BB, Bruchas MR, Schattauer S, Giardino WJ, Aita M, Messinger D, Hnasko TS, Palmiter RD, Chavkin C (2009) Activation of the kappa opioid receptor in the dorsal raphe nucleus mediates the aversive effects of stress and reinstates drug seeking. Proc Nat Acad Sci USA 106:19168–19173
Leriche M, Cote-Vélez A, Méndez M (2007) Presence of pro-opiomelanocortin mRNA in the rat medial prefrontal cortex, nucleus accumbens and ventral tegmental area: studies by RT-PCR and in situ hybridization techniques. Neuropeptides 41:421–431
Lutter M, Nestler EJ (2009) Homeostatic and hedonic signals interact in the regulation of food intake. J Nutr 139:629–632
MacRae PG, Spirduso WW, Walters TJ, Farrar RP, Wilcox RE (1987) Endurance training effects on striatal D2 dopamine receptor binding and striatal dopamine metabolites in presenescent older rats. Psychopharmacology (Berlin) 92:236–240
Mansour A, Fox CA, Akil H, Watson SJ (1995) Opioid-receptor mRNA expression in the rat CNS: anatomical and functional implications. Trends Neurosci 18:22–29
Meeusen R, Piacentini MF, De Meirleir K (2001) Brain microdialysis in exercise research. Sports Med 31:965–983
Morgan WP (1997) Methodological considerations. In: Morgan WP (ed) Physical activity and mental health. Taylor & Francis, Washington, DC, pp 3–32
Nestler EJ, Carlezon WA Jr (2006) The mesolimbic dopamine reward circuit in depression. Biol Psychiatry 59:1151–1159
Nikolarakis K, Pfeiffer A, Stalla GK, Herz A (1987) The role of CRF in the release of ACTH by opiate agonists and antagonists in rats. Brain Res 421:373–376
Nybo L, Secher NH (2004) Cerebral perturbations provoked by prolonged exercise. Prog Neurobiol 72:223–261
Perrine SA, Sheikh IS, Nwaneshiudu CA, Schroeder JA, Unterwald EM (2008) Withdrawal from chronic administration of cocaine decreases delta opioid receptor signaling and increases anxiety- and depression-like behaviors in the rat. Neuropharmacology 54:355–364
Persson S, Jónsdóttir IH, Thorén P, Post C, Nyberg F, Hoffmann P (1993) Cerebrospinal fluid dynorphin-converting enzyme activity is increased by voluntary exercise in the spontaneously hypertensive rat. Life Sci 53:643–652
Persson AI, Naylor AS, Jonsdottir IH, Nyberg F, Eriksson PS, Thorlin T (2004) Differential regulation of hippocampal progenitor proliferation by opioid receptor antagonists in running and non-running spontaneously hypertensive rats. Eur J Neurosci 19:1847–1855
Pert CB, Bowie DL (1979) Behavioral manipulations of rats causes alterations in opiate receptor occupancy. In: Usdin E, Bunney WE, Kline NS (eds) Endorphins in mental health. Oxford University Press, New York, pp 93–104
Physical Activity Guidelines Advisory Committee (2008) Physical Activity Guidelines Advisory Committee Report, 2008. U.S. Department of Health and Human Services, Washington, DC, pp 1–683
Post RM, Ballenger JC (eds) (1984) Neurobiology of mood disorders. Williams and Wilkins, Baltimore, MD, pp 1–887

Risch SC, Pickar D (eds) (1983) Symposium on endorphins. Psychiatr Clin North Am 6: 363–521

Robbins TW, Everitt BJ (1996) Neurobehavioural mechanisms of reward and motivation. Curr Opin Neurobiol 6:228–236

Sforzo GA, Seeger TF, Pert CB, Pert A, Dotson CO (1986) In vivo opioid receptor occupation in the rat brain following exercise. Med Sci Sports Exerc 18:380–384

Shippenberg TS, Rea W (1997) Sensitization to the behavioral effects of cocaine: modulation by dynorphin and kappa-opioid receptor agonists. Pharmacol Biochem Behav 57:449–455

Smith KS, Berridge KC (2007) Opioid limbic circuit for reward: interaction between hedonic hotspots of nucleus accumbens and ventral pallidum. J Neurosci 27:1594–1605

Smith MA, Lyle MA (2006) Chronic exercise decreases sensitivity to mu opioids in female rats: correlation with exercise output. Pharmacol Biochem Behav 85:12–22

Stubbe JH, Boomsma DI, Vink JM, Cornes BK, Martin NG, Skytthe A, Kyvik KO, Rose RJ, Kujala UM, Kaprio J, Harris JR, Pedersen NL, Hunkin J, Spector TD, de Geus EJ (2006) Genetic influences on exercise participation in 37.051 twin pairs from seven countries. PLoS One 1:e22

Thoren P, Floras JS, Hoffmann P, Seals DR (1990) Endorphins and exercise: physiological mechanisms and clinical implications. Med Sci Sports Exerc 22:417–428

Torregrossa MM, Jutkiewicz EM, Mosberg HI, Balboni G, Watson SJ, Woods JH (2006) Peptidic delta opioid receptor agonists produce antidepressant-like effects in the forced swim test and regulate BDNF mRNA expression in rats. Brain Res 1069:172–181

van Praag H (2008) Neurogenesis and exercise: past and future directions. Neuromolecular Med 10:128–140

Wardlaw SL, Frantz AG (1980) Effect of swimming stress on brain β-endorphin and ACTS (abstract). Clin Res (Lond) 28:482

Waters RP, Renner KJ, Pringle RB, Summers CH, Britton SL, Koch LG, Swallow JG (2008) Selection for aerobic capacity affects corticosterone, monoamines and wheel-running activity. Physiol Behav 93:1044–1054

Werme M, Thorén P, Olson L, Brené S (2000) Running and cocaine both upregulate dynorphin mRNA in medial caudate putamen. Eur J Neurosci 12:2967–2974

Werme M, Messer C, Olson L, Gilden L, Thoren P, Nestler EJ, Brené S (2002) Delta FosB regulates wheel running. J Neurosci 22:8133–8138

Wise RA (2004) Dopamine, learning and motivation. Nat Rev Neurosci 5:483–494

Wise RA (2008) Dopamine and reward: the anhedonia hypothesis 30 years on. Neurotoxicol Res 14:169–183

Zangen A, Ikemoto S, Zadina J, Wise RA (2002) Rewarding and psychomotor stimulant effects of endomorphin-1: anteroposterior differences within the ventral tegmental area and lack of effect in nucleus accumbens. J Neurosci 22:7225–7233

Chapter 4
The Monoaminergic System in Animal Models of Exercise

Romain Meeusen and Vinciane Fontenelle

Abstract This chapter will deal with exercise and neurotransmitters. First, we will present studies that examined the exercise-induced effect on neurotransmitter concentrations; this is followed by studies that used microdialysis to measure the "in vivo" release of neurotransmitters during exercise. Acute exercise increases the release of neurotransmitters in the synaptic cleft, while exercise training will eventually lead to a receptor adaptation leading to lower baseline output.

4.1 Introduction

Healthy lifestyle factors are increasingly being recognized to play an important role in the maintenance of cognitive and brain function. Physical exercise is one of the simple but efficient means to maintain and improve neural function. Research into the physiological effects of exercise usually ends at the muscular or neuromuscular level even though it is apparent that there is also an influence on the central nervous system, since there is convincing evidence that several neuromodulators and neurotransmitters are involved in control of locomotion, and exercise plays an important role in cognition and neurogenesis (Freed and Yamamoto 1985; Gil et al. 1992; Hassler 1978; Jacobs 1991; Jacobs and Fornal 1993; Marsden 1982; Prakash et al. 2011; Wilckens et al. 1992). It is of interest to examine the effect of acute and chronic exercise on brain neurochemistry, since movement initiation and control of locomotion have been shown to be related to striatal neurotransmitter function, and exercise may also prove to be a tool in the prevention and treatment of neurological and mental disorders (see also Chaps. 1 and 2).

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Until very recently most experimental studies on brain chemistry were conducted with postmortem tissue. However, in part because of shortcomings with postmortem methods, and in part because of the desire to be able to directly relate neurochemistry to behavior, there has been considerable interest in the development of "in vivo" neurochemical methods. Because total tissue levels may easily mask small but important neurochemical changes related to activity, it is important to sample directly in the extracellular compartment of nervous tissue in living animals. Since the chemical interplay between cells occurs in the extracellular fluid, there is a need to access this compartment in intact brain of living and freely moving animals.

4.2 Exercise and Brain Neurotransmitter Concentrations

The first reports that examined the influence of exercise on brain neurotransmitters mostly used exercise as a stress model, or compared exercise with other stressors such as exposure to cold, foot shock, tail pinch, immobilization, or restraint (Meeusen and De Meirleir 1995). Other studies described the influence of exercise on brain monoamines as a possible intervention in affective disorders (Elam et al. 1987; Hoffmann et al. 1994) and depression (de Castro and Duncan 1985; Dey 1994; Dey et al. 1992). Most of these animal studies examined brain monoamine levels with acute and chronic exercise protocols to explore the effects of a physiological stimulus on brain neurotransmission.

4.3 Whole Brain Neurotransmitter Concentrations

Studies that examined whole brain noradrenaline (NA) concentration after acute bouts of exercise (running or swimming) mostly found a decrease (Barchas and Freedman 1963; Cicardo et al. 1986; Moore and Lariviere 1964), no effect (Moore 1968; Sheldon et al. 1975), or a small not significant increase in brain NA concentration (Acworth et al. 1986; de Castro and Duncan 1985). Whole brain NA concentrations increased after chronic exercise training (Acworth et al. 1986; Brown et al. 1979; Brown and Van Huss 1973; de Castro and Duncan 1985; Östman and Nyback 1976).

Beyond metabolic increase due to exercise (Chaouloff et al. 1987), whole brain dopamine (DA) concentration was increased in trained rats killed 48 h after an 8-week training period (de Castro and Duncan 1985). However, other studies (Acworth et al. 1986; Brown and Van Huss 1973) did not find any difference in whole brain DA concentrations. Whole brain serotonin (5-HT) and its metabolite 5-hydroxyindoleacetic acid (5-HIAA) were shown to increase following an acute bout of exercise (Acworth et al. 1986; Barchas and Freedman 1963; Romanowski and Grabiec 1974). However, in trained rats' brain 5-HT concentration is unaltered while 5-HIAA concentration increases.

It seems that measurements of the concentration of a neurotransmitter or its metabolite in postmortem tissue preparations are only estimates of what happens in the brain during exercise (Meeusen and De Meirleir 1995).

4.4 Neurotransmitters Concentrations in Specific Brain Regions

Later studies examined the effects of acute and chronic exercise on neurotransmitter concentrations in specific brain regions. These studies have found both increased and decreased concentrations and turnover of neurotransmitters and their metabolites, depending on the brain region of interest (Table 4.1).

In the striatum, 5-HT, 5-HIAA, NA, and DA concentrations increased after a training session, or after an acute bout of exercise in trained rats (Meeusen and De Meirleir 1995). NA concentrations decreased due to *acute exercise* in brain stem (Gordon et al. 1966; Heyes et al. 1985, 1988; Stone 1973), hippocampus (Rea and Hellhammer 1984), pons-medulla (Sudo 1983), midbrain (Sudo 1983), and hypothalamus (Heyes et al. 1988; Lukaszyk et al. 1983; Stone 1973; Sudo 1983), while hippocampal and midbrain 5-HT and 5-HIAA concentrations increased. The level of DA and its metabolites was found to increase in hypothalamus (Bailey et al. 1993; Brown et al. 1992; Chaouloff et al. 1987), midbrain (Bailey et al. 1992, 1993; Chaouloff et al. 1987), prefrontal cortex (Chaouloff et al. 1987), and hippocampus (Bailey et al. 1992; Chaouloff et al. 1987). Interestingly, hypothalamic NA levels increased in food-restricted rats (Rea and Hellhammer 1984). Studies that examined the effects of *exercise training* on NA levels in different brain regions found mostly an increase or no significant result (Blomstrand et al. 1989; Brown et al. 1979, 1992; Brown and Van Huss 1973).

From these studies one can only draw very general conclusions, but it seems that acute exercise results in a depletion of brain NA probably due to an acceleration in

Table 4.1 Acute exercise effects on monaminergic neurotransmitter concentrations in brain area's tissue preparations (postmortem). Some studies measured the neurotransmitters and/or their metabolites. These measurements can only give a general estimation of what happens in the brain during exercise

	Serotonin	Noradrenaline	Dopamine
Striatum	↑	↑	↑
Hippocampus	↑	↓	↑
Midbrain	↑		↑
Brainstem		↓	
Pons-medulla		↓	↑
Hypothalamus		↓	
Cortex		↑	
Pre-optic area		↑	
Prefrontal Cortex			↑

NA turnover by activating tyrosine hydroxylase activity (Chaouloff 1989), while chronic exercise has been found to elevate brain NA levels. These adaptations are region specific. The dopaminergic nerve terminals appear to play an important role in the regulation of locomotor activity (Boldry et al. 1991), and it seems that the influence of acute or chronic exercise is region specific. One must consider, however, that the so-called motor circuit containing neurons from the striatum, substantia nigra, cerebral cortex, and thalamus interact constantly through several transmitters and receptor types. It is difficult, if not impossible, to register this dynamic and constant interaction with brain homogenate preparations; furthermore, there is no uniformity in study designs, exercise protocols, brain regions of interest, and measuring methods (Meeusen and De Meirleir 1995).

Also, sample analysis could play a role. The first studies used fluorescence spectrometry to determine transmitter concentrations, while later studies used more sensitive methods such as high-performance liquid chromatography (HPLC), which allow measurement of multiple neurotransmitters and metabolites within the same sample (Meeusen and De Meirleir 1995). Most studies used different exercise triggers varying from forced locomotion on a treadmill, running wheel, spontaneous running, or swimming. Animals that were tested after a single exercise session ran at different speeds.

Determining neurotransmitter concentrations in homogenates makes no distinction between extracellular and intracellular concentrations, and gives no indication of neurotransmitter release, and the measurement of single neurotransmitter concentrations does not provide much information on the relationships between neurotransmitters.

To conclude, although it is difficult to compare the above mentioned studies, it seems that physical exercise influences the synthesis and metabolism of monoamines in various brain regions.

4.5 Measuring Neurotransmitter Release

The review of the literature demonstrates that serotonergic, noradrenergic, and dopaminergic neuronal systems are influenced in different ways during exercise. However, most of the studies we reviewed in the previous part were postmortem experiments which used indirect measurements such as the ratio neurotransmitter/metabolites, or the ratio precursor/neurotransmitter to predict neurotransmitter release during exercise. Changes in the brain content of monoamine transmitters with tissue assay are now regarded as a rather inaccurate method to estimate changes in the release rate of these transmitters. New techniques such as microdialysis and voltammetry were introduced to measure in vivo release of neurotransmitters. The voltammetry method is based on the application of a potential to an electrode in a conducting solution. The electrodes are implanted in the brain and an oxidation current is generated as molecules in the extracellular fluid are oxidized at the electrode surface (Meeusen et al. 2001). Microdialysis is a method to assess alterations in neurotransmitter release in

brain extracellular space. It can collect virtually any substance from the brains of freely moving animals with a limited amount of tissue trauma (Benveniste and Huttemeier 1990).

4.6 Advantages and Disadvantages of Microdialysis

The idea of using the principles of dialysis to sample extracellular fluid in the brain is 45 years old. Bito et al. (1966) implanted "dialysis sacs" into the subcutaneous tissue of the neck and into the parenchyma of the cerebral hemispheres of dogs. Later, Delgado et al. (1972) developed a "diatrode" which was very similar to the present microdialysis probes. The method has been continuously refined, and today it is used in a large variety of experiments for bioanalytical sampling of substances from the brain and other tissues.

The microdialysis technique employs the dialysis (from Greek: to separate) principle in which a membrane, permeable to water and small solutes, separates two fluid compartments (Fig. 4.1a, b).

The principle is based on the kinetic dialysis principle: the membrane is continuously flushed on one side with a solution that lacks the substances of interest, whereas the other side is in contact with the extracellular space. Provided that no osmolarity (pressure) and electrical potential differences exist across the membrane, solutes' transport between the two compartments is governed only by diffusion, i.e., concentration gradients causing diffusion of substances from the extracellular space into the dialysis probe (and vice versa).

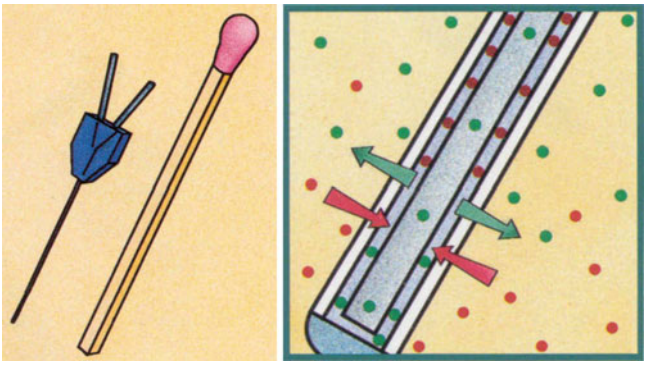

Fig. 4.1 The microdialysis probe is a small hollow needle that is implanted in the brain region of interest. At the tip of the probe there is a membrane that allows migration of molecules through a concentration gradient. The length of the probe and the speed of the perfusion fluid that flows through the probe are determinants for the recovery of neurotransmitters from the extracellular space

Table 4.2 Advantages and disadvantages of microdialysis

Features of microdialysis	
Advantages	Disadvantages
• Sample the extracellular fluid	• Only a small sample (e.g. 20–40 µl) is collected
• Sample almost every organ and tissue of the body	• Time resolution is usually between 5 and 20 min
• Sample intact tissue of living, awake and freely moving animals	• Membrane properties determine sampling efficiency
• Sample continuously	• Recovery depends on length of the dialysis membrane
• Reduce intersubject variation	• Recovery depends on flow of the perfusion fluid
• Recover and/or introduce endogenous and exogenous substances in the tissue	• Recovery depends on speed of diffusion through the extracellular fluid
• Collect a representative sample of all substances in the extracellular fluid	
• Samples are relatively clean and ready for analysis	
• Tissue damage is minimal	

4.6.1 Advantages

Microdialysis has several advantages (Table 4.2). It samples the extracellular fluid as distinct from the whole tissue collected by biopsies, punches, or dissections. It can be performed locally in almost every organ and tissue of the body in intact tissue of living, awake, and freely moving animals, distinguishing it from other preparations such as slices and synaptosomes. Microdialysis makes it possible to sample continuously for hours or days in a single animal, which, in addition to other advantages, decreases the number of animals needed in an experiment. Because the microdialysis probe may remain implanted in a single animal over a full experimental period, sampling via microdialysis can be used to reduce intersubject variation. This method can be used for recovering and/or introducing endogenous and exogenous substances in the tissue. Microdialysis collects a representative sample of all substances in the extracellular fluid (provided that they pass the membrane), and carries them out of the body for further analysis. The samples are relatively clean and ready for analysis, because large molecules (enzymes) do not pass the membrane due to its molecular cutoff weight. Several experimental studies (Benveniste et al. 1984; Tossman and Ungerstedt 1986; Westerink and De Vries 1988; Zetterstrom et al. 1982) have shown that the damage to the blood–brain barrier is minimal. The created tissue damage is negligible compared to other intracerebral sampling techniques, because there is no direct contact between the liquid flowing inside the membrane and the cell of the tissue.

4.6.2 Disadvantages

Of course, there are some concerns for the use of microdialysis. Since the sample volume collected during one experiment is depending on the duration of collection and the flow rate of the perfusion fluid, only a small sample (e.g. 20–40 μl) is collected. The sampling time is often determined by the detection limit of the compound (Westerink 1992). Because of this need for sufficient volume, the time resolution is usually between 5 and 20 min. This means that the amount of fluid recovered in one sample contains the amount of substances (transmitters) harvested during the total collection time. In case of behavioral studies, it is very important to register any disturbances that occur during the ongoing experiment in order to create a full picture of all the events (sometimes also unwanted effects such as disturbance of the animal) that occur during sampling.

Sampling efficiency depends on several factors such as membrane properties, perfusion flow rate, and possible interactions between the membrane and specific substances. Therefore, it is important to standardize probe implantation and to verify the recovery of the probe before implantation.

The *recovery* of the probe is the ratio between the concentration of a substance in the outflow solution and the concentration of the same solution outside the probe. Because the dialysis probe is continuously flushed, the concentrations of substances in the dialysate (outflow solution) are only reflections of the true extracellular fluid. The recovery of substances from the extracellular fluid depends on the length of the dialysis membrane, the flow of the perfusion fluid, the speed of diffusion of the substance through the extracellular fluid, and the properties of the membrane. For small molecules such as the monoamine transmitters, the limiting factor of recovery is usually the speed of diffusion through the extracellular fluid, not the diffusion through the membrane.

One of the great advantages of microdialysis is that experiments on awake animals are relatively easy. Working on awake animals implies, however, that the animals are susceptible to all kinds of influences ranging from conceivable pain of the implantation and restraint by tubing and wires to reactions in response to a new environment (Meeusen et al. 2001). When doing experiments on awake animals, it is of utmost importance to control the setup of the experiment. It is also important to consider the diurnal rhythm of the animals and therefore to perform the experiments during the same period of the day. In order to avoid that the trauma of probe implantation interferes with the results of the experiment, a guide cannula is implanted prior to probe implantation. The probe is inserted once the animal has recovered from surgery.

The composition of the perfusion fluid should be as close as possible to that of the extracellular fluid. The Ca^{2+} concentration of the perfusion fluid varies among studies from 1.2 to 3.4 mM. The basal output of neurotransmitters is strongly Ca^{2+} dependent and the neurotransmitter output is nearly linearly related to Ca^{2+} concentrations. As a sampling technique, microdialysis is not directly coupled to any particular method of chemical analysis, but in order to being able to analyze the sometimes very small

amounts of chemicals in the dialysate, it is necessary to have a sufficiently sensitive analytical method (Westerink 1992). Because blood cells, proteins, and other large molecules cannot enter the dialysate, the sample is automatically cleaned up and can be injected without further purification into the HPLC system.

In order to reliably interpret the results of behavioral studies, it becomes important to establish very stable baseline levels upon which the effects of experimental manipulations can be assessed. Which means that before starting the behavioral manipulation, one has to verify that the basic neurotransmitter output does not vary too much.

The extracellular space in the brain is large; of course, during sampling in a specific brain area one can only give an impression of the neurotransmitter variation in the region of interest in the vicinity of the probe.

4.7 Microdialysis and Exercise

A primary advantage of in vivo microdialysis is that it can be used to examine neurochemistry in behaving animals. Several kinds of behavior have been studied such as feeding and drinking (Bassareo and Di Chiara 1999; Kurose and Terashima 1999; Rada et al. 2000; Voigt et al. 2000), orientation to sensory stimuli (Paredes et al. 1999), and locomotion (De Parada et al. 2000; Di Chiara et al. 1994; Takahashi et al. 2000); also, animal models of depression, anxiety, and stress are frequently used. Ideally, samples of extracellular fluid should be collected without any disruption in behavior. Similarly, behavior should not disrupt the collection of samples. In contrast to pharmacological manipulation (which mostly create huge increases in extracellular neurotransmitter concentrations), behavioral studies sometimes only create small disturbances of transmission.

4.8 Exercise and Neurotransmitter Release

Several studies explored the effect of exercise on neurotransmission. The first studies examined walking and running on a treadmill, measuring neurotransmitters and their metabolites. Mild exercise (treadmill speed ca. 5–15 m/min) increases extracellular levels of neurotransmitters in different brain areas (Bland et al. 1999; Kurosawa et al. 1993; McCullough and Salamone 1992; Sabol et al. 1990). It has been shown that extracellular acetylcholine (Ach), regardless of the brain area sampled, responds by an increased output even when the rat initiates locomotor output (Westerink 1995). It seems that running intensity and running duration will influence neurotransmitter release. We collected extracellular concentrations of DA from the striatum of male albino Wistar rats. One of the following protocols was used: running at 12 m/min during 20 min, running at 12 m/min during 60 min, running at 26 m/min during 20 min, and running at 26 m/min during 60 min. In all groups

extracellular DA levels significantly increased during and following exercise. With an exercise duration of 60 min extracellular DA levels stayed significantly elevated until the end of the experiment in both groups (128.3% low speed; 153.3% high speed). Although the 20 min duration groups showed no significant difference between high and low speed, extracellular DA levels rose faster and stayed relatively higher in the high speed group. Our results demonstrated that extracellular DA levels are more likely to be linked to the exercise duration than to exercise speed and that the perturbation of extracellular DA levels lasts for a longer time period when exercise duration is longer (Meeusen et al. 2003). Also for other transmitters, treadmill running increases extracellular 5-HT levels in the hippocampus or NA in the cortex (Meeusen et al. 1996; Pagliari and Peyrin 1995a, b; Wilson and Marsden 1996). Pagliari and Peyrin (1995a, b) examined the effect of exercise on the in vivo cerebral release and turnover in trained rats running on a treadmill for 60 min. The authors used a chronic probe implantation in the frontal cortex. NA turnover and release increased during exercise and even further increased when exercise time was prolonged to 2 h of running. In their second study, rats were trained during 2 weeks to run on a treadmill. Prior physical conditioning greatly influenced central NA response: 1 h trained rats experienced 2 h running as extremely stressful, creating a high NA release of short duration, whereas the 2 h trained animals exhibited a progressive sustained NA efflux (Pagliari and Peyrin 1995b).

4.9 Neurotransmitter Manipulation, Exercise, and Microdialysis

Precursor manipulation or influencing brain neurotransmitter levels by pharmacological manipulation shows that there is a clear interaction between the periphery (precursors, hormonal output) and brain neurotransmitter levels (Piacentini et al. 2003a, b). We examined whether exercise-elicited increases in brain tryptophan (TRP) availability (and in turn 5-HT synthesis) alters 5-HT release in the hippocampus of food-deprived rats (Meeusen et al. 1996). To this end, we compared the respective effects of acute exercise, administration of TRP, and the combination of both treatments, upon extracellular 5-HT and 5-HIAA levels in 24 h food-deprived rats. Acute exercise increased, in a time-dependent manner, extracellular 5-HT levels, these levels returning to baseline within the first hour of the recovery period. Acute administration of a tTRP dose (L-TRP, 50 mg/kg i.p.) that increased extracellular 5-HIAA (but not 5-HT) levels in fed rats increased within 60 min extracellular 5-HT and 5-HIAA levels in food-deprived rats. Whereas 5-HT levels returned toward their baseline levels within the 160 min that followed TRP administration, extracellular 5-HIAA levels rose throughout the experiment. Lastly, treatment with TRP (60 min beforehand) before acute exercise led to marked increases in extracellular 5-HT (and 5-HIAA levels) throughout the 240 min that followed TRP administration (Meeusen et al. 1996). This study indicates that exercise stimulates 5-HT release in the hippocampus of fasted rats, and that a pretreatment with TRP (at a

dose increasing extracellular 5-HT levels) amplifies exercise-induced 5-HT release. It should be noted that in this study none of the animals showed any sign of fatigue during the exercise session, although extracellular 5-HT levels increased markedly, especially in the L-TRP and exercise trial. Furthermore, since it was shown that during exercise 5-HT, DA, NA, and glutamate (GLU) release increases in striatum (Meeusen et al. 1994, 1997), as well as 5-HT release increases in hippocampus (Bland et al. 1999) without affecting running capacity of the animals, the direct relationship between increased 5-HT release and fatigue could not be established.

4.10 Microdialysis, Exercise and Animal Models of Neurological Disorders

Several authors used an animal model of a neurological disorder to examine the effect of exercise on the release of neurotransmitters. Hattori et al. (1993) combined microdialysis with running in order to evaluate motor deficit and improvement following dopaminergic grafts in 6-hydroxydopamine (6-OHDA) lesioned rats. DA and its metabolites significantly increased during the treadmill exercise in their control animals. In another study (Castaneda et al. 1990a, b) the "walking" behavior in animals that were 6-OHDA depleted as neonates was examined (walking speed: 3 m/min). There was no significant change in extracellular DA compared to baseline during treadmill walking in 6-OHDA control animals. It seems that as if there is a threshold speed (between 3 and 6.6 m/min) above which striatal DA release increases. Once above this (low) speed it seems that extracellular DA increases during and about 40–60 min following treadmill exercise (Hattori et al. 1994). Bland et al. (1999) implanted bilateral probes in the forelimb sensorimotor cortex. One forelimb was immobilized by means of a plaster cast. GLU, aspartate, serine, and taurine levels were quantified. In casted animals, dialysate GLU levels were lower on the side contralateral to the immobilized limb during both quiescence and movement stress. Aspartate and taurine, but not serine levels, increased during movement stress in both the side contralateral and the side ipsilateral to the immobilized limb. These results suggest that there is extracellular overflow of GLU and other neuroactive amino acids during spontaneous movement, and chronic disuse can suppress extracellular GLU levels (Bland et al. 1999). To investigate the effects of exercise on spinal cord 5-HT, Gerin et al. (1994) used an interesting approach by chronically implanting a microdialysis probe in the ventral horn of the lumbar spinal cord of rats. The probe was kept in place during 40 days. In the ventral horn, extracellular release of 5-HT did not increase during 60 min of exercise. In a follow-up study, the dialysis probes were chronically implanted in the ventral funiculus of the spinal cord and significant increases of 5-HT, DA, and their metabolites (5-HIAA, MHPG) during locomotion were found (Gerin et al. 1995). In order to define precisely the relation between descending monoaminergic systems and the motor system, the same authors (Gerin and Privat 1998) measured the variations of extracellular concentrations of 5-HT, 5-HIAA, DA, and MHPG in the ventral horn of spinal cord of

adult rats. Measurements were performed with microdialysis probes implanted permanently for 45 days during rest, endurance running on a treadmill, and a postexercise period. They found a slight decrease in both 5-HT and 5-HIAA during locomotion with a more marked decrease during the postexercise period compared to the mean of rest values. In contrast, the concentration of DA and MHPG increased slightly during the exercise and decreased thereafter. These results, when compared with those of a previous study (Gerin et al. 1995), which measured monoamines in the spinal cord white matter, highlight the complex regulation of the release of monoamines that occurs in the ventral horn. Recently, they examined if endogenous 5-HT release is involved in the recovery of motor function after spinal cord injury (Gerin et al. 2010). A microdialysis probe was implanted in the ventral horn of rats where the spinal cord was partially lesioned (subhemi-lesioned). Concentrations of 5-HT in the lumbar ventral horn were measured during periods of rest (90 min), treadmill run (60 min), and postexercise rest (90 min) for a 1-month time period of recovery following the surgical lesion. Within the same period of time, 5-HT levels varied significantly. A significant (202%) increase was observed at day 18 postlesion relative to day 8, and a 16.4% decrease was observed at day 34 relative to day 18. Treadmill exercise challenge induced a 10% decrease of 5-HT release relative to rest at days 18 and 34. They concluded that the changes in serotonergic system occurred within the same time frame than locomotor recovery using treadmill challenge (Gerin et al. 2010).

Several models of ischemia have been used: (Jia et al. 2009) evaluated the effects of pre-ischemic treadmill training on the release of GLU and GABA from the striatum in a rat middle cerebral artery occlusion (MCAO) model. Microdialysis was used to collect dialysates from the striatum immediately before ischemia, and at 40, 80, and 120 min after ischemia, as well as at 40, 80, 120, 160, 200, and 240 min after reperfusion. Pre-ischemic treadmill training decreased glutamate release and increased GABA release during the acute phase of cerebral ischemia/reperfusion. Treadmill training for at least 2 weeks produced statistically significant changes in GABA/glutamate release. This study suggests that treadmill training inhibits the excessive release of glutamate, by stimulating GABA release during the acute phase of cerebral ischemia. This may be one of the important mechanisms to protect the striatal neurons from ischemic damage (Jia et al. 2009).

Treadmill exercise and neuromuscular electrical stimulation are common clinical approaches for stroke rehabilitation. Both animal and clinical studies have shown the functional improvements after these interventions. However, the neurochemical effects on the ischemic brain had not been well studied. Leung et al. (2006) used treadmill exercise and neuromuscular electrical stimulation (NMES), during a 2-week training, to study the levels of aspartate, GLU, taurine, and GABA in the hippocampus following transient focal cerebral ischemia. Microdialysis technique was used to collect dialysates from ipsilesional hippocampus in vivo. It was found that the GLU level was increased significantly during treadmill exercise and then returned to baseline level. Both interventions did not trigger significant effects on aspartate and GLU basal levels during the 2 weeks. GABA and aspartate levels did not show significant changes over the 2 weeks in all groups. These results provide

insights to explain the neurochemical effects on the ischemic injured brain during the course of rehabilitation (Leung et al. 2006).

4.11 Microdialysis, Exercise Training and Thermoregulation

The therapeutic effects of exercise are also translated into a chronic exercise regimen. Many patients perform exercises during several weekly sessions. To examine the effect of training (chronic exercise), we registered extracellular levels of neurotransmitters in the striatum of trained and untrained rats (Meeusen et al. 1997). We further evaluated the influence of 1 h of exercise on striatal release of DA, NA, GLU, and GABA in trained and untrained rats. Male Wistar were randomly assigned to a training or control group. The exercise training consisted of running on a treadmill for 6 weeks, 5 days/week; running time and speed gradually increased from 30 min at 19 m/min during the first week to 80 min at 26 m/min during the final training week. Control animals were placed on the treadmill twice a week, and received a total of four "adaptation sessions" in which they exercised 15–45 min at 26 m/min. The remarkable result of this study was that basal concentrations of DA, NA, and GLU were significantly lower for the trained compared to control animals. Sixty minutes of exercise significantly increased extracellular DA, NA, and GLU levels in both control and trained animals. There was no statistical significant difference in the exercise-induced increase between trained and control animals (Meeusen et al. 1997). The results indicate that exercise training appears to result in diminished basal activity of striatal neurotransmitters, while maintaining the necessary sensitivity for responses to acute exercise.

Hasegawa et al. (2000) examined the role of monoamines and amino acids in thermoregulation. They measured their concentrations in the preoptic area and anterior hypothalamus (PO/AH) in exercising rats, using an in vivo microdialysis technique. The data indicate that dopamine breakdown processes in the PO/AH are activated during exercise. DA in the PO/AH may be involved in the heat loss mechanisms for thermoregulation when body temperature rises during exercise (Hasegawa et al. 2000). In a follow-up study, we perfused tetrodotoxin (TTX) solution into the PO/AH to investigate whether this manipulation can modify thermoregulation in exercising rats. Body core temperature (Tb), heart rate (HR), and tail skin temperature (Ttail) were measured. Rats ran for 120 min at speed of 10 m/min, with TTX perfused into the left PO/AH during the last 60 min of exercise through a microdialysis probe. Tb, HR, and Ttail increased during the first 20 min of exercise. Thereafter, Tb, HR, and Ttail were stable in both groups. Perfusion of TTX into the PO/AH evoked an additional rise in Tb, with a significant decrease in Ttail, and a significant increase in HR. These results suggest that the TTX-induced hyperthermia was the result of both an impairment of heat loss and an elevation of heat production during exercise. We therefore propose the PO/AH as an important thermoregulatory site in the brain during exercise (Hasegawa et al. 2005). In the next study, we examined which neurotransmitter systems play an important role in thermoregulation during exercise.

We implanted microdialysis probes in the PO/AH, and injected a dual DA/NA reuptake inhibitor (bupropion). We examined exercise performance, thermoregulation, and neurotransmitters in the preoptic area and anterior hypothalamus (PO/AH) of the rat during exercise in the heat. Running time to exhaustion was significantly influenced by the ambient temperature, and it was increased by bupropion in the heat. Core temperature (Tcore) and brain temperature (Tbrain) at exhaustion were significantly higher in the bupropion group compared to the cool and hot groups, respectively. Tail temperature (Ttail) measured at exhaustion was not significantly different between the two hot conditions. Extracellular concentrations of DA and NA in the PO/AH increased during exercise, and was significantly higher in the bupropion than in cool and hot groups. No differences were observed between groups for 5-HT levels. These results suggest that DA and NA in the PO/AH might be responsible for the increase in exercise performance and Tcore and Tbrain in the bupropion group in hyperthermia. Moreover, these results support previous findings in humans (Roelands et al. 2008; Watson et al. 2005) that acute bupropion ingestion increases Tcore during exercise in the heat, indicating the possibility of an important role for DA and NA in thermoregulation (Hasegawa 2008). Finally, we tried to examine the role of 5-HT in the PO/AH during exercise in the heat. Rats were made to run for 120 min on a treadmill at the ambient temperature of 30°C. Both Tcore and Ttail increased during the first 20 min of exercise and remained stable until the end of the exercise period. Low intensity exercise did not induce any changes in 5-HT release in the PO/AH, although the levels of NA and DA were increased. Moreover, increased extracellular 5-HT by local perfusion of 1 mM citalopram (selective 5-HT reuptake inhibitor; SSRI) in the PO/AH had no effect on the thermoregulatory response during acute low intensity exercise in a warm environment. These results suggest that enhanced release of only 5-HT in the PO/AH may not intervene thermoregulation during exercise in a warm environment (Takatsu et al. 2010).

As it has been shown that exercise and training influence neurotransmitter release in various brain regions, it seems important to further link these findings with peripheral measures. Exercise training appears to result in diminished basal activity of striatal neurotransmitters, while maintaining the necessary sensitivity for responses to acute exercise. These observations raise the possibility that there could exist an exercise-induced change in receptor sensitivity. A possible dysregulation at this level could play a key role in the maladaptation to the "stress" of exercise, training and overtraining, which should also be explored in the near future (see also Chaps. 8 and 22).

4.12 Conclusions

Neurotransmitters and neuromodulators play an important role in brain homeostasis. Changes in the concentrations of these substances reflect the dynamic interaction that happens in the brain during behavior. Exercise is a powerful tool to disturb homeostasis and is often used as the primary intervention in neurological and other

disorders. Measuring the concentrations of the neurotransmitters during ongoing behavior can give us an insight on what really happens in the brain during exercise. Microdialysis is an elegant method to measure the release of neurotransmitters during exercise. It can be used in alive and freely moving animals during ongoing behavior. There have been several studies using this method to explain mechanisms, and link neurotransmitters to pathology and rehabilitation. New imaging methods such as fMRI and PET are emerging that can be used in animals and humans, but the microdialysis technique has its place in brain research, being a tool that is valuable for measuring the release of neurotransmitters during ongoing behavior especially during exercise.

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References

Acworth I, Nicholass J, Morgan B, Newsholme EA (1986) Effect of sustained exercise on concentrations of plasma aromatic and branched-chain amino acids and brain amines. Biochem Biophys Res Commun 137:149–153

Bailey SP, Davis JM, Ahlborn EN (1992) Effect of increased brain serotonergic activity on endurance performance in the rat. Acta Physiol Scand 145:75–76

Bailey SP, Davis JM, Ahlborn EN (1993) Neuroendocrine and substrate responses to altered brain 5-HT activity during prolonged exercise to fatigue. J Appl Physiol 74:3006–3012

Barchas JD, Freedman DX (1963) Brain amines: response to physiological stress. Biochem Pharmacol 12:1232–1235

Bassareo V, Di Chiara G (1999) Differential responsiveness of dopamine transmission to food-stimuli in nucleus accumbens shell/core compartments. Neuroscience 89(3):637–641

Benveniste H, Huttemeier PC (1990) Microdialysis – theory and application. Prog Neurobiol 35:195–215

Benveniste H, Drejer J, Schousboe A, Diemer NH (1984) Elevation of the extracellular concentrations of glutamate and aspartate in rat hippocampus during transient cerebral ischemia monitored by intracerebral microdialysis. J Neurochem 43:1369–1374

Bito L, Davson H, Levin E, Murray M, Snider N (1966) The concentrations of free amino acids and other electrolytes in cerebrospinal fluid, in vivo dialysate of brain, and blood plasma of the dog. J Neurochem 13:1057–1067

Bland ST, Gonzales RA, Schallert T (1999) Movement-related glutamate levels in rat hippocampus, striatum, and sensorimotor cortex. Neurosci Lett 277:119–122

Blomstrand E, Perrett D, Parry-Billings M, Newsholme EA (1989) Effect of sustained exercise on plasma amino acid concentrations and on 5-hydroxytryptamine metabolism in six different brain regions in the rat. Acta Physiol Scand 136:473–481

Boldry RC, Willins DL, Wallace LJ, Uretsky NJ (1991) The role of endogenous dopamine in the hypermotility response to intra-accumbens AMPA. Brain Res 559:100–108

Brown BS, Van Huss W (1973) Exercise and rat brain catecholamines. J Appl Physiol 34:664–669

Brown BS, Payne T, Kim C, Moore G, Krebs P, Martin W (1979) Chronic response of rat brain norepinephrine and serotonin levels to endurance training. J Appl Physiol 46:19–23

Brown B, Piper E, Riggs C, Gormann D, Garzo E, Dykes D (1992) Acute and chronic effects of aerobic and anaerobic training upon brain neurotransmitters and cytochrome oxydase activity in muscle. Intern J Sports Med 13:92–93

Castaneda E, Whishaw IQ, Lermer L, Robinson TE (1990a) Dopamine depletion in neonatal rats: effects on behavior and striatal dopamine release assessed by intracerebral microdialysis during adulthood. Brain Res 508:30–39

Castaneda E, Whishaw IQ, Robinson TE (1990b) Changes in striatal dopamine neurotransmission assessed with microdialysis following recovery from a bilateral 6-OHDA lesion: variation as a function of lesion size. J Neurosci 10:1847–1854

Chaouloff F (1989) Physical exercise and brain monoamines: a review. Acta Physiol Scand 137:1–13

Chaouloff F, Laude D, Merino D, Serrurrier B, Guezennec Y, Elghozi JL (1987) Amphetamine and alpha-methyl-p-tyrosine affect the exercise-induced imbalance between the availability of tryptophan and synthesis of serotonin in the brain of the rat. Neuropharmacology 26:1099–1106

Cicardo VH, Carbone SE, de Rondina DC, Mastronardi IO (1986) Stress by forced swimming in the rat: effects of mianserin and moclobemide on GABAergic-monoaminergic systems in the brain. Comp Biochem Physiol C 83:133–135

de Castro JM, Duncan G (1985) Operantly conditioned running: effects on brain catecholamine concentrations and receptor densities in the rat. Pharmacol Biochem Behav 23:495–500

De Parada MP, Parada MA, Rada P, Hernandez L, Hoebel BG (2000) Dopamine-acetylcholine interaction in the rat lateral hypothalamus in the control of locomotion. Pharmacol Biochem Behav 66:227–234

Delgado JM, DeFeudis FV, Roth RH, Ryugo DK, Mitruka BM (1972) Dialytrode for long term intracerebral perfusion in awake monkeys. Arch Int Pharmacodyn Ther 198:9–21

Dey S (1994) Physical exercise as a novel antidepressant agent: possible role of serotonin receptor subtypes. Physiol Behav 55:323–329

Dey S, Singh RH, Dey PK (1992) Exercise training: significance of regional alterations in serotonin metabolism of rat brain in relation to antidepressant effect of exercise. Physiol Behav 52:1095–1099

Di Chiara G, Morelli M, Consolo S (1994) Modulatory functions of neurotransmitters in the striatum: ACh/dopamine/NMDA interactions. Trends Neurosci 17:228–233

Elam M, Svensson TH, Thoren P (1987) Brain monoamine metabolism is altered in rats following spontaneous, long-distance running. Acta Physiol Scand 130:313–316

Freed CR, Yamamoto BK (1985) Regional brain dopamine metabolism: a marker for the speed, direction, and posture of moving animals. Science 229:62–65

Gerin C, Privat A (1998) Direct evidence for the link between monoaminergic descending pathways and motor activity: II. A study with microdialysis probes implanted in the ventral horn of the spinal cord. Brain Res 794:169–173

Gerin C, Legrand A, Privat A (1994) Study of 5-HT release with a chronically implanted microdialysis probe in the ventral horn of the spinal cord of unrestrained rats during exercise on a treadmill. J Neurosci Methods 52:129–141

Gerin C, Becquet D, Privat A (1995) Direct evidence for the link between monoaminergic descending pathways and motor activity. I. A study with microdialysis probes implanted in the ventral funiculus of the spinal cord. Brain Res 704:191–201

Gerin CG, Hill A, Hill S, Smith K, Privat A (2010) Serotonin release variations during recovery of motor function after a spinal cord injury in rats. Synapse 64:855–861

Gil M, Marti J, Armario A (1992) Inhibition of catecholamine synthesis depresses behavior of rats in the holeboard and forced swim tests: influence of previous chronic stress. Pharmacol Biochem Behav 43:597–601

Gordon R, Spector S, Sjoerdsma A, Udenfriend S (1966) Increased synthesis of norepinephrine and epinephrine in the intact rat during exercise and exposure to cold. J Pharmacol Exp Ther 153:440–447

Hasegawa H (2008) Effect of a dopamine/noradrenaline reuptake inhibitor on exercise performance and thermoregulation of the rat in a warm environment. J Physiol 586:141–149

Hasegawa H, Yazawa T, Yasumatsu M, Otokawa M, Aihara Y (2000) Alteration in dopamine metabolism in the thermoregulatory center of exercising rats. Neurosci Lett 289:161–164

Hasegawa H, Ishiwata T, Saito T, Yazawa T, Aihara Y, Meeusen R (2005) Inhibition of the preoptic area and anterior hypothalamus by tetrodotoxin alters thermoregulatory functions in exercising rats. J Appl Physiol 98:1458–1462

Hassler R (1978) Striatal control of locomotion, intentional actions and of integrating and perceptive activity. J Neurol Sci 36:187–224

Hattori S, Li Q, Matsui N, Nishino H (1993) Treadmill running combined with microdialysis can evaluate motor deficit and improvement following dopaminergic grafts in 6-OHDA lesioned rats. Res Neurol Neurosci 6:65–72

Hattori S, Naoi M, Nishino H (1994) Striatal dopamine turnover during treadmill running in the rat: relation to the speed of running. Brain Res Bull 35:41–49

Heyes MP, Garnett ES, Coates G (1985) Central dopaminergic activity influences rats ability to exercise. Life Sci 36:671–677

Heyes MP, Garnett ES, Coates G (1988) Nigrostriatal dopaminergic activity is increased during exhaustive exercise stress in rats. Life Sci 42:1537–1542

Hoffmann P, Elam M, Thoren P, Hjorth S (1994) Effects of long-lasting voluntary running on the cerebral levels of dopamine, serotonin and their metabolites in the spontaneously hypertensive rat. Life Sci 54:855–861

Jacobs BL (1991) Serotonin and behavior: emphasis on motor control. J Clin Psychiatry 52(Suppl):17–23

Jacobs BL, Fornal CA (1993) 5-HT and motor control: a hypothesis. Trends Neurosci 16:346–352

Jia J, Hu YS, Wu Y, Liu G, Yu HX, Zheng QP, Zhu DN, Xia CM, Cao ZJ (2009) Pre-ischemic treadmill training affects glutamate and gamma aminobutyric acid levels in the striatal dialysate of a rat model of cerebral ischemia. Life Sci 84:505–511

Kurosawa M, Okada K, Sato A, Uchida S (1993) Extracellular release of acetylcholine, noradrenaline and serotonin increases in the cerebral cortex during walking in conscious rats. Neurosci Lett 161:73–76

Kurose Y, Terashima Y (1999) Histamine regulates food intake through modulating noradrenaline release in the para-ventricular nucleus. Brain Res 828:115–118

Leung LY, Tong KY, Zhang SM, Zeng XH, Zhang KP, Zheng XX (2006) Neurochemical effects of exercise and neuromuscular electrical stimulation on brain after stroke: a microdialysis study using rat model. Neurosci Lett 397:135–139

Lukaszyk A, Buczko W, Wisniewski K (1983) The effect of strenuous exercise on the reactivity of the central dopaminergic system in the rat. Pol J Pharmacol Pharm 35:29–36

Marsden CD (1982) The mysterious motor function of the basal ganglia: the Robert Wartenberg Lecture. Neurology 32:514–539

McCullough LD, Salamone JD (1992) Involvement of nucleus accumbens dopamine in the motor activity induced by periodic food presentation: a microdialysis and behavioral study. Brain Res 592:29–36

Meeusen R, De Meirleir K (1995) Exercise and brain neurotransmission. Sports Med 20:160–188

Meeusen R, Sarre S, Michotte Y, Ebinger G, De Meirleir K (1994) The effects of exercise on neurotransmission in rat striatum, a microdialysis study. In: Louilot A, Durkin T, Spampinato U, Cador M (eds) Monitoring molecules in neuroscience. University of Bordeaux, Talence, pp 181–182

Meeusen R, Thorre K, Chaouloff F, Sarre S, De Meirleir K, Ebinger G, Michotte Y (1996) Effects of tryptophan and/or acute running on extracellular 5-HT and 5-HIAA levels in the hippocampus of food-deprived rats. Brain Res 740:245–252

Meeusen R, Smolders I, Sarre S, de Meirleir K, Keizer H, Serneels M, Ebinger G, Michotte Y (1997) Endurance training effects on neurotransmitter release in rat striatum: an in vivo microdialysis study. Acta Physiol Scand 159:335–341

Meeusen R, Piacentini MF, De Meirleir K (2001) Brain microdialysis in exercise research. Sports Med 31:965–983

Meeusen R, Sarre S, De Meirleir K, Ebinger G, Michotte Y (2003) The effects of running speed and running duration on extracellular dopamine levels in rat striatum, measured with microdialysis. Medicina Sportiva 7:29–36

Moore KE (1968) Development of tolerance to the behavioral depressant effects of alpha-methyltyrosine. J Pharm Pharmacol 20:805–807
Moore KE, Lariviere EW (1964) Effects of stress and D-amphetamine on rat brain catecholamines. Biochem Pharmacol 13:1098–1100
Östman I, Nyback H (1976) Adaptive changes in central and peripheral noradrenergic neurons in rats following chronic exercise. Neuroscience 1:41–47
Pagliari R, Peyrin L (1995a) Norepinephrine release in the rat frontal cortex under treadmill exercise: a study with microdialysis. J Appl Physiol 78:2121–2130
Pagliari R, Peyrin L (1995b) Physical conditioning in rats influences the central and peripheral catecholamine responses to sustained exercise. Eur J Appl Physiol Occup Physiol 71:41–52
Paredes D, Rada P, Bonilla E, Gonzalez LE, Parada M, Hernandez L (1999) Melatonin acts on the nucleus accumbens to increase acetylcholine release and modify the motor activity pattern of rats. Brain Res 850:14–20
Piacentini MF, Clinckers R, Meeusen R, Sarre S, Ebinger G, Michotte Y (2003a) Effect of bupropion on hippocampal neurotransmitters and on peripheral hormonal concentrations in the rat. J Appl Physiol 95:652–656
Piacentini MF, Clinckers R, Meeusen R, Sarre S, Ebinger G, Michotte Y (2003b) Effects of venlafaxine on extracellular 5-HT, dopamine and noradrenaline in the hippocampus and on peripheral hormone concentrations in the rat in vivo. Life Sci 73:2433–2442
Prakash RS, Voss MW, Erickson KI, Lewis JM, Chaddock L, Malkowski E, Alves H, Kim J, Szabo A, White SM, Wojcicki TR, Klamm EL, McAuley E, Kramer AF (2011) Cardiorespiratory fitness and attentional control in the aging brain. Front Hum Neurosci 4:229
Rada PV, Mark GP, Yeomans JJ, Hoebel BG (2000) Acetylcholine release in ventral tegmental area by hypothalamic self-stimulation, eating, and drinking. Pharmacol Biochem Behav 65:375–379
Rea MA, Hellhammer DH (1984) Activity wheel stress: changes in brain norepinephrine turnover and the occurrence of gastric lesions. Psychother Psychosom 42:218–223
Roelands B, Hasegawa H, Watson P, Piacentini MF, Buyse L, De Schutter G, Meeusen RR (2008) The effects of acute dopamine reuptake inhibition on performance. Med Sci Sports Exerc 40:879–885
Romanowski W, Grabiec S (1974) The role of serotonin in the mechanism of central fatigue. Acta Physiol Pol 25:127–134
Sabol KE, Richards JB, Freed CR (1990) In vivo dialysis measurements of dopamine and DOPAC in rats trained to turn on a circular treadmill. Pharmacol Biochem Behav 36:21–28
Sheldon MI, Sorscher S, Smith CB (1975) A comparison of the effects of morphine and forced running upon the incorporation of 14-C-tyrosine into 14-C-catecholamines in mouse brain, heart and spleen. J Pharmacol Exp Ther 193:564–575
Stone EA (1973) Accumulation and metabolism of norepinephrine in rat hypothalamus after exhaustive stress. J Neurochem 21:589–601
Sudo A (1983) Time course of the changes of catecholamine levels in rat brain during swimming stress. Brain Res 276:372–374
Takahashi H, Takada Y, Nagai N, Urano T, Takada A (2000) Serotonergic neurons projecting to hippocampus activate locomotion. Brain Res 869:194–202
Takatsu S, Ishiwata T, Meeusen R, Sarre S, Hasegawa H (2010) Serotonin release in the preoptic area and anterior hypothalamus is not involved in thermoregulation during low-intensity exercise in a warm environment. Neurosci Lett 482:7–11
Tossman U, Ungerstedt U (1986) Microdialysis in the study of extracellular levels of amino acids in the rat brain. Acta Physiol Scand 128:9–14
Voigt JP, Kienzle F, Sohr R, Rex A, Fink H (2000) Feeding and 8-OH-DPAT-related release of serotonin in the rat lateral hypothalamus. Pharmacol Biochem Behav 65:183–189
Watson P, Hasegawa H, Roelands B, Piacentini MF, Looverie R, Meeusen R (2005) Acute dopamine/noradrenaline reuptake inhibition enhances human exercise performance in warm, but not temperate conditions. J Physiol 565:873–883
Westerink BHC (1992) Monitoring molecules in the conscious brain by microdialysis. Trends Anal Chem 11:176–182

Westerink BHC (1995) Brain microdialysis and its application for the study of animal behaviour. Behav Brain Res 70:103–124

Westerink BHC, De Vries JB (1988) Characterization of in vivo dopamine release as determined by brain microdialysis after acute and subchronic implantations: methodological aspects. J Neurochem 51:683–687

Wilckens T, Schweiger U, Pirke KM (1992) Activation of 5-HT1C-receptors suppresses excessive wheel running induced by semi-starvation in the rat. Psychopharmacology (Berl) 109:77–84

Wilson WM, Marsden CA (1996) In vivo measurement of extracellular serotonin in the ventral hippocampus during treadmill running. Behav Pharmacol 7:101–104

Zetterstrom T, Vernet L, Ungerstedt U, Tossman U, Jonzon B, Fredholm BB (1982) Purine levels in the intact rat brain. Studies with an implanted perfused hollow fibre. Neurosci Lett 29:111–115

Part II
Methods for Human Neuroimaging in Exercise and Sport Sciences: Theoretical Background and Practical Aspects

Chapter 5
Methods for Measurement of Physical Fitness and Training Recommendations in Studies on Humans

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Abstract This chapter addresses methods for testing endurance and strength performance capacity. Following a short discussion about the physiological aspects of endurance and strength demands, contraindications for participating in physical fitness testing are presented. This is followed by examples of specific methods for measuring these states of fitness. Subsequently, how training recommendations can be derived from the respective test results and transferred into experimental protocols focusing on the effects of exercise on brain function is described.

5.1 Introduction

Physical fitness can be defined as readiness to perform a specific motor task (Hollmann and Strüder 2009). Therefore, differentiation must occur between motor system demands whereby specific methods for measurement and specific training stimuli are needed to address these components of physical fitness. Five principal forms of motor system demands can be distinguished under physiological aspects. These are endurance, coordination, strength, speed and flexibility, with each demand also having several subcategories (Hollmann 1967; Fig. 5.1). Naturally, interactions exist between these physical demands. According to the focus of this book, this chapter will concentrate on endurance and strength exercise and provide information on physiological aspects, specific methods for fitness measurement and training recommendations.

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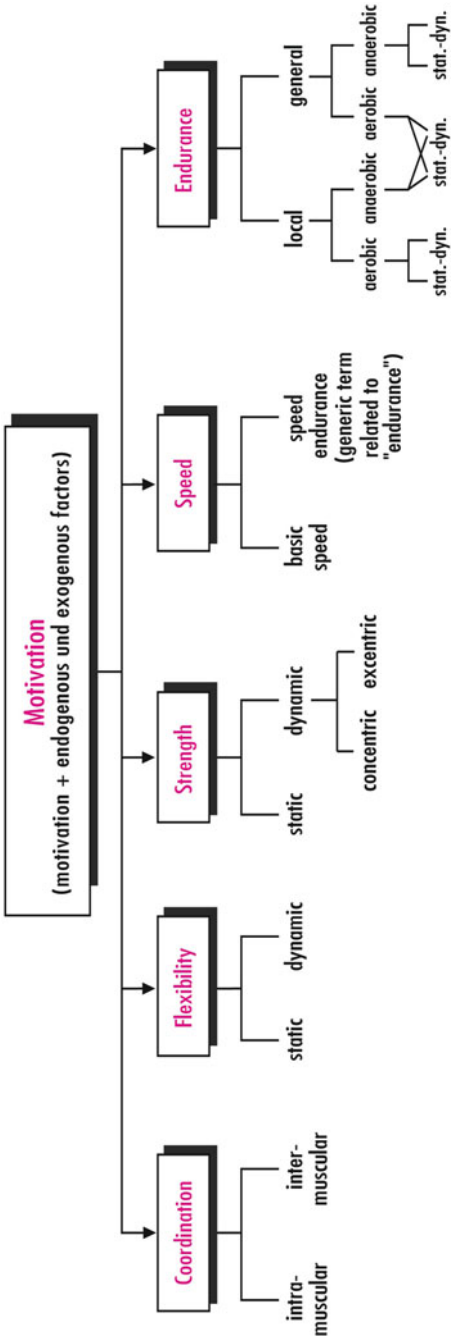

Fig. 5.1 Basic scheme showing forms of motor demands (Hollmann 1967)

5.2 Physiological Aspects of Endurance and Strength Exercise

5.2.1 Endurance Exercise

Endurance is understood as the ability to sustain a neuromuscular strain at a given load level. General (meaning the use of more than 1/6 to 1/7 of the whole muscle mass), aerobic, dynamic endurance is of particular interest because the respective physical demands are determined first and foremost here by the capacity of the cardiovascular and respiration systems, metabolism and cerebral factors. It is well established that maximal oxygen uptake ($\dot{V}O_2$max) is the gross criterion of performance capacity of the cardiopulmonary-metabolic system (Hill 1925, 1934). This parameter expresses the capability of the body to take up oxygen from the atmosphere and transport it to the working musculature. It must be differentiated between the absolute and the relative $\dot{V}O_2$max. If the performance capacity of the cardiopulmonary system is to be determined, then the value of the absolute $\dot{V}O_2$max uptake is sufficient. In contrast, should one refer to the endurance capacity, the $\dot{V}O_2$max per kilogram bodyweight (relative $\dot{V}O_2$max) is preferred. The $\dot{V}O_2$max in untrained males is in the range of 3.0–3.5 l/min. An elite athlete in endurance training condition achieves maximum values of about 7 l/min. In healthy females, this value is approximately 25–30% lower (Fig. 5.2). In the course of a lifetime, $\dot{V}O_2$max is reached at the age of 16 years in females and at the age of 19 years in males. To a large extent, $\dot{V}O_2$max remains unchanged up to the age of 30–35 years and then decreases with progressive age. The magnitude of this decline in performance is strongly affected by the aerobic training state. With each successive decade of life, $\dot{V}O_2$max is reduced by 8–10% in untrained persons, while the reduction in endurance-trained persons is only the half of this. Performance-limiting factors for $\dot{V}O_2$max are the internal factors of:

- Motivation
- Cardiac output
- Respiration
- Oxygen-binding capacity of human blood
- Blood distribution
- Arteries and arteriole diameter and density
- Endothelial function
- Capillarization of the skeletal musculature
- Mitochondrial lume of the skeletal musculature
- Nutritional condition

External factors are:

- Mode of physical demand
- Size and type of musculature employed
- Body position when working
- Partial oxygen pressure in the inspiration air and climate (Hollmann 1967)

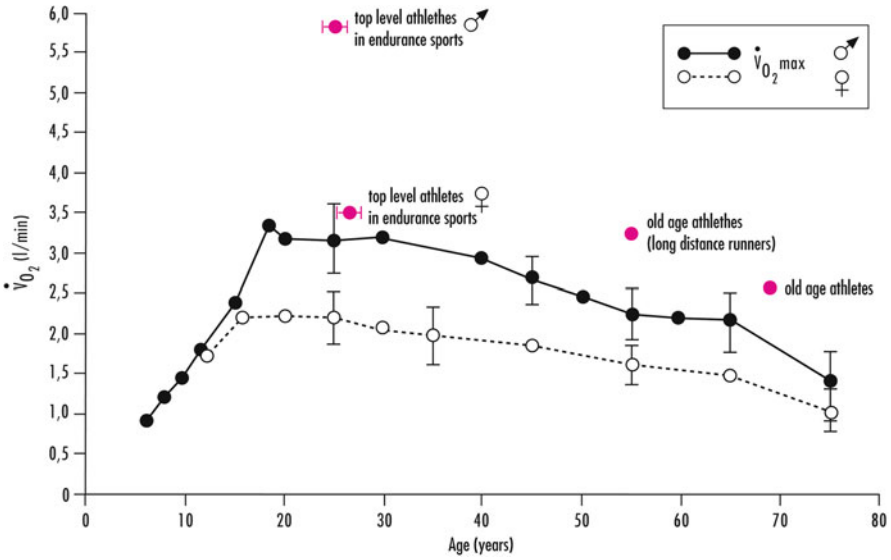

Fig. 5.2 The maximal oxygen uptake/min in healthy males and females between 8 and 80 years of age ($n = 2{,}834$). Bicycle ergometer exercise in the sitting position breathing atmospheric air (Hollmann 1963)

Muscular work raises the energy turnover and thus necessitates increased oxygen uptake of the active musculature. The cardiac output rate and the respiration increase while the arterial blood vessels and the capillaries dilate, causing a redistribution of blood into the active muscles. The amount of oxygen uptake per unit time corresponds to the product of the arteriovenous O_2 difference ($avDO_2$) and the cardiac output per minute. Up to an individual threshold of the performance capacity, the oxygen uptake/min increases linearly with a progressively increasing intensity of the physical demand, until reaching an individual $\dot{V}O_2max$, to then remain constant. In contrast to the oxygen uptake, the respiratory minute volume increases in a curvilinear fashion with increasing intensity of work. The respiratory minute volume only increases slightly up to an oxygen uptake in the order of 30–50% of the maximum value and then increases more and more steeply. The same applies to the arterial blood lactate concentration, and, indeed, the curves for the respiratory minute volume and the lactate concentration run practically in parallel (for details, see Hollmann and Strüder 2009).

The work-related increase in cardiac output can be caused by an increase in heart rate as well as an increase in the stroke volume. A greater significance by far is attributable to the heart rate. During exercise in the upright position, the stroke volume increases with increasing heart rate to about 110–120 beats/min and then remains constant up to the limit of performance capacity. While the cardiac output under rest condition amounts to 4–6 l/min, this can increase to 45 l/min in elite athletes at the capacity limit with heart rates ranging from 180 to 210/min. Untrained males in their thirties rarely achieve values greater than 20 l/min. The corresponding values for untrained females amount to 12–14 l/min, and those for endurance-trained females amount to 20–30 l/min.

A major factor influencing the economy of cardiac work is the blood pressure. Peripheral resistance, blood volume and cardiac output determine blood pressure in the body's circulatory system. Under loading, peripheral resistance is reduced to approximately one third of the value at rest. As the cardiac output increases disproportionately to this, general aerobic endurance demands are accompanied by a marked increase in the systolic blood pressure and a reduction in diastolic blood pressure. In the range of the $\dot{V}O_2$max during cycle ergometer testing, intra-arterial systolic blood pressures of 200–220 mm Hg and diastolic values of 90 mm Hg are measured. During treadmill testing, no diastolic blood pressure increases are usually observed (Rost and Hollmann 1978).

The blood volume plays a role for the magnitude of the stroke volume as well as for blood pressure. There are considerable individual differences, with average blood volumes of 5–6 l in adult males and 4–4.5 l in adult females, whereas high-endurance-trained persons can have blood volumes of 7–8 l. During intensive physically exhausting exercise, a haemoconcentration occurs along with a reduction of intravascular blood volume, whereby the $avDO_2$ is of particular importance for $\dot{V}O_2$max. In untrained persons, $avDO_2$ reaches an average value of 5 Vol.-% at rest and of 10–12 Vol.-% for maximum work. Only high-endurance-trained athletes are able to achieve maximum $avDO_2$ values of 16–19 Vol.-%. This increase in the $avDO_2$ enables a correspondingly higher oxygen uptake increase in the lungs.

Ventilation (VE) has no significance as a performance-limiting factor in a healthy person. Maximal breathing capacity, as an expression of the ventilatory capacity, is not reached during physical exertion. The oxygen demand of the respiratory muscles, rather than the ventilatory capacity, can become a significant factor for limiting performance. This is particularly true if exercise is done at high altitude. The maximum diffusion capacity of the lungs can also be performance determining at intermediate and high altitudes. As a consequence of increased heart rate and the associated acceleration of blood flow, the contact time between the erythrocyte and the alveolar membrane is not sufficient to achieve complete oxygen saturation of red blood cells from the venous blood. This is also valid for highly trained endurance elite athletes, who possess a high $avDO_2$; the arterial PO_2 value then falls accordingly.

In conclusion, numerous factors can affect the $\dot{V}O_2$max as the gross criterion of the cardiopulmonary capacity. During exhausting maximal demands, performance can be impaired through limitations of different system levels. The cardiac output, the maximum oxygen diffusion capacity of the lungs, the extent of blood flow in the active musculature and the cellular metabolic capacity all play a dominant role. Thus, under normal conditions (normoxia, no excessive temperature or air humidity), one can observe that the intracellular oxygen supply (partial pressure of oxygen) is decisive for the general aerobic physical capacity.

5.2.2 Strength Exercise

The skeletal muscle develops strength through tension. In the case of striated muscles, this tension is mainly transmitted to the skeletal system by creating a torque around a single joint or around multiple joints, because the majority of locomotor

muscles span over joints from their origin to their point of insertion. Due to their main demands, the activation of the muscles can either be tonic or phasic. Tonic activation occurs in muscles which maintain body posture where they have to ensure a permanent control of body position and need to be ready to fine tune and react to any perturbations. The phasic activation mode is required to control position and movements of extremities, if required. The torque created by a particular muscle tension around a joint depends on the:

- Distance between the point of insertion and the joints' centre of rotation
- Respective joint angle (setting the force–length relation of myofibrillar structures)
- Contraction mode (isometric, concentric, eccentric or combinations of the latter two)
- Contraction velocity
- Muscle architecture (fusiform, unipinnate, bipinnate)
- Mechanical properties of the muscle tendon unit (stiffness, elasticity, compliance) involved

Any change of limb position requires a modification of muscle tension, which subsequently alters the torque around the particular joint by altering one or more of the above-mentioned factors. Isolated muscle contraction seldom occurs in single muscles; an interaction of synergistic and antagonistic muscle groups coordinated by the central nervous system is more general.

Almost all forms of human movement comprise a combination of eccentric followed by concentric contraction modes (stretch-shortening cycle, SSC). For practical purposes, the different types of strength are categorized according to the mode of contraction: maximum static strength, maximum dynamic strength, (explosive) power and strength endurance. The underlying contraction modes are:

- Static or isometric (the distance between muscle origin and point of insertion remains constant)
- Dynamic positive or concentric contraction mode (associated with decreasing the distance between muscle origin and point of insertion)
- Dynamic negative or eccentric contraction mode (acts as a braking force during muscle elongation from a starting length)
- Stretch-shortening cycle or ballistic movement (a combination of eccentric and concentric contractions as is often found in multiple locomotor tasks)

The amount of muscle tension developed under standard conditions depends mainly on the number and size of motor units involved as well as the frequency of depolarizing motor unit action potentials (MUAPs). At least under isometric conditions, the recruitment of motor units within a muscle follows the so-called size principle (Henneman 1981), i.e. an increasing number of motor units within a single muscle become involved as the external load is steadily increased according to the size of motor units. The size of motor units refers to the number of muscle fibres innervated by a single α-motor neuron and the size and type of the muscle fibres themselves. Small motor units of mainly fatigue resistant type 1 muscle fibres are

recruited first, before motor units of predominantly type 2a muscle fibres are activated. Motor units consisting mainly of fast fatigueable type 2× fibres are recruited when the strength demand is close to the maximum capacity of the muscle's isometric (static) maximum strength. This recruitment order of motor units corresponds well to systematic variability of motoneuron cell membrane resistivity (Gardiner 2011; Kernell 2006).

Hence, static strength is muscle tension, which occurs when a muscle or muscle group in a certain position is able to apply against a certain fixed resistance. The magnitude of the maximum static strength is determined by the:

- Number and type of muscle fibres
- Extent of muscle fibre recruitment
- Muscle fibre cross-sectional area
- Structure and biochemistry of the muscle fibres
- Muscle fibre length and angle of tension
- Contraction of antagonists
- The motivation of the subject

However, in sports, pure sustained isometric contraction conditions are rare, and more dynamic contraction types of mainly stretch-shortening type are predominant. The eccentric contraction mode in the stretch enhances muscle power right at the start of the following concentric phase by taking advantage of the elastic properties of the muscle tendon units (MTUs). Under particular preconditions for the stretch (precontraction of the target muscle), rapid elongations of the MTUs can also involve reflex-regulated potentiation of motor drive to the muscles and increase the number and tension of recruited motor units (reactive strength) (Zatsiorsky and Kraemer 2006).

The muscle fibre cross-sectional area, which is approximately 75% in females of that in males, has the main impact on maximum static strength. Muscle growth is achieved primarily through an increase in the cross-sectional area of the individual muscle fibres. Important physiological adaptations (Cardinale et al. 2011; Baechle and Earle 2008) to strength training are:

- Hypertrophy
- Hyperplasia (possibly)
- Increase in the DNA and RNA content as well as the asparagine aminotransferase
- Increase in the number of myofibrils and actin and myosin molecules
- Increase in the creatine phosphate concentration and possibly also in the concentration of ATP and myosin ATPase
- Mass increase in the slow and fast muscle fibres, dependent on the type of strength training
- Enlargement of bone and diaphyseal diameters in the thickness of the cortical layer and enlargement of the bony prominence at the insertion of the tendon
- Densification of the bone structure (formation of bone trabeculae)
- Increase in thickness of articular cartilage
- Hypertrophy of tendon fibres and ligaments

5.3 Physical Fitness Measurement

5.3.1 Contraindications for Participation in Fitness Testing

Especially in case of patients or older adults, it should be left to a physician to decide on a case to case basis, how far an individual can be subjected to physical exertion. Contraindications are:

- Acute infection with fever
- Myocarditis, endocarditis or pericarditis
- Congestive heart failure of differing genesis
- High-grade aortic stenosis
- Serious hypertrophic cardiomyopathy (HCM)
- Malignant arrhythmias
- Symptomatic high-grade atrioventricular block (insofar not congenital)
- Blood pressure level at rest of more than 200/120 mm Hg
- Serious pulmonary hypertension
- Recent heart attack or stroke
- Recent thromboembolism

Special care is required for:

- Congenital or acquired vitia
- Vitia associated with syncopes
- Early stages after heart attack or recently suffered stroke
- Atrioventricular block (II and III degree)
- Left bundle branch block
- Complex ventricular arrhythmias (due to an earlier exertion or in a long-term ECG)
- Sick sinus syndrome
- Aneurysm
- Exceptionally enlarged heart

5.3.2 Specific Methods: Endurance Tests

5.3.2.1 Graded Exercise Test to Exhaustion (GTX) with Measurement of $\dot{V}O_2max$

The development of spiroergometry by Knipping made an exact continuous measurement and registration of breathing gases including oxygen uptake and carbon dioxide exhalation possible (Knipping 1929; Knipping et al. 1955/60). Initially, the examiner used a rotary crank with an extended grip, which was turned by the test person in the standing position while breathing in pure oxygen. In 1954, Hollmann introduced the bicycle ergometer into the so-called Knipping School. Here, the load

was applied with the test person in the sitting position breathing in atmospheric air. This was the beginning of bicycle ergometer-aided performance examinations in clinics. Today, it is well established that spiroergometry is the most reliable and valid method for qualitative and quantitative assessment of the cardiocirculatory, pulmonary and metabolic responses to exercise (Jorgensen et al. 2009). The measurement of oxygen consumption, carbon dioxide production, minute by minute ventilation and heart rate provides substantial diagnostic and prognostic information in a wide variety of clinical and experimental settings (Wonisch et al. 2003).

In healthy people, $\dot{V}O_2max$ during GTX is influenced by a variety of factors, including the mode of operation (e.g. standing, sitting or lying), the kind of demand (e.g. cycling, running, rowing, canoeing, etc.) and the examination procedure with respect to the magnitude of the incremental load increases. Although different test protocols for GTX affect the results of $\dot{V}O_2max$, the underlying methodological principle is identical. The physiological responses of different parameters are obtained for stepwise increases in load and set in relation to the respective loading. The ergometric performance is regulated through the wattage and the treadmill performance through the running speed and/or gradient. An adaptation period for the cardiovascular system of at least 2 min as well as 3 min for the metabolic and respiratory parameters is required for a steady state condition to be reached. A maximum degree of standardization of the test conditions is obligatory for the external boundary conditions (e.g. time of day, temperature, humidity) as well as for the biological pretest conditions (e.g. nutritional status, physical preloading, warming-up phase, menstrual cycle and/or contraception). Alongside cardiovascular (e.g. heart rate, blood pressure), metabolic (e.g. concentrations of blood lactate, ammonia, glucose) and respiratory parameters (e.g. respiratory minute volume, ventilation, oxygen uptake, exhaled carbon dioxide), the register of parameters also includes the subjective rating of perceived exertion (RPE) of the active test person (Borg et al. 1987).

Because of its artefact-free depiction of both the ECG and blood pressure measurement, the bicycle ergometry is given preference for clinical indications (Löllgen et al. 2009). Generally, a 3-min rest phase is documented, which is followed by the respective test protocol. Various ergometric protocols are available depending on the aim of test and type of clientele, for example, for low-performance, older or internal medical patients, the WHO (World Health Organization) scheme (starting at 25 W, with an increase of 25 W every 2 min). Examples for other well-established test procedures are the Hollmann/Venrath scheme (starting at 30 W, with an increase of 40 W every 3 min), which is used for healthy untrained middle-aged test persons, and the BAL scheme (starting with 50 or 100 W, with an increase of 50 W every 3 or 5 min, repectively) for well-trained athletes (Liesen and Hollmann 1981; Löllgen et al. 2009). Furthermore, weight-based ergometric protocols can be used, particularly for children and juveniles (Washington et al. 1994). The form of the loading protocols specific to running reflects the named principles, whereby the starting speeds of the test persons, depending on their physical condition, are 1.5, 2.0 or 2.5 m/s with incremental increases of 0.5 m/s. To correspond to an energetic consumption for natural running in the open air, the treadmill is to be adjusted to a 1% gradient (Löllgen et al. 2009).

To precisely obtain $\dot{V}O_2max$, the ramp protocol with a short test time slot is preferred. After a short warm-up, the maximum effort is reached with a very steep rate of load increase, but the attainment of the maximum values is being limited by the cumulative loading. All test procedures after maximum effort are by standard followed by a recovery phase of at least 5 min with medical supervision and accompanying documentation. In spite of the differing ergometric forms of loading, the results can be compared by applying the metabolic equivalent (MET). With regard to more in-depth information, the reader is referred to the guidelines of the recognized medical and sport-scientific associations (Gibbons et al. 2002; ACSM 2010).

The only criterion for assessing whether individual $\dot{V}O_2max$ has been reached during GTX is a plateau in oxygen consumption. In unspecific trained individuals, this is reached on a bicycle ergometer in only about 20% of the cases, whereby this can be observed in about 50% on a treadmill (Hollmann and Strüder 2009). Thus, one must apply additional criteria to roughly assess to what extent maximal performance capacity has been reached during the GTX. Relevant criteria for healthy test persons are:

- Exceeding a heart rate of 190 beats per minute (bpm) for persons in their thirties. In younger and older males and females, a rule of thumb of 220 minus age in years can be assumed.
- Exceeding a respiratory equivalent value of 30–35. This is related to the quotient of respiratory minute volume/l divided by the oxygen uptake in ml for the same period.
- Discontinuation of a further increase in the oxygen pulse, which then follows a curvilinear increase of loading intensity with a tendency to abruptly flatten out at the constant performance limit.
- Lactate concentration in the arterial blood of at least 8–10 mmol/l.

During GTX, the respiratory equivalent plays a leading role for the above listed points. To begin, increasing physical demands during GTX effects a falling-off of the respiratory equivalent, which on average reaches its lowest value in both males and females in their thirties with pulse rates of 120–130/min. Thus, the respiratory economy in this loading range is more effective than with the body at rest. With a further rise in loading level, this quotient increases as a function of the intensity and type of exercise, mass of the activated muscle, training status, sex and age, as well as the external conditions. High-endurance-trained persons as well as patients with cardiopulmonary dysfunctions or damage can reach or even exceed values of 40–50. The graphical plot of the respiratory equivalent during the increasing levels of exercise runs parallel to the respiratory minute volume (Hollmann 1963). A working insufficiency of the heart is revealed in a spiroergometric examination through an increased respiratory equivalent already at quite low working intensities.

The respiratory exchange ratio (RER) is a dimensionless quotient, which specifies the ratio of the exhaled quantity of carbon dioxide to the inhaled volume of oxygen per unit time: CO_2 exhaled $(l \cdot min^{-1})/O_2$ inhaled $(l \cdot min^{-1})$. With the body at rest, one assumes a mixed supply with an average RER of 0.85. With an increasing ergometer loading during GTX, the carbon dioxide production is increased with a resulting

increase in the RER. This value increases to 1.0 when virtually only carbohydrates are used at the individual threshold of the submaximal capacity. Maximum endurance demands can lead to RER values above 1.0. Through this specific behaviour, the RER is also a workout criterion in spiroergometric examinations. At demands above the anaerobic threshold (over 60–70% of $\dot{V}O_2$max), additional carbon dioxide, so-called excess carbon dioxide occurs, following bicarbonate buffering because of the increased formation of lactate. This over-proportional increase in the RER can be used to determine the ventilatory threshold during GTX (Wasserman et al. 1973). Athletes with a high anaerobic capacity are able to achieve maximum RER values of over 1.15. The larger the aerobic capacity is, the less the achievable maximum RER. Performance-weak test persons or patients reach limiting values of about 1.0, even at relatively low oxygen uptake values.

5.3.2.2 Submaximal Exercise Testing With Measurement of the Aerobic–Anaerobic Threshold

The determination of individual $\dot{V}O_2$max during GTX has two significant disadvantages. In addition to the possible health hazard to patients under maximum loading, the results are strongly dependent on the motivation of the person examined. Hollmann discovered that the respiratory minute volumes and the arterial lactate concentration exhibited almost parallel characteristics (Hollmann 1959a, b). As both parameters first begin to increase with a curvilinear progress above an average magnitude of approximately 60% of the $\dot{V}O_2$max, a line can be drawn perpendicular to the abscissa from this point, on which the loading level and degree of oxygen uptake, respectively, was entered. Hollmann (1959b) designated the associated magnitude of the respiratory minute volumes as the "point of the optimal ventilatory efficiency" (PoW), while the associated loading level was designated the "continuous performance threshold" (Fig. 5.3; Hollmann 1959b; Hollmann 1961; Hollmann 1963). Wasserman and Mellroy published a congeneric procedure in 1964, which was termed "anaerobic threshold"; the term which later found international acceptance (Wasserman et al. 1986, 1973; Wasserman and Mellroy 1964). This procedure made it possible to obtain an objective prediction about the cardiopulmonary capacity during exercise testing, without subjecting an ailing patient to a maximum exercise demand and which was also independent of the patient's motivation (Fig. 5.4). Nowadays, this examination method is still the "gold standard" for assessing the aerobic capacity.

Mader et al. (1976) first described the "4-mmol/l-lactate threshold", which corresponds to the highest exercise intensity that can be physically sustained over a long period without a further increase in the blood lactate concentration (Beneke and Duvillard 1996). The defined maximum lactate steady state (maxLass) is an important parameter with regard to the registration of aerobic capacity (Dekerle et al. 2003; Mattern et al. 2003). Apart from the levels of lactate, this also pertains to the parameters $\dot{V}O_2$, $\dot{V}CO_2$, the RER and the pH value (Baron et al. 2003), which depending on endurance capacity, lie between 65% and 85% of the $\dot{V}O_2$max (Billat et al. 2003).

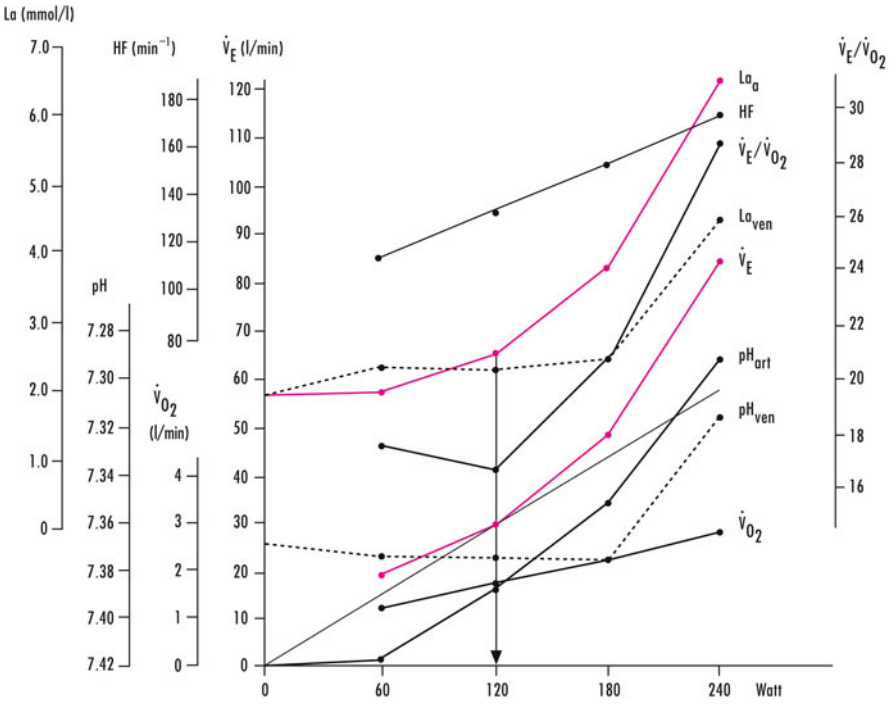

Fig. 5.3 First published representation for detecting the aerobic–anaerobic transition during bicycle ergometer exercise of increasing intensity. The oxygen uptake ($\dot{V}O_2$), the heart rate (HF), the respiratory minute volume (VE), respiratory equivalent (VE/VO_2) of the arterial lactate value (La_a), the venous lactate value (La_{ven}), the arterial pH value (pH_{art}) and the venous pH value (pH_{ven}) ($n = 17$ male sports students). The vertical *arrow* marks the aerobic–anaerobic transition for the respiratory minute volume as well as for the arterial lactate value (Hollmann 1959)

The 4.0 mmol/l threshold has been comprehensively, empirically and physiologically analysed and validated (Heck et al. 1985a, b; 1990; Föhrenbach et al. 1987). The following can be deduced from the aerobic–anaerobic threshold:

- That rate of oxygen uptake/min during increasing workload levels, beyond which the anaerobic-energy-supplying mechanisms increase
- That rate of oxygen uptake during increasing workload levels, beyond which a metabolic acidosis occurs
- That magnitude of exercise intensity during increasing workload levels, beyond which the plasma bicarbonate concentration decreases in inverse proportion to the lactate concentration increase

Further threshold concepts followed since then, whereby the principle described is used as a basis in each case. The threshold concept as well as the conclusions that can be drawn from this is the subject of a controversial sport-scientific discussion now in process, whereby it is basically differentiated between “fixed” and “individual”

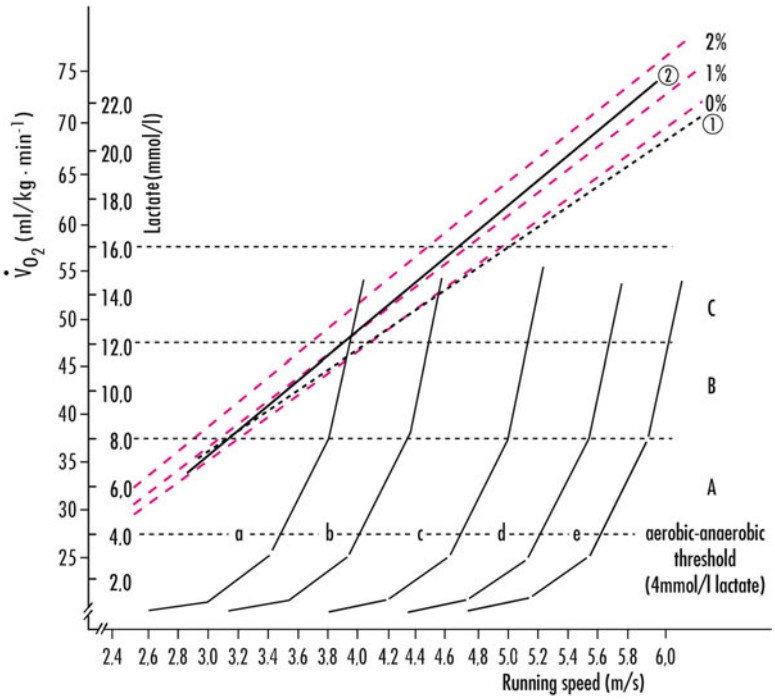

Fig. 5.4 Arterial lactate level and oxygen uptake per minute in persons on the treadmill (a = untrained, e = top class athletes) of differing endurance performance capabilities (Mader et al. 1976)

procedures describing the threshold, which on the basis of mathematical–graphical models point to significant process points. When validating the lactate threshold concepts, the maxLass value, in particular, is applied (Kilding and Jones 2005; Laplaud et al. 2006), in addition to the long-term test procedure (Bacon and Kern 1999; Baldari and Guidetti 2000). For further information on this point, the interested reader is referred to the in-depth reviews by Faude et al. (2009) and Heck and Beneke (2008).

5.3.2.3 Time Trial

A further method used in several experimental studies to assess endurance performance is a time trail (Jeukendrup et al. 1996). For the laboratory time trial, the test person must either do the greatest possible amount of exercise within a defined period of time or do a defined amount of exercise in the shortest possible time. The duration of the predefined time slot of 30–60 min corresponds to the endurance capacity. The defined amount of exercise to be completed over the variable time slot is based on the GTX test results. The time trial test procedure, with its proven validity (Coyle et al. 1991), is comparable to competition conditions and often serves for

checking the training effects (Lindsay et al. 1996) as well as the influence of dietary supplements or psychological support on performance (Bishop 1997). In order to obtain reproducible results, the test person must be in good physical condition and familiar with the test procedure.

5.3.2.4 Field Tests

The Cooper test (a maximal 12-min run test, which is usually carried out on a track and assesses the distance run during this time frame) is strongly related to the criterion for determining $\dot{V}O_2$max in adults ($r = 0.48$–0.92) and children ($r = 0.9$). During this test, however, inexperienced runners often have difficulty finding the optimal speed, which often leads to an underestimation of their $\dot{V}O_2$max. The test is most suitable for individuals with sufficient fitness and motor skills and who are considerably motivated (Jorgensen et al. 2009).

Another performance test is the Rockport-fitness 1-mile track walk test (1-MWT), which is applied to estimate the $\dot{V}O_2$max values across a range of fitness levels and age groups (Kline et al. 1987). This test only requires simple equipment and employs the very familiar activity of fast walking. The test person is required to walk one mile (1,609 m) as quickly as possible. Before, during and after walking, the heart rate is monitored and recorded. At least two tests must be carried out, whereby the duration of the tests must not deviate by more than 30 s from one another. The walking time, the recorded heart rate and the weight of the person are plugged into the regression equation to obtain the $\dot{V}O_2$ value. Although this test cannot replace tests in the laboratory, the 1-MWT can be applied to a wide range of individuals to even include elderly persons.

An accurate field test for evaluating endurance capacity via lactate thresholds in a large group of individuals is the field-step-test (FST) (Dickhuth et al. 1996). The FST is carried out in a group on a 400-m track. Analogous to a treadmill laboratory test, the defined running speeds are generated over given track distances and with the aid of an acoustic pace maker. The advantages of the FST, in addition to its practicability and independence of the laboratory, are its time-saving quality and excellent transferability for test results under normal outdoor running conditions.

5.3.3 Specific Methods: Strength Tests

5.3.3.1 In Vivo Direct Muscle Strength Measurements

Muscle strength can be measured directly, but the techniques used are invasive and therefore are limited to clinical and experimental applications (Komi et al. 1987, 1996; Fukashiro et al. 1995; Arndt et al. 1998). These techniques involve the implementation of a force sensor into the tendon, which connects the muscle to the limb it is attached to and measures the tension, which the muscle develops through

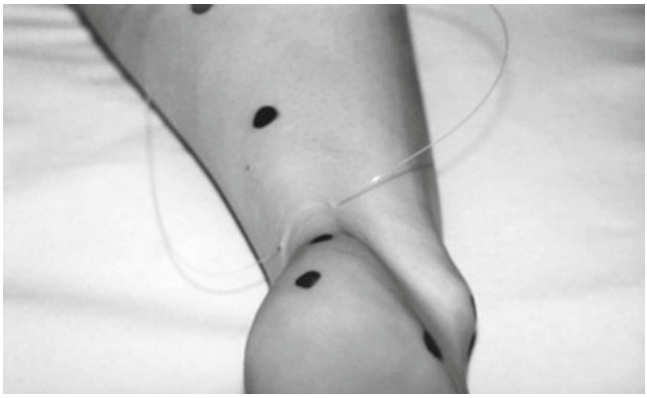

Fig. 5.5 Optic fibre in situ to measure Achilles tendon forces during locomotor tasks like jumping, landing running, etc

contraction. Buckle transducers with strain gauges have been implanted into tendons to directly measure forces in situ but require surgical treatment with a considerable risk of infection for the test subjects (Komi et al. 1987). A less invasive technique was introduced by the research group of Paavo Komi from Finland, who led an optical fibre (Fig. 5.5) through the tendons and registered the change of the light spectrum due to the deformation of the tendon and hence the optical fibre under tension. This was equivalent to a voltage change calibrated to the respective force output. This technique also enabled the test subjects to perform virtually any movement without restrictions (Finni et al. 2000, 2001; Arndt et al. 1998).

5.3.3.2 Qualitative Maximum Strength Estimations

For practical reasons and in the absence of strength quantifying devices, the one repetition maximum (1RM) is often taken to estimate the maximum capacity of a group of muscles involved in a specific strength training exercise with the help of estimation tables (Baechle and Earle 2008) or the well-established Brzycki equation (Mayhew et al. 1995). These methods attempt to predict the maximum load that can be overcome in one attempt in a particular strength exercise by means of a proper movement execution.

5.3.3.3 Force Measurements in Strength Training Machines

Measuring the tension of a muscle or muscle group directly is reserved for very special purposes as mentioned before. The quantification of strength, however, is done indirectly by observing and registering the effects muscle tension has when applied to an object. Either this force will cause a deformation or an acceleration of the object, both of which can be measured by special transducers of various types.

Mainly strain gauge force transducers are used to measure forces within the transmission belts or cables of strength training machines. A high degree of standardization is needed to render results comparable, whereby the mechanics of the force transmission must be taken into account when relating the results to strength abilities. Strength training machines often take joint angle strength relations into consideration in the design of contoured transmission cam discs. This means that the external lever arm varies over the range of motion inversely to the muscle insertion to joint configuration. Thus, joint angle-related force output data become biased. Frictional forces within the bearings and pulleys, the elastic nature of the transmission cables and belts together with the inertial properties of machine parts such as load plates are further sources of measurement errors in dynamic movements, which require careful consideration before taking measurements. Often, only static measurements are recommendable due to limited validity and reliability of the measurement environment.

5.3.3.4 Isokinetic Dynamometers

Isokinetic dynamometers register the torque—angle relation of a lever arm—which is driven by muscular work and regulate the achievable movement velocity at the same time. Although the measurement precision in some of the devices is exquisitely high and reliable, one must bear in mind that the output data cannot be equated to muscle moments acting around the respective joint. Even the most careful procedure will not be able to bring the rotation axis of the isokinetic actuator into agreement with the anatomical axis of the respective joint. Differences between measured torques and resultant joint moments were found to be in a range of 16–23% in a strongly controlled measurement situation (Arampatzis et al. 2005). Taking these limitations into account, isokinetic dynamometers represent the state-of-the-art diagnostic tool to quantify strength–joint angle relations (corresponding to MTU–length) statically and dynamically as well as strength–movement velocity relationships for concentric as well as for eccentric contraction conditions. Particular makes of isokinetic dynamometers allow for adjusting operating modes of lever-arm acceleration to also mimic highly dynamic non-isokinetic movements such as throwing and kicking (Figs. 5.6 and 5.7).

5.3.3.5 Power Tests for Lower Extremity Musculature

Tests of vertical and horizontal jump performance have long been used to estimate the strength of the extension muscles acting around the ankle, knee and hip joints. They are considered to be tests of muscle power function under different contraction conditions and to be highly related to sport performance. Jumping height is the most common parameter for muscular performance during jumping and can be obtained in its simplest way by comparing chalk marks taken at standing height and the highest point of a jump by the jumper himself in the jump and reach test. As this procedure

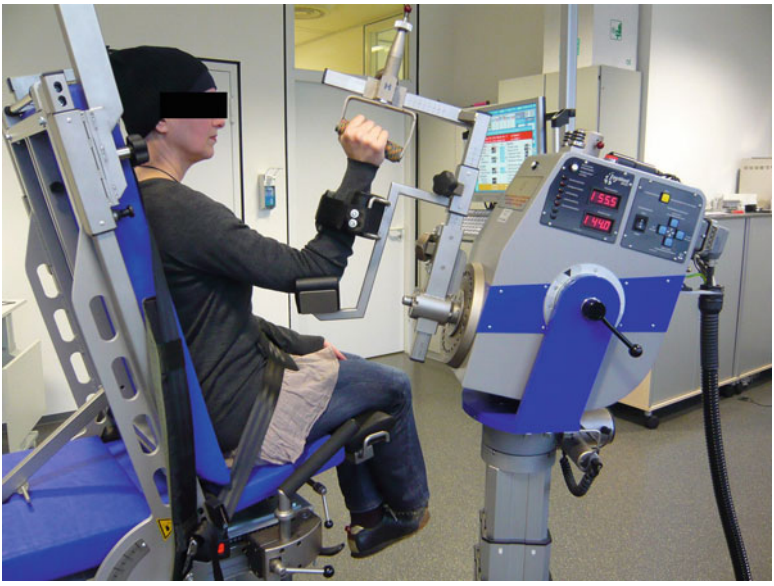

Fig. 5.6 Patient positioned on an isokinetic dynamometer (IsoMed2000, Hemau, Germany) for shoulder inward/outward rotation

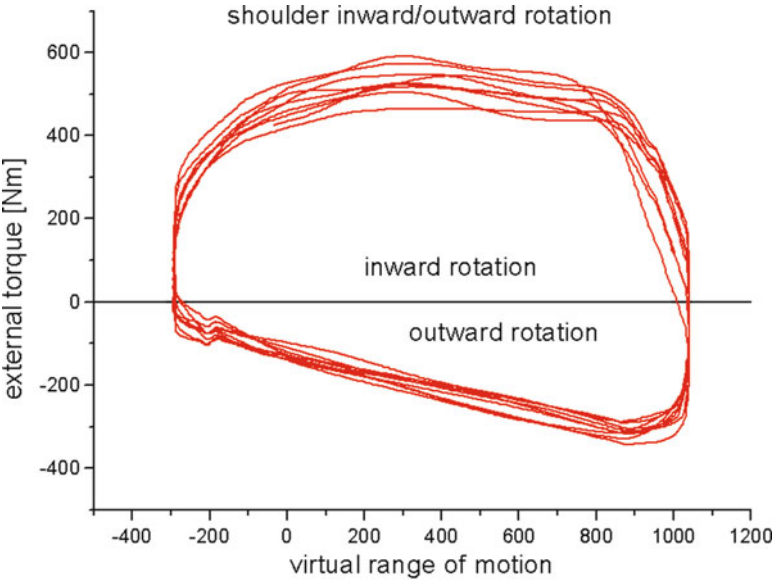

Fig. 5.7 Example graph of data obtained with an IsoMed2000 isokinetic dynamometer for nine repetitions of shoulder concentric inward/concentric outward rotation at 100 s^{-1}

is neither very valid nor reliable, the measurement errors can be rather large with only a weak repeatability of results. Another possible method is the application of flight time to calculate jump height by utilizing contact mats or photocells mounted into floor panels. Under careful control of movement execution, the results show reasonable repeatability and reliability. The method with the highest accuracy utilizes force platforms to measure the ground reaction forces during the take-off phase of the jumps. Jump height is then calculated by the vertical impulse generated during ground contact, and any movement error can immediately be detected online. Besides being pure strength tests, the jump tests also provide information about the power produced during the acceleration of the body when jumping as high as possible (Dias et al. 2011; Newton et al. 2011).

Jumps used for diagnostic purposes are:

- The squat jump (SJ), which yields information about the individual's ability to produce muscle power by concentric contraction of the muscles extending ankle, knee and hip joint.
- The countermovement jump (CMJ), which involves a long stretch-shortening cycle (SSC) into the jump action by allowing for a preceding lowering of the centre of gravity prior to the actual push-off from the ground. The strength in the squat position is thereby raised to a higher level than in the pure SJ and consequently jump heights attained in CMJ are higher than in SJ.
- The drop jump (DJ), which also involves a SSC but the eccentric phase is much shorter than in the CMJ as the DJ, is executed with a preceding drop from an elevated platform. After touchdown, the individuum is supposed to leave the ground as rapidly and/or as forcefully as possible. This requires a preactivation of the muscles involved in decelerating the fall from the drop. During ground contact, these muscles together with the respective tendinous structures are stretched very fast. It was shown that stretch reflexes are exited and together with the energy stored in the passive structures of the muscle tendon unit can enhance the force output during ground contact (Albracht and Arampatzis 2006; Gollhofer et al. 1990).

5.3.3.6 EMG and Muscle Activation Measures

Although there is only limited direct correspondence between electromyographic (EMG) signal qualities and muscular strength measures, EMG can provide additional valuable information about muscles involved in a particular movement and their level of activation. Intramuscular needle and fine wire sensors are used to investigate single-fibre and single-motor unit activation patterns. Non-invasive surface electrodes measure rating and recruitment of superimposed motor unit action potentials. If carefully applied to the skin on top of the muscles of interest, surface EMG measurements provide information about intermuscular coordination, the extent of intramuscular motor unit recruitment and their frequency rating. Thus, EMG can specify how muscular work (strength) is administered within

a particular movement or exercise. EMG also provides an estimation of neuromuscular fatigue due to exercise or competition (Cairns et al. 2005; Knicker et al. 2011). With the combination of electromyostimulation pulses applied at maximum voluntary contractions, it is possible to differentiate between peripheral and central fatigue contributions in vivo (Colson et al. 2009; Paillard 2008; Gregory and Bickel 2005). Latest advances in EMG also allow single-motor unit activation patterns to be calculated from surface EMG measurements by breaking down the superimposed signal into single-motor unit action potentials (De Luca et al. 2006; Nawab et al. 2010). Tensiomyography (TMG) and myotonometry (MMT) are methods developed over the last 15 years. They have been used to measure contraction time and displacement, muscle tone, fibre type (TMG) and muscle stiffness (MMT) (Ditroilo et al. 2011).

5.4 Training Recommendations

5.4.1 Endurance Training

When applying the above test procedure, a register of valid metabolic and cardiopulmonary parameters are available for the individual control of aerobic endurance training (Gibbons et al. 2002; ACSM 2010). In particular, when planning individual training regimes, the characteristic physiological process obtained through respiratory and muscle-metabolic means as well as the $\dot{V}O_2$max represent key parameters for determining the intensity of loading (Meyer et al. 2005a, b; Plato et al. 2008; Solberg et al. 2005). Only with knowledge of this individual profile can the corresponding energy rate to the musculature concerned be regulated, thus allowing the endurance adaptations relevant for the study to be realized. The following presents a cursory guideline-oriented aid to interpreting the raw test data for specific areas of training, in the sense of an appropriate choice of intensity, as well as the practical implementation in training with suitable field parameters.

5.4.1.1 Endurance Performance Analysis, Classification and Training Management Applying Respiratory Thresholds and Lactate Kinetics

In addition to the $\dot{V}O_2$max absolute criterion, significant spiroergometric recorded process points, in particular in the aerobic–anaerobic threshold range, can provide important information about the individual status of the energy-supplying systems relevant for training (Hollmann 1963; Bentley et al. 2007). In the ramp test as well as the step test, the respiratory equivalent for O_2 and CO_2 as well as the $\dot{V}E$ (Wasserman et al. 2005; Beaver et al. 1986) can be used to detect the aerobic threshold range (vAT) as well as the "respiratory compensation point" (RCP) (Wasserman et al. 2005), which in turn can be applied to training management (Amann et al. 2004; Dekerle et al. 2003). Because the above-mentioned intensity range can be

determined by respiratory means and also by lactate measurement, the relevant physiological connections and conclusions are discussed within the context of the following for a better understanding.

In all endurance-specific forms of movement, great importance is attached to the lactate-performance curve (LPC), which is generated from the loading-specific blood lactate concentration, which in turn is obtained using the GXT procedure (Fabian et al. 1997; Faude et al. 2009). The LPC is a valid and practice-established performance diagnostic instrument for classifying performance, for determining individual intensity ranges as well as for prognosticating performance in competitions (Mader et al. 1976; Svedahl and MacIntosh 2003). It has a markedly high test reliability, whereby the biological variability with a scatter of about 1–3% can be neglected (Katch et al. 1982; Pfitzinger and Freedson 1998; Heitkamp et al. 1991). When defining the areas of training, the application of the LPC is to be preferred to the HFmax and $\dot{V}O_2$max procedures (Faude et al. 2009). Furthermore, the LPC reacts more sensitively to training stimuli than the $\dot{V}O_2$max determination (Denis et al. 1982; Sjodin et al. 1982).

During the test, which starts from a basal lactate level with the test person at rest and a low test intensity, a specific lactate-performance behaviour can be identified as well as specific points during the process can be calculated, which in the phenomenological sense, can be designated as "threshold" or "transition point" and which can be used to define the intensity of training (Faude et al. 2009; Föhrenbach et al. 1987). Thus, the aerobic threshold range of muscular metabolism, corresponding to the so-called basic endurance training I (GA_1) for a first-time increase of the lactate level below 2.0 mmol/l lactate, as well as the respiratory equivalent for oxygen at a low RER value, can be detected (Hollmann 1963; Wasserman et al. 2005). This intensity is associated with a high rate of lipometabolism, a 70–80% maximum heart rate, a subjective perceived exertion of RPE 11–13 and easy breathing. The objective of GA_1 training stimuli is the initiation and development of general endurance as well as an improvement in aerobic capacity (Neumann et al. 2000; Wiksten and Peters 2000). Intensities at the level of the anaerobic transition, with corresponding lactate level increases up to a maxLass of about 4.0 mmol/l lactate, as well as an accompanying increase in the respiratory equivalent for VCO_2, indicate an increase in the respiratory work. This occurs at about 85–90% of the maximum heart rate and perceived at RPE values of 14–16. The corresponding demands of the basic endurance training II (GA_2) are characterized by an increase in the proportion of carbohydrate in the aerobic energy metabolism. At the centre of the GA_2 training loads stands the development and improvement of the general endurance as well as an increase in the aerobic–anaerobic capacity (Neumann et al. 2000; Wiksten and Peters 2000). A further increase in the intensity without an adjustment of dynamic equilibrium is not a practical training methodology for the continuous method at constant loading intensity, because the accumulating lactate levels with ensuing acidosis and the increasing muscular fatigue lead to a break off in loading (Pringle and Jones 2002). This range of intensity is reserved for interval training.

5.4.1.2 Endurance Performance Analysis, Classification and Training Management Applying $\dot{V}O_2max$

The $\dot{V}O_2max$ values obtained in graded exercise tests to exhaustion (GTX) can be used for determining the endurance capacity or for management of training (Kuipers et al. 2003; Roffey et al. 2007). In cross-sectional and longitudinal studies, the absolute and relative $\dot{V}O_2max$ values are to be ascertained in a standard fashion, as they facilitate an inter-individual and intra-individual comparison on a broad data range (Wilmore and Costill 2004). For normally healthy but untrained test persons, the $\dot{V}O_2max$ can be approximately estimated based on a comprehensive anthropometric dataset, whereby a standard error of about 5 ml/min/kg must be taken into account (Jackson et al. 1990).

Analogous to the maximum heart rate oriented procedure, the $\dot{V}O_2max$ is relevant in training practice (Tanaka et al. 2001; Gellish et al. 2007), whereby, based on the individual maximum values, interpolation is used to obtain the above-mentioned intensity and effect ranges GA_1 und GA_2 (ACSM 1998; Wiksten and Peters 2000; Karvonen et al. 1957). Thus, an applied loading of less than 60% of $\dot{V}O_2max$ can be defined as low intensity, aerobic and with very high relative fat-burning proportion in the working musculature metabolism (Neumann et al. 2000; Zintl and Eisenhut 2001). Moderate endurance loadings of 60–80% of $\dot{V}O_2max$ correspond to GA_1 training, which puts the neurophysiological adaptations, inherent in the present focus of interest into practice. Intensities of 80–90% of the $\dot{V}O_2max$ are to be assigned to the aerobic–anaerobic GA_2 area of training, which is characterized by an increasing proportion of carbohydrates and incipient lactate accumulation (Neumann et al. 2000; Zintl and Eisenhut 2001).

5.4.1.3 Implementation of the Training Intensity in Training Practice

The implementation of the detected ranges of intensity in training practice can be achieved by using physical or biological field parameters. In training practice, the application of variables of different management parameters in combination has proven advantageous. Obviously, the physical performance from the test procedure for the related training area can be applied for an exact regulation of the intensity. In the case of running exercises for instance, this would be the correlated running speed or a defined wattage for ergometer training. Because the physical performance varies linearly with the heart rate until 90% of the $\dot{V}O_2max$, the intensity can be controlled through the heart rate during training. This, however, is subject to different loading-independent influences (Grosser et al. 2001). Because there is a close correlation between the subjective RPE value and the heart rate, the blood lactate level, the $\dot{V}O_2$ as well as the breathing frequency (Borg et al. 1987; Borg 1998; Froelicher and Myers 2000; Löllgen et al. 1980), it is reasonable to regulate the intensity transfer in training through the subjective loading perception. The application of an innovative measuring system monitoring heart rate, distance covered and

speed is obligatory for the scientific documentation, control and analysis of the training data. The equipment-aided training heart rate control enables an effective biofeedback for improving the movement-specific body awareness. In addition, the data documentation can be used to convey motivational and didactic effects, which promote the compliance of the test person.

5.4.2 Strength Training

Strength training exercises can be differentiated according to their primary aims:

- Hypertrophy
- Intramuscular coordination
- Specific power
- Stabilization

5.4.2.1 Hypertrophy

Strength training for hypertrophy aims to increase functional muscle mass. Under constant load conditions, as in free weight training, up to five sets of exercises with 8–12 repetitions each are given as a standard range of volume and intensity in training recommendation. The load corresponds to 70–85% of the 1RM with a break of 3–5 min between sets. The level of load also determines the maximum speed at which the exercise can be executed. Based on methods primarily used by body builders, a maximum speed of movement well below that for one repetition and repetitions until exhaustion is also known to have a muscle mass-enhancing effect. Besides these recommendations, one must bear in mind that the mechanical load on the muscle fibres is the one stimulus for adaptations. It is just the range of intensity and volume described above, which has been shown to cause apparent hypertrophy effects although also lower intensities and higher volumes will cause muscle fibres to increase in size, but probably not to the same extent. The lower the intensity, the larger the extent this targets type 1 muscle fibres. To start with, neural adjustments can be expected to occur beyond cellular hypertrophic adaptation, even before muscle fibre hypertrophy effects on strength become apparent. Improvements of intra- and intermuscular coordination and individual accommodation to the training exercise take place within the first training sessions and will result in considerable strength improvements, which must not be attributed to muscle hypertrophy at that time (Sale 2003; Zatsiorsky and Kraemer 2006; Frost et al. 2010).

5.4.2.2 Intramuscular Coordination

Intramuscular coordination is particularly enhanced when loads are further increased to 85–100% of the 1RM and the number of repetitions is reduced to a third and repeated in 3–5 sets. Movement velocities must be slow due to the heavy load.

Intramuscular coordination exercises are meant to improve the recruitment of large motor units of predominantly type 2 muscle fibres and to enhance the rating of efferent motor unit action potentials.

5.4.2.3 Specific Power

In specific power, the close association of strength and speed becomes apparent. Specific power exercises are designed to match or correspond to respective movement requirements of a sport or discipline and improve neural regulation of muscle strength provision under specific working conditions. Throwers in field athletics, for example, spend considerable hours in the free weight room, building muscle mass and improving intramuscular coordination. As previously described, heavy weights need to be moved to achieve a desired level of strength. The athletes, however, need to handle weights in their disciplines, which are only a small fraction in weight of those used during strength training. Thus, specific power exercises need to transfer the general strength abilities into the desired movement execution and—to stay with our example of throwers—make the strength available under the specific conditions of the discipline, namely, to move light weights to a maximum speed in a limited range of motion. The rate at which muscle strength needs to be available and the ability to produce muscle strength despite constantly decreasing resistance during the throwing action becomes the main task. It is of no use to produce peak power at a resistance of 30 kg when the shot the athlete needs to put in competition weighs only 4 kg (Bourdin et al. 2010).

On the basis of a well-developed maximum strength level, specific power exercises, on the one hand, will introduce additional weights into the actual movement execution (e.g. sprinting against resistance weights or parachutes, throwing with overweight implements, jumps with weight jackets, etc.). In contrast, the movement execution will be alleviated to develop speed abilities by reducing loads below competition conditions (e.g. assisted sprints, throwing with lighter weights, rubber bands assisting jumps, etc.). As the nature of these exercises is special and requires careful consideration of individual determining factors, it is beyond the scope of this chapter to give recommendations for general training to promote specific power abilities.

5.4.2.4 Stabilization

Isometric strength training, where a load is held stationary for a certain time over 3–5 sets, is not common in sports except for static stabilization. This might, however, be the method of choice in special patient populations with movement limitations.

A particular form of static as well as dynamic strength training exercise is subsumed under the method of stabilization training. The aim of stabilization training, on the one hand, is to prevent injury and, on the other hand, to improve the torso's ability to act as a bearing/support for the limbs during movement execution (Saeterbakken et al. 2011; Judge et al. 2003). Exercises for novices are designed to enable the test person to hold his/her body in a stationary position, by using:

- A limited number of support points, which are progressively reduced in the course of training (push up position on both hands or one hand and both feet or one foot)
- A combination of flexible support surfaces (soft mats, trampolines, balance boards)

Further improvements of stability can be obtained by including:

- Dynamic limb movements with or without external resistance (elastic rubber bands, medicine balls, hand weights)
- Further sources of external perturbations (e.g. catching balls, swinging vibration sticks, juggling while balancing on unstable surface)

The main objective of stabilization exercises for joints is to improve the strength and coordination of agonist–antagonist contractions and to enhance sensory feedback of limb position and joint configuration and the respective motor response (Bruhn et al. 2001; Melnyk et al. 2009). The latter training mode is also known as sensorimotor training (Granacher et al. 2011).

5.5 Summary

Performance diagnostic is the prerequisite for assessing the status of health and performance capability of top athletes down to medical patients. Physical fitness can be distinguished in regard to five principal forms of motor system demands, namely, endurance, strength, coordination, speed and flexibility, whereby only endurance and strength are dealt with in this chapter.

Endurance includes dynamic work of more than 1/6 to 1/7 of the whole muscle mass with regard to the highest and continuous performance capability. Pivotal measuring parameters of this form of endurance are the maximum rate of oxygen uptake and the lactate-performance curve, which can be best assessed during incrementally graded exercise tests. The test results in turn can also be used to determine the physical demands for controlled training regimes. Differing training goals such as the improvement of aerobic or aerobic–anaerobic capacity, respectively, are to be considered when structuring the endurance training in respect to exercise intensity and duration (e.g. basic endurance training I or II).

Strength is the magnitude of dynamic or static muscular performance done, with the dynamic-concentric, dynamic-eccentric and static forces being of paramount importance. However, human movements usually comprise a combination of eccentric followed by concentric contraction mode. The amount of muscle tension developed depends mainly on the number and size of motor units involved as well as the frequency of depolarizing motor unit action potentials. The muscle fibre cross-sectional area has the main impact on maximum static strength. Methods for assessing muscle strength include, for example, direct in vivo measurements with implementation of a force sensor into a tendon, qualitative maximum strength estimations (1 repetition maximum), force measurements in strength training machines or the use of isokinetic dynamometers. The method of choice depends on the experimental setting

and the required accuracy. Strength training regimes differ depending on their primary aims, which can be hypertrophy, intramuscular coordination, specific power or stabilization.

References

Albracht K, Arampatzis A (2006) Influence of the mechanical properties of the muscle-tendon unit on force generation in runners with different running economy. Biol Cybern 95:87–96

ACSM Position Stand (1998) The recommended quantity and quality of exercise for developing and maintaining cardiorespiratory and muscular fitness and flexibility in healthy adults. Med Sci Sports Exerc 30(6):975–991

ACSM's Guidelines for Exercise Testing and Prescription (2010) 8th Edn. American College of Sports Medicine. Lippincott Williams and Wilkins, Baltimore, MD

Amann M, Subudhi AW, Walker J, Eisenman P, Shultz B, Foster C (2004) An evaluation of the predictive validity and reliability of ventilatory threshold. Med Sci Sports Exerc 36: 1716–1722

Arampatzis A, Morey-Klapsing G, Karamanidis K, DeMonte G, Stafilidis S, Brüggemann GP (2005) Differences between measured and resultant joint moments during isometric contractions at the ankle joint. J Biomech 38:885–892

Arndt AN, Komi PV, Brüggemann GP, Lukkariniemi J (1998) Individual muscle contributions to the in vivo achilles tendon force. Clin Biomech 13:532–541

Bacon L, Kern M (1999) Evaluating a test protocol for predicting maximum lactate steady state. J Sports Med Phys Fitness 39:300–308

Baron B, Dekerle J, Robin S, Neviere R, Dupont L, Matran R, Vanvelcenaher J, Robin H, Pelayo P (2003) Maximal lactate steady state does not correspond to a complete physiological steady state. Int J Sports Med 24(8):582–587

Baechle T, Earle RW (eds) (2008) Essentials of strength training and conditioning. Human Kintetics, Champaign

Baldari C, Guidetti L (2000) A simple method for individual anaerobic threshold as predictor of max lactate steady state. Med Sci Sports Exerc 32:1798–1802

Beneke R, Duvillard S (1996) Determination of maximal lactate steady state in selected sports events. Med Sci Sports Exerc 28:241–246

Beaver WL, Wasserman K, Whip BJ (1986) A new method for detecting anaerobic threshold by gas exchange. J Appl Physiol 60:2020–2027

Bentley DJ, Newell J, Bishop D (2007) Incremental exercise test design and analysis: implications for performance diagnostics in endurance athletes. Sports Med 37(7):575–586

Billat VL, Sirvent P, Py G, Koralsztein JP, Mercier J (2003) The concept of maximal lactate steady state: a bridge between biochemistry, physiology, and sport science. Med Sci Sports Exerc 33(6):407–426

Bishop D (1997) Reliability of a 1-h endurance performance test in trained female cyclists. Med Sci Sports Exerc 29:554–559

Borg G, Hassman P, Langerstrom M (1987) Perceived exertion in relation to heart rate and blood lactate during arm and leg exercise. Eur J Appl Physiol 65:679–685

Borg G (1998) Borg's perceived exertion and pain scales. Human Kinetics, Champaign IL

Bourdin M, Rambaud O, Dorel S, Lacour JR, Moyen B, Rahmani A (2010) Throwing performance is associated with muscular power. Int J Sportsmed 31:505–510

Bruhn S, Gollhofer A, Gruber M (2001) Proprioception training for prevention and rehabilitation of knee joint injuries. Eur J Sports Traumatol Rel Res 23:82–89

Cairns S, Knicker AJ, Thompson MW, Sjøgaard G (2005) Evaluation of models used to study neuromuscular fatigue. Exerc Sport Sci Rev 33(1):9–16

Cardinale M, Newton R, Nosaka K (2011) Strength and conditioning – biological principles and practical applications. Wiley Blackwell, Chichester, UK
Colson SS, Martin A, Van Hoecke J (2009) Effects of electromyostimulation versus voluntary isometric training on elbow flexor muscle strength. J Electromyogr Kinesiol 19(5):311–319
Coyle EF, Feltner ME, Kautz SA (1991) Physiological and biomechanical factors associated with elite endurance cycling performance. Med Sci Sports Exerc 23:93–107
De Luca CJ, Adam A, Wotiz R, Gilmore LD, Nawab SH (2006) Decomposition of surface EMG signals. J Neurophysiol 96:1646–1657
Dekerle J, Baron B, Dupont L, Vanvelcenaher J, Pelayo P (2003) Maximal lactate steady state, respiratory compensation threshold and critical power. Eur J Appl Physiol 89(3–4):281–288
Denis C, Foujuet R, Poty P, Geyssant A, Lacour JR (1982) Effects of 40 weeks of endurance training on the anaerobic threshold. Int J Sports Med 3:208–214
Dias JA, Dal Pupo JD, Reis DC, Borges L, Santos SG, Moro ARP, Borges NG Jr (2011) Validity of two methods for estimation of vertical jump height. J Strength Cond Res 25(7):2034–2039
Dickhuth HH, Röcker K, Mayer F, Nieß A, Horstmann T, Heitkamp HC (1996) Bedeutung der Leistungsdiagnostik und Trainingssteuerung bei Ausdauer- und Spielsportarten. Dt Zeit Sportmed 47:183–189
Ditroilo M, Hunter AM, Haslam S, De Vito G (2011) The effectiveness of two novel techniques in establishing the mechanical and contractile responses of biceps femoris. Physiol Meas 32:1315–1326
Fabian K, Eisenkolb E, Sauermann A (1997) Praktikable Trainingssteuerung im leichtathletischen Langsprint durch Blutlaktatmessung. Leistungssport 27 (1997) 4:14–16
Faude O, Kindermann W, Meyer T (2009) Lactate threshold concepts: how valid are they? Sports Med 39:469–490
Finni T, Komi PV, Lepola V (2000) In vivo human triceps surae and quadriceps femoris muscle function in a squat jump and counter movement jump. Eur J Appl Physiol 83(4–5):416–426
Finni T, Komi PV, Lepola V (2001) In vivo muscle mechanics during locomotion depend on movement amplitude and contraction intensity. Eur J Appl Physiol 85(1–2):170–176
Föhrenbach R, Mader A, Hollmann W (1987) Determination of endurance capacity and prediction of exercise intensities for training and competition in marathon runners. Int J Sports Med 8:11–18
Froelicher V, Myers JN (2000) Exercise and the heart, 4th edn. Saunders, Philadelphia
Frost DM, Cronin J, Newton RU (2010) A biomechanical evaluation of resistance: fundamental concepts for training and sports performance. Sports Med (Auckland, NZ) 40(4):303–326
Fukashiro S, Komi PV, Järvinen M, Miyashita M (1995) In vivo Achilles tendon loading during jumping in humans. Eur J Appl Physiol Occup Physiol 71(5):453–458
Gardiner PF (2011) Advanced neuromuscular exercise physiology. Human Kinetics, Champaign
Gellish RL, Goslin BR, Olson RE, McDonald A, Russi GD, Moudgil VK (2007) Longitudinal modeling of the relationship between age and maximal heart rate. Med Sci Sports Exerc 39(5):822–829
Gibbons RJ, Balady GJ, Bricker JT, Chaitman BR, Fletcher GF, Froelicher VF, Mark DB, McCallister BD, Mooss AN, O'Reilly MG, Winters WL, Gibbons RJ, Antman EM, Alpert JS, Faxon DP, Fuster V, Gregoratos G, Hiratzka LF, Jacobs AK, Russell RO, Smith SC (2002) ACC/AHA guideline update for exercise testing. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). Circulation 106:1883–1892
Gollhofer A, Horstmann GA, Schmidtbleicher D, Schönthall D (1990) Reproducibility of electromyographic patterns in stretch-shortening type contractions. Eur J Appl Physiol Occup Physiol 60:7–14
Granacher U, Muehlbauer T, Taube W, Gollhofer A, Gruber M (2011) Sensorimotor training. In: Cardinale M, Newton R, Nosaka K (eds) Strength and conditioning – biological principals and practical applications, 1st edn. Wiley Blackwell, Chichester, UK, pp 399–409
Gregory CM, Bickel CS (2005) Recruitment patterns in human skeletal muscle during electrical stimulation. Phys Ther 85(4):358–364
Grosser M, Starischka S, Zimmermann E (2001) Das neue Konditionstraining für alle Sportarten, für Kinder, Jugendliche und Aktive. BLV Verlagsgesellschaft GmbH, München

Heck H, Mader A, Hess G, Mücke S, Müller P, Hollmann W (1985a) Justification of the 4-mmol/l lactate threshold. Int J Sports Med 6(3):117–130
Heck H, Hess G, Mader A (1985b) Vergleichende Untersuchungen zu verschiedenen Laktat-Schwellenkonzepten. Dtsch Z Sportmed 1:19–25
Heck H (1990) Laktat in der Leistungsdiagnostik. Wissenschaftliche Schriftenreihe des Deutschen Sportbundes. Karl Hofmann, Schorndorf
Heck H, Beneke R (2008) 30 Jahre Laktatschwellen – was bleibt zu tun? Dtsch Z Sportmed 59:297–302
Heitkamp HC, Holdt M, Scheib K (1991) The reproducibility of the 4 mmol/l lactate threshold in trained and untrained women. Int J Sports Med 12:363–368
Henneman E (1981) Recruitment of motor units: the size principle. In: Desmedt JE (ed) Motor unit types, recruitment and plasticity in health and disease. Karger, New York, pp 26–60
Hill AV (1925) Muscular activity. Williams and Wilkins, Baltimore
Hill AV (1934) The efficiency of bicycle pedaling. J Physiol 82:207–210
Hollmann W (1959a) Report on the Pan-American Congress of sport physicians in Chicago (1959 Sep 1–2) [in German]. Sportarzt Sportmed 10(12):285–6
Hollmann W (1959b) The relationship between pH, lactic acid, potassium in the arterial and venous blood, the ventilation, PoW and pulse frequency during increasing spiroergometric work in endurance-trained and untrained persons. 3. Pan-American Congress for Sports Medicine, Chicago
Hollmann W (1961) The problem of endurance performance capacity [in German]. Fortschr Med 79:439
Hollmann W (1963) Maximal and endurance performance capacity of untrained and endurance-trained persons [in German]. Barth, Munich
Hollmann W (1967) Zur Trainingslehre: Muskuläre Beanspruchungsformen und ihre leistungsbegrenzenden Faktoren. Sportarzt Sportmed 11:443
Hollmann W, Strüder HK (2009) Sportmedizin Grundlagen für körperliche Aktivität. Training und Präventivmedizin. New York Schattauer, Stuttgart
Jackson AS, Blair SN, Mahar MT, Wier LT, Ross RM, Stuteville JE (1990) Prediction of functional aerobic capacity without exercise testing. Med Sci Sports Exerc 22(6):863–870
Jeukendrup A, Sarris WH, Brouns F, Kester AD (1996) A new validated endurance performance test. Med Sci Sports Exerc 28:266–270
Jorgensen T, Andersen LB, Froberg K, Maeder U, von Huth SL, Aadahl M (2009) Position statement: testing physical condition in a population – how good are the methods. Eur J Sport Sci 9:257–267
Judge LW, Moreau C, Burke JR (2003) Neural adaptations with sport-specific resistance training in highly skilled athletes. J Sports Sci 21(5):419–427
Karvonen MJ, Kentala E, Mustala O (1957) The effect of training on heart rate. A longitudinal study. Ann Med Exp Biol Fenn 35:307–315
Katch VL, Sady SS, Freedson P (1982) Biological variability in maximum aerobic power. Med Sci Sports Exerc 14(1):211–215
Kernell D (2006) The motoneuron and its muscle fibre. Oxford University Press, New York
Kilding AE, Jones AM (2005) Validity of a single-visit protocol to estimate the maximum lactate steady state. Med Sci Sports Exerc 37(10):1734–1740
Kline GM, Porcari JP, Hintermeister R, Freedson PS, Ward A, McCarron RF, Ross J, Rippe JM (1987) Estimation of $\dot{V}O_2$max from a one-mile track walk, gender, age, and body weight. Med Sci Sports Exerc 19:253–259
Knicker AJ, Renshaw I, Oldham ARH, Cairns SP (2011) Interactive processes link the multiple symptoms of fatigue in sport competition. Sports Med (Auckland, NZ) 41(4):307–328
Knipping HW (1929) The economy of muscle work in healthy and sick persons [in German]. Z Gesamte ExpMed 66:517
Knipping HW, Bolt W, Valentin H et al (1955/60) Examination and evaluation of heart patients [in German]. Enke, Stuttgart
Komi PV, Salonen M, Järvinen M, Kokko O (1987) In vivo registration of Achilles tendon forces in man. I. Methodological development. Int J Sports Med 8(1):3–8
Komi PV, Belli A, Huttunen V, Bonnefoy R, Geyssant A, Lacour JR (1996) Optic fibre as a transducer of tendomuscular forces. Eur J Appl Physiol 72:278–280

Kuipers H, Rietjens G, Verstappen F, Schoenmakers H, Hofman G (2003) Effects of stage duration in incremental running tests on physiological variables. Int J Sports Med 24:486–491
Laplaud D, Guinot M, Favre-Juvin A, Flore P (2006) Maximal lactate steady state determination with a single incremental test exercise. Eur J Appl Physiol 96(4):446–452
Liesen H, Hollmann W (1981) Ausdauersport und Stoffwechsel. Hofmann, Schorndorf
Lindsay FH, Hawley JA, Myburgh KH, Schomer HH, Noakes TD, Dennis SC (1996) Improved athletic performance in highly trained cyclists after interval training. Med Sci Sports Exerc 28:1427–1434
Löllgen H, Graham T, Sjogaard G (1980) Muscle metabolites, force and perceived exertion bicycling at varying pedal rates. Med Sci Sports Exerc 12:345–351
Löllgen H, Erdmann E, Gitt A (eds) (2009) Ergometrie – Belastungsuntersuchungen in Klinik und Praxis, 3rd edn. Berlin, Springer
Mader A, Liesen H, Heck H, Philippi H, Rost R, Schürch P, Hollmann W (1976) Evaluation of sports specific endurance capacity in the laboratory [in German]. Sportarzt Sportmed 27(4): 80(5):109
Mattern CO, Gutilla MJ, Bright DL, Kirby TE, Hinchcliff KW, Devor ST (2003) Maximal lactate steady state declines during the aging process. J Appl Physiol 95:2576–2582
Mayhew JL, Prinster JL, Ware JS, Zimmer DL, Arabas JR, Bemben MG (1995) Muscular endurance repetitions to predict bench press strength in men of different training levels. J Sports Med Phys Fitness 35(2):108–113
Melnyk M, Schloz C, Schmitt S, Gollhofer A (2009) Neuromuscular ankle joint stabilisation after 4-weeks WBV training. Int J Sports Med 30(6):461–466
Meyer T, Lucia A, Earnest CP, Kindermann W (2005a) A conceptual framework for performance diagnosis and training prescription from submaximal gas exchange parameters-theory and application. Int J Sports Med 26(1):38–48
Meyer T, Davison RC, Kindermann W (2005b) Ambulatory gas exchange measurements – current status and future options. Int J Sports Med 26:19–27
Nawab SH, Chang SS, De Luca CJ (2010) High yield decomposition of surface EMG signals. Clin Neurophysiol 121:1602–1615
Newton R, Cormie P, Cardinale M (2011) Principles of athletic testing. In: Cardinale M, Newton R, Nosaka K (eds) Strength and conditioning – biological principals and practical applications. Wiley Blackwell, Chichester, UK, pp 255–276
Neumann G, Pfützner A, Hottenrott K (2000) Alles unter Kontrolle: Ausdauertraining. Meyer and Meyer, Aachen
Paillard T (2008) Combined application of neuromuscular electrical stimulation and voluntary muscular contractions. Sports Med (Auckland, NZ) 38(2):161–177
Pfitzinger P, Freedson PS (1998) The reliability of lactate measurements during exercise. Int J Sports Med 19:349–357
Plato PA, McNulty M, Crunk SM, Tug EA (2008) Predicting lactate threshold using ventilatory threshold. Int J Sports Med 29:732–737
Pringle JS, Jones AM (2002) Maximal lactate steady state, critical power and EMG during cycling. Eur J Appl Physiol 88(3):214–226
Roffey DM, Byrne NM, Hills AP (2007) Effect of stage duration on physiological variables commonly used to determine maximum aerobic performance during cycle ergometry. J Sports Sci 25:1325–1335
Rost R, Hollmann W (1978) Herz, Gefäßsystem und Sport. Mod Ther 1:46–58
Saeterbakken AH, van den Tillaar R, Seiler S (2011) Effect of core stability training on throwing velocity in female handball players. J Strength Cond Res/National Strength and Conditioning Association 25(3):712–718
Sale DG (2003) Neural adaptation to strength training. In: Komi PV (ed) Strength and power in sport, 2nd edn. Blackwell, Oxford, pp 281–314
Sjodin B, Jacobs I, Svedenhag J (1982) Changes in the onset of blood lactate accumulation (OBLA) and muscles enzymes after training at OBLA. Eur J Appl Physiol 49:45–57
Solberg G, Robstad B, Skjonsberg OH, Borchsenius F (2005) Respiratory gas exchange indices for estimating the anaerobic threshold. J Sports Sci Med 4:29–36

Svedahl K, MacIntosh BR (2003) Anaerobic threshold: the concept and methods of measurement. Can J Appl Physiol 28:299–323

Tanaka H, Monahan KD, Seals DR (2001) Age-predicted maximal heart rate revisited. J Am Coll Cardiol 37:153–156

Washington RL, Bricker JT, Alpert BS, Daniels SR, Deckelbaum RJ, Fisher EA, Gidding SS, Isabel-Jones J, Kavey RE, Marx GR (1994) Guidelines for exercise testing in the pediatric age group. From the Committee on Atherosclerosis and Hypertension in Children, Council on Cardiovascular Disease in the Young, the American Heart Association. Circulation 90:2166–2179

Wasserman K, Mellroy MB (1964) Detecting the threshold of anaerobic metabolism in cardiac patients during exercise. Am J Cardiol 14:844

Wasserman K, Whipp BJ, Koyal SN, Beaver WL (1973) Anaerobic threshold and respiratory gas exchange during exercise. J Appl Physiol 35(2):236

Wasserman K, Beaver WL, Whipp BJ (1986) Mechanisms and patterns of blood lactate increase during exercise in man. Med Sci Sports Exerc 18(3):344

Wasserman K, Hansen J, Darryl Y, Whipp B (2005) Principles of exercise testing and interpretation, 4th edn. Philadelphia, Lippincott Williams & Wilkins

Wiksten D, Peter C (2000) The athletic trainer's guide to strength and endurance training. SLACK Incorporated, Thorofare, NJ

Wilmore JH, Costill DL (2004) Cardiovascular and respiratory adaptation to training. In: Wilmore JH, Costill DL (eds) Physiology of sport and exercise. Human Kinetics, Champaign, pp 270–304

Wonisch M, Hofmann P, Pokan R, Kraxner W, Hödl R, Maier R, Watzinger N, Smekal G, Klein W, Fruhwald FM (2003) Spiroergometry in cardiology – physiology and terminology (German). J Kardiol 10:383–390

Zatsiorsky VM, Kraemer WJ (2006) Krafttraining – Praxis und Wissenschaft. Meyer und Meyer, Aachen

Zintl F, Eisenhut A (2001) Ausdauertraining. Grundlagen, Methoden, Trainingssteuerung. BLV Verlagsgesellschaft, München

Chapter 6
Psychological Assessments in Physical Exercise

Marcel Daamen and Markus Raab

Abstract This chapter will present a short review of psychological assessment techniques which are frequently used to measure cognitive and affective functions. If available, these measurement approaches are illustrated with examples from recent sports- and exercise-related studies. In addition, the chapter will discuss important caveats and methodological perspectives and that may be relevant for future studies in this research field, especially in the context of neuroimaging applications.

6.1 Introduction

The development of modern neuroimaging techniques, such as magnetic resonance imaging (MRI), positron emission tomography (PET), and near-infrared spectroscopy (NIRS), along with technical improvements in electroencephalography (EEG), has provided us with methodological tools that give unprecedented insights into human brain function. In recent years, researchers have also started to utilize these methods to elucidate the physiological mechanisms that mediate the acute and chronic influences of physical exercise on human brain function. Yet, to appraise the functional significance of physiological effects that are observed with these neuroimaging tools, they should be correlated with complementary observations of psychological and behavioral outcome measures. Accordingly, the careful selection

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of psychological and behavioral measures is a methodological issue that is also relevant for designing neuroimaging studies aimed at understanding the effects of exercise on brain function.

This chapter will provide a short review of psychological assessment techniques, concentrating on psychological functions that play a prominent role in the recent exercise-related neuroscience literature. These functional domains are divided into two broader classes: *Cognitive functions* and *affective functions*. After providing brief outlines of key theoretical concepts that are central for our current understanding of these functional domains, we review assessment techniques that are typically used to operationalize these psychological constructs. If possible, the approaches will be illustrated with relevant sports- and exercise-related studies, and we will discuss methodological perspectives that may be interesting for future studies. The final section will conclude with some general considerations for the practical use of psychological tests, including possible applications in, and adaptations to, neuroimaging studies.

6.2 Cognitive Functions

In recent years, the relationship between physical activity and cognitive function has received considerable attention (Hillman et al. 2008; Etnier 2009). There is accumulating evidence that behavioral interventions that aim to increase physical fitness can have a beneficial effect on cognitive function in older adults (Colcombe and Kramer 2003). This observation has important public health implications, as regular physical activity may help to protract age-related cognitive decline, or ameliorate the progression of dementia disorders (Etnier 2009). In addition, recent studies suggest that physical fitness may also influence cognitive development in children and adolescents (Hillman et al. 2008; Chaddock et al. 2010).

Although there are several cognitive domains that might be influenced by exercise-induced brain changes, this review will mainly concentrate on four specific aspects which are frequently assessed in contemporary exercise-related studies: *short-term and working memory*, *long-term memory*, *attention*, and *executive control functions* (see Table 6.1, for a short overview). In addition, we will include a short discussion on *global cognitive measures*. Although these measures do not necessarily qualify as sensitive outcome variables, the global functional level of an individual can be an important background characteristic (e.g., as a confounding or moderator variable).

6.2.1 General Background

Most contemporary models of higher mental functions (e.g., attention, vision, memory, and language) are based on the *cognitive processing approach*, which means that they conceptualize the human mind as an information processing

Table 6.1 Cognitive domains, task formats and exercise-related applications

Functional domain	Typical paradigms	Exercise-related applications
Working memory		
• *Short-term retention*	Forward digit span	Voss et al. (2010)
• *Manipulation*	Backward digit span	Voss et al. (2010)
• *Updating*	N-back	Stroth et al. (2010)
• *Inhibition*	Operation span, reading span	Sibley and Beilock (2007)
Long-term memory		
• *Declarative*	Word list learning and retrieval	Pereira et al. (2007)
	Story recall	Stroth et al. (2009)
	Associative learning	Chaddock et al. (2010)
• *Nondeclarative*	Implicit word stem completion	Eich and Metcalfe (2009)
Attention		
• *Intensity*	Simple reaction time	Smiley-Oyen et al. (2008)
	Sustained attention (e.g., CPT)	Del Giorno et al. (2010)
• *Selectivity*	Visual search (e.g., TMT-part A)	
	Cancellation tests	Stroth et al. (2009)
	Digit symbol coding (e.g., DSST)	Williamson et al. (2009)
	Global-local processing	Pesce et al. (2007)
	Divided attention (e.g., PASAT)	Del Giorno et al. (2010)
Executive control functions		
• *Set shifting*	Wisconsin card sorting test	Dietrich and Sparling (2004)
	TMT-part B	
	Task-switching paradigms	EEG: Themanson et al. (2006)
• *Inhibition*	Stroop task	Smiley-Oyen et al. (2008)
	Eriksen Flanker task	EEG: Themanson and Hillman (2006)
		fMRI: Colcombe et al. (2004)
	Go/Nogo tasks	Smiley-Oyen et al. (2008)
	Stop signal task	Kramer et al. (1999)

TMT Trail-making test, *DSST* Digit symbol substitution test, *CPT* Continuous performance test, *PASAT* Paced auditory serial addition test, *EEG* electroencephalography, *fMRI* functional magnetic resonance imaging

system that analyzes incoming sensory stimuli, evaluates the sensory input in comparison to stored memory representations, and uses the information to plan, generate, and regulate appropriate behavioral responses (Audiffren 2009; Tomporowski 2009). Psychological functions are interpreted as the product of latent cognitive processes that are not accessible to direct observation or subjective experience, but have to be inferred from behavior. Typically, this is achieved by analyzing the consequences of task manipulations on behavioral output parameters, such as reaction times and error rates. While cognitive sciences show a traditional focus on verbal and overt motor responses (e.g., buttons presses), it should be noted that there are several other response modalities available, including psychophysiological measures (e.g., skin conductance, electromyography, blood pressure, and heart rate responses).

6.2.2 Short-term and Working Memory

The assumption that memory is not a unitary faculty, but can be divided into some kind of *short-term memory*, which keeps a limited amount of information highly accessible for a time frame of a few seconds, and *long-term memory*, which is theoretically capable to store unlimited amounts of information for days, weeks, and years, became especially popular with the advent of cognitive psychology, and is a key aspect of the influential "modal model" of memory (Atkinson and Shiffrin 1968). Building on the idea that short-term memory is a store with limited capacity, short-term memory tasks typically probe *how much* and *how long* information can be maintained. A classic example is the *forward digit span task*, which is included both in the *Wechsler Memory Scales* (*WMS*: Wechsler 2009) and *Wechsler Adult Intelligence Scale* (*WAIS*: Wechsler 2008): In this task, orally presented sequences of digits have to be repeated in identical order (e.g., "5-6-2-9" → "5-6-2-9"), and the length of the sequences is increased incrementally to determine the maximum number of elements that can be repeated correctly.

While the classical concept of human *working memory* (Baddeley and Hitch 1974) is based on the distinction between short-term and long-term memory, it emphasizes that short-term memory is not just a passive store that maintains information, but serves as an active workspace for a wide range of complex cognitive operations. Therefore, this model not only introduces modality-specific short-term storage systems (a "phonological loop" for verbal information, a "visuospatial scratchpad" for visual object and spatial information, and an "episodic buffer", which interfaces the other short-term stores with long-term memory). Moreover, the model adds a "central executive" component, which is thought to regulate inflow and active manipulation of information within these short-term memory stores, and their interactions with long-term memory (see Baddeley 2003, for a more comprehensive review).

The functional differentiation between storage and regulatory processes has implications for the practical measurement of working memory: While traditional short-term memory measures are mainly focused on the temporary maintenance of information, human working memory paradigms typically include additional task requirements that call for some kind of top-down control. For example, these requirements may encompass the active manipulation of items that are currently represented in short-term memory. Classical examples are the *WAIS backward digit span task*, where sequences of orally presented numbers have to be recalled in the reversed order (e.g., "5-6-2-9" → "9-2-6-5"), or the *WAIS letter–number sequencing task*, where sequences of letters and numbers are presented randomly but have to be reproduced in alphabetical and numerical order (e.g., "D-4-A-3" → "A-D-3-4": Wechsler 2008). Other tasks require a continuous updating of stored information, for example in *N*-back tasks, where series of items (e.g. letters, numbers, geometric figures) are presented one at a time, and subjects have to indicate whether the *current* item is identical to the item presented *N* trials (typically 1, 2 or 3) *before* (Lezak et al. 2004). Other paradigms capture the ability to suppress interfering

information that is presented during retention intervals. Typical examples are *reading span* and *operation span tasks* (Miyake et al. 2000; Sibley and Beilock 2007), where subjects have to memorize a sequence of items, but critically, these relevant items are interleaved with distracting information, for example by reading short sentences or completing mathematical operations.

Many of the earlier exercise-related studies were unable to find associations between exercise and "working memory" functions, both on the acute (Coles and Tomporowski 2008; Tomporowski and Ganio 2006, but see Pontifex et al. 2009) and chronic level (Smith et al. 2010). On the one hand, it is possible that physical exercise had effects on task performance that were too subtle to be substantiated with these behavioral measures: Here, neuroimaging techniques may provide a more sensitive tool (e.g., EEG—see also Chap. 18). On the other hand, the failure to find behavioral changes may be partially attributable to the predominant use of classic short-term memory paradigms that primarily measure the temporary maintenance of information (e.g., digit span tasks). It was suggested that working memory paradigms may provide a more sensitive target for investigation, since they additionally tax the central executive (McMorris 2008; McMorris et al. 2011), but this will have to be corroborated in future studies.

In addition, the quality of the maintained information may play a decisive role, because this has a necessary influence on the brain circuits that are critically implicated in information storage. Traditionally, short-term memory functions were primarily associated with fronto-parietal, neocortical networks (Baddeley 2003). Since global amnesic patients with hippocampal damage typically show normal performance in traditional short-term memory tasks (e.g., digit span), it was assumed that the human hippocampus plays no significant role in short-term memory, but is primarily involved in the transfer of declarative information from short-term into long-term memory (Nadel and Hardt 2011). Meanwhile, there is recent neuropsychological and neuroimaging evidence that the hippocampus does participate in certain short-term memory functions, although this may only become apparent in specific task settings where the retention of situation-specific configurations or associations between distinct items (e.g., spatial relations of objects in spatial memory tasks) is important to discriminate between similar stimuli (Bird and Burgess 2008; Nadel and Hardt 2011). Considering the various animal studies that found a modulating effect of regular physical exercise on hippocampal function and spatial memory performance in rodents (Cotman et al. 2007; see also Chap. 1), it can be speculated that complementary links may also be present in humans, given that appropriate task material is used. Consistent with this view, a cross-sectional study with older adults found that the physical fitness level was correlated with the performance in a spatial memory task that measured the short-term retention of the positions of one, two, or three dots in a random spatial arrangement: Critically, the statistical relationship was mediated by the hippocampal volumes, as obtained from structural MRI data (Erickson et al. 2009; see also Chap. 17). These findings suggest that this specific kind of short-term memory paradigm (or similar paradigms presenting complex relational information) provides an interesting tool for future studies. In particular, functional neuroimaging

data are needed to test whether physical fitness differences in hippocampal volume translate into differential brain activation patterns during the performance of this kind of paradigm.

6.2.3 Long-term Memory

Long-term memory refers to the ability to maintain and retrieve information about past experiences that happened minutes, days, months, or years ago. The appearance of these long-term memory abilities is quite heterogeneous, and the available psychological and neuroscientific literature suggests that they do not reflect the labor of a unitary faculty, but are the products of multiple memory systems that work in parallel, and are specialized for the acquisition, storage, and retrieval of different kinds of information (Squire 2004; Nadel and Hardt 2011). There is a broad consensus that long-term memory contents can be dichotomized into at least two broader domains: *declarative* and *nondeclarative memory* functions (e.g., Squire 2004).

6.2.3.1 Declarative Memory

Declarative (or explicit) memory refers to those forms of long-term memory where the recall of information causes a subjective feeling of "knowing" or "remembering" (e.g., Squire 2004). It encompasses *semantic memory*, which contains the factual knowledge that we acquire about regularities in our world (e.g., what a chair looks like and what to do with it, "Paris is the capital of France," "2 + 2 = 4"), and *episodic memory*, which contains our recollections of unique events that we experience as our own past (e.g., marriage, birth of a child, burial of a close friend).

Most of the available standardized tests for long-term memory are related to declarative memory: Subjects are explicitly asked to memorize presented stimulus material and deliberately try to remember the material after a specified time delay. While a variety of materials are used (e.g., abstract visual stimuli, geometric figures, faces, objects, sounds; see Lezak et al. 2004; Strauss et al. 2006, for more detailed reviews), many of the common long-term memory tests are based on the oral presentation of verbal stimuli, especially word lists (e.g., the *Rey Auditory Verbal Learning Test*, RAVLT) and story passages (e.g., the *WMS Logical Memory subtest*: Wechsler 2009). In many cases, the presentation and subsequent retrieval of the same material is repeated over multiple trials, which allows measuring learning curves (e.g., the number of trials necessary for learning the complete stimulus set). Retrieval performance can be tested immediately after presentation of the material, or after a certain delay (typically in the range of several minutes): Notably, delayed retrieval provides a more reliable indicator of long-term memory, as the time gap reduces the possibility that reproduced items are actually recalled from short-term memory (which would be possible for items that were presented immediately before retrieval).

Turning to the exercise-related literature, many earlier reviews found little evidence for a modulating influence of *acute* physical exercise on declarative long-term memory (e.g., Tomporowski 2009), but an updated meta-analysis (Lambourne and Tomporowski 2010) has challenged this conclusion: In fact, recent studies suggest that exercise-induced arousal can indeed have a beneficial effect on declarative learning and memory, at least *after* acute bouts of exercise (e.g., Winter et al. 2007; Coles and Tomporowski 2008, but see Eich and Metcalfe 2009). From a methodological perspective, it is interesting that positive findings were mainly found for demanding memory paradigms (e.g., by asking subjects to learn associations between pseudowords and familiar objects, or by presenting a 40-item word list only once before testing free recall), indicating that the modulating effects are subtle and may only become apparent in sufficiently difficult task conditions.

Meanwhile, there is substantial evidence for a link between *chronic* exercise and long-term memory function: On the one hand, rodent studies have shown that chronic exercise regimens can improve learning and memory performance in a variety of long-term memory tasks that are known to depend on hippocampal function, and there is accumulating evidence that hippocampal plasticity processes play a key role in the expression of these exercise-induced memory effects (Cotman et al. 2007; see also Chap. 1). On the other hand, a plethora of neuropsychological data from brain-damaged patients indicates that the human hippocampus (and surrounding regions of the medial temporal lobe) is especially critical for the acquisition of declarative long-term memory representations. In fact, behavioral performance in declarative memory tests is traditionally used to make inferences about hippocampal function in clinical patients (Bird and Burgess 2008; Squire 2004; Nadel and Hardt 2011). Therefore, observations from exercise-related studies which found positive associations between regular physical activity and declarative memory performance (e.g., Pereira et al. 2007; Stroth et al. 2009; Smith et al. 2010) may be interpreted as indirect evidence for a facilitating effect of physical exercise on human hippocampal function. Corroborating this view, one of these studies (Pereira et al. 2007) provided initial human evidence for a direct link between improved hippocampal function and verbal declarative memory (see also Chap. 16).

While the above-mentioned investigations used standard memory tests (e.g., word list learning paradigms), it is interesting to note that recent behavioral studies have adapted experimental paradigms that were originally developed to provoke hippocampal activations in functional neuroimaging studies: For example, two recent studies with preadolescent children tested the learning and subsequent recall of novel, arbitrary associations between faces and houses (Chaddock et al. 2011), or between triplets of senseless fractal images (Chaddock et al. 2010). They found that children with lower fitness levels showed a specific deficit in the associative learning of the *item combinations*, but not in *single-item* recognition. Intriguingly, one of these studies (Chaddock et al. 2010) found that the association between fitness and relational memory was mediated by hippocampal volume. These findings concur with classical neuropsychological theories that emphasize the central role of the hippocampus for the long-term storage of complex object associations and relations (Bird and Burgess 2008; Nadel and Hardt 2011), and are compatible with the above-mentioned

observations by Erickson et al. (2009), although it has to be acknowledged that the retention intervals in the latter study (~3 s) were only tapping short-term retention. Again, it would be interesting to test whether brain activation patterns *during* the performance of these paradigms show complementary physical fitness effects. While there is still a general lack of functional neuroimaging studies that investigated the influence of exercise on declarative memory functions, this seems to be a promising starting point.

6.2.3.2 Nondeclarative Memory

In contrast to declarative memory, the activation of nondeclarative (or implicit) memory representations causes no subjective memory experience but is expressed implicitly, by changes in behavioral performance that would not appear without practical experience with the task at hand. The most dramatic support for this claim comes from amnesic patients who show training-related behavioral changes in many nondeclarative memory tasks but have no declarative memories of the training sessions (e.g., Graf and Schacter 1985; Foerde 2010). This class of memory functions encompasses a heterogeneous variety of abilities, such as *motor skills* (e.g., swimming, riding a bicycle) and *perceptual skills* (e.g., mirror reading), *perceptual* and *conceptual priming* (i.e., facilitated perceptual or semantic processing of a stimulus after experience with this specific stimulus), *habit learning* (i.e., the feedback-based learning of automated stimulus–response associations), and simple forms of *Pavlovian conditioning* (e.g., learned fear responses) (Squire 2004; Foerde 2010).

To date, nondeclarative memory tests are virtually lacking in the sports and exercise literature. In a rare exception, Eich and Metcalfe (2009) tested marathon runners with a so-called *implicit word stem completion task* (Graf and Schacter 1985): Subjects were initially asked to rate the pleasantness of a presented word list (e.g., *sport*, *flower*,…). Most importantly, no reference was made to the retention of the material which would be subsequently tested. Next, the experimenters presented a list of three-letter word stems (e.g., SPO__, FLO___), and subjects were instructed to complete them with the first words that came to their mind. Critically, half of these word stems belonged to words that were taken from the previously rated list. Although this fact is never made explicit in this kind of paradigm, participants will sometimes complete these word stems with corresponding items from the previous word list (e.g., SPO__ → *sport*, FLO___ → *flower*), which is interpreted as an implicit (i.e., incidental, automatic) retrieval of the familiar material that is probably facilitated (or "primed") by the previous activation of the respective word representations during rating. Although they are not explicitly instructed to recall the word list, it is possible that participants just recognize the items spontaneously (i.e., show an incidental recall from declarative memory). Therefore, the final experimental condition presented another list of word stems which were all derived from the other half of the word list, and participants were explicitly instructed to complete the word stems with items from the previous list (i.e., the word stems were used to provoke *cued recall* from declarative memory). Intriguingly, previous studies using this

paradigm indicate that amnesic patients fail to remember the word list items deliberately in the declarative recall condition, but perform similar to controls in the implicit recall condition (e.g., Graf and Schacter 1985). This functional dissociation suggests that explicit and implicit recall depend on divergent memory processes, which may show a differential sensitivity for alterations of brain function. In fact, Eich and Metcalfe (2009) found that runners who were tested immediately after a marathon showed a *weaker* explicit, but *better* implicit recall than a control sample of marathon runners who were tested before completing a marathon. These divergent effects suggest that the strenuous exercise regimen exerted opposing subacute effects on declarative and nondeclarative memory performance, possibly via neurohumoral stress mechanisms that may facilitate some brain systems, and inhibit others (Eich and Metcalfe 2009).

Possibly, there are other forms of nondeclarative memory that may also prove to be sensitive to the effects of physical exercise, but this has not, to the best of our knowledge, been tested directly. For example, it may be worthwhile to investigate the *feedback-based learning of probabilistic stimulus–response associations*: In these paradigms, correct responses have to be learned by trial and error feedback, which is thought to be strongly associated with dopaminergic function, especially in the basal ganglia (Foerde 2010). Although the available evidence is mainly based on clinical populations, especially patients with Parkinson's disease (Shohamy et al. 2008), it would be interesting to speculate about the possible impact of exercise-induced acute changes in dopaminergic neurotransmitter release, which are discussed in the recent literature (e.g., McMorris 2008), on performance in this kind of task.

6.2.4 Attention

Attentional mechanisms are ubiquitous to cognitive processing. Given that a vast number of sensory inputs, activated memory representations, and internally generated thoughts are continuously streaming into consciousness and compete for the available processing resources, the cognitive system must select those information aspects that are currently most relevant for adaptive behavior, and neglect, or even suppress, representations that are irrelevant. This attentional selection process is often compared with a spotlight, and although this analogy is most appropriate for the specific case of visuospatial attention processes, it provides a nice illustration of two basic characteristics which are typically measured with attentional tasks: *intensity* and *selectivity* (van Zomeren and Brouwer 1994).

6.2.4.1 Intensity of Attention

The intensity aspect of attention relates to the varying amount of attentional resources that are available for energizing sensory and cognitive processing, which

can, metaphorically speaking, be compared to the brightness of a spotlight (van Zomeren and Brouwer 1994). These energizing mechanisms are somewhat neglected by modern theories of attention, but there is a long tradition of neurophysiological studies which indicate that the mesencephalic reticular formation and its diffuse afferent projections to various higher brain regions (which are collectively known as the ascending reticular activation system, ARAS) are crucial for the regulation of the brain activation level (see Audiffren 2009; van Zomeren and Brouwer 1994, for detailed reviews).

This activation (often referred to as "arousal") is thought to determine the alertness level, that is, the preparedness of an organism to respond to external stimuli, or in terms of cognitive models, the basic processing speed of the information processing system. The current alertness level is typically measured with task formats that include only elementary stimulus detections or discriminations, such as *simple reaction time tasks*, where the appearance of a specific target stimulus (e.g., a tone or a visual stimulus) is associated with a single response option (e.g., a button press), as compared to *choice reaction time tasks*, where discriminative responses for different stimuli have to be made (van Zomeren and Brouwer 1994; Lezak et al. 2004; McMorris 2008). As these tasks afford a minimum of sensory and motor processing (without complex cognitive operations that could delay the response), systematic variations in reaction time are supposed to reflect latent differences in the brain arousal level. Although alertness is often measured for task blocks of a few minutes' duration, it is also possible to extend the task duration (from several minutes up to hours), which creates sustained attention tasks, such as the *Continuous Performance Test*, where participants have to react to target stimuli which are randomly interspersed into streams of distractor items (van Zomeren and Brouwer 1994).

Brain arousal is a key variable in many explanatory models for the *acute* cognitive effects of physical exercise: They assume that physical exercise modulates the intrinsic brain activation systems, which broadens (or narrows) the basic energetic resources available for information processing (e.g., "cognitive-energetic" approaches: McMorris 2008; Audiffren 2009). Probably, these modulating effects are mediated by a homeostatic cascade of neuroendocrine adaptations (both in the periphery and in the brain), which eventually increase ARAS transmitter release, especially for dopamine (DA) and norepinephrine (NE: e.g., McMorris 2008). The relationship between exercise, arousal, and cognition is often described by an inverted U-curve function (*Yerkes–Dodson law*). In this model, low levels of activation (e.g., during sleepiness, fatigue) are considered suboptimal for cognitive processing. Moderate aerobic exercise is thought to increase the activation level, which optimizes the stimulation level for improved information processing. In contrast, strenuous (e.g., anaerobic) forms of exercise are supposed to generate extreme levels of brain arousal that cause overstimulation and hence, degradation of processing efficiency. Unfortunately, the available literature provides only limited evidence for this simple kind of dose–response relationships, although it has to be acknowledged that the heterogeneity of the studies (e.g., regarding specific task demands, exercise duration or intensity) complicates firm conclusions (see McMorris 2008, for a more detailed discussion of factors which may contribute to these conflicting results).

In addition, the use of reaction time measures as a behavioral indicator for exercise-induced arousal suffers from certain methodological drawbacks. This interpretation is generally hampered by the fact that reaction time (which is usually defined by the time window between stimulus onset and detection of the overt reaction, e.g., a button press) conflates the influences of several processing stages, including stimulus identification, response selection, but also response *execution*. Thus, faster response times after acute exercise might not (or not only) reflect speeded information processing on the brain level, but also faster electromechanical signal transduction in the peripheral motor pathway (McMorris et al. 2011). This assumption is supported by recent studies that complemented reaction time paradigms with electromyographic (EMG) measurements of peripheral motor activity (see Davranche and Audiffren 2009, for a review). An alternative strategy, which circumvents contamination with motor processes and gives *direct* insights into processing speed on the brain level, is the EEG acquisition of event-related potentials (ERP), which can, for example, be analyzed for amplitude and latency differences (see also Chap. 18).

6.2.4.2 Selectivity of Attention

Modern theories of attention usually emphasize the selectivity aspect of attention, that is, the focusing (or distribution) of the available attentional resources on specific stimuli or stimulus attributes. Metaphorically speaking, this corresponds to the beam radius of the attentional spotlight, which can be zoomed out or in for a broader or narrower view, and shifted in different spatial directions (van Zomeren and Brouwer 1994). This attentional selectivity is supposed to be regulated by both involuntary and voluntary mechanisms. A practical example of an involuntary attentional selection is the orienting response, where novel, unexpected, intense, or biologically significant external stimuli automatically shift attention in the spatial direction of the critical stimulus (van Zomeren and Brouwer 1994). Yet, most tests for attentional function assess the *voluntary* control of selective attention, for example, the ability to "concentrate" on task-relevant stimuli or response options.

There is a whole variety of task paradigms which are difficult to categorize into one comprehensive taxonomic framework. Hence, the following paragraphs can only present some typical examples for this test category (for more extensive reviews, see van Zomeren and Brouwer 1994; Strauss et al. 2006).

A traditional method for measuring selective attention is the use of *visual search* and *cancellation tests*, where subjects have to find critical target stimuli under speeded testing conditions (van Zomeren and Brouwer 1994; Lezak et al. 2004; Strauss et al. 2006): For example, in the *Trail-Making Test Part A* (TMT-A), a set of numbered circles distributed in a random spatial arrangement are presented, and subjects are instructed to connect these numbers in ascending order (Fig. 6.1). While the TMT-A allows subjects to shift attentional focus in a self-determined manner, *cancellation tasks* typically present structured displays (e.g., rows with random sequences of letters or digits) and ask subjects to scan this stimulus display systematically (e.g., line by line) to mark a specified class of target stimuli (e.g., mark all *Fs* and *Rs*).

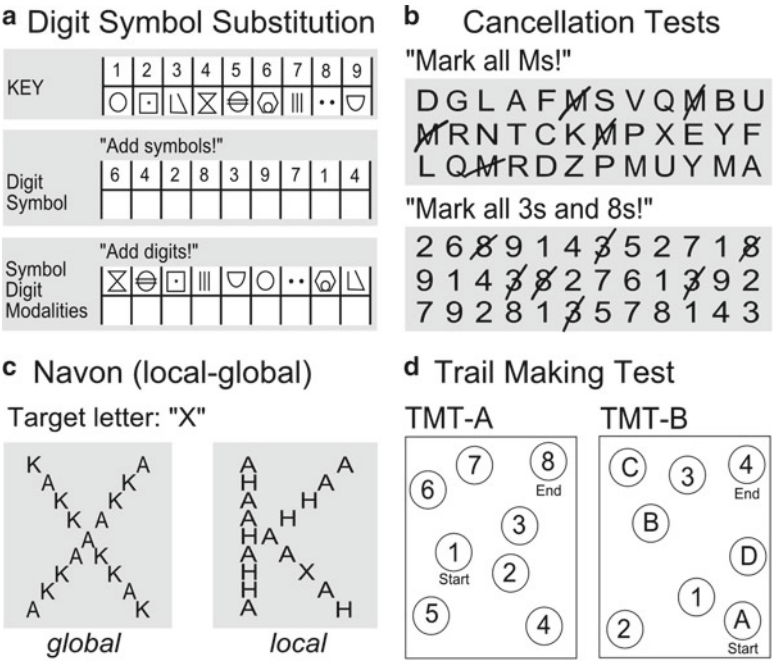

Fig. 6.1 Examples for attentional tasks. Schematic description of stimulus characteristics. See text for details

The ability to control the attentional focus is also critical for successful performance in another classical concentration test format, the *WAIS Digit Symbol Substitution Test* (DSST: Wechsler 2008), and the analogous *Symbol Digit Modalities Test* (SDMT: Smith 1982). Both tasks present a table that assigns each of the digits 1–9 to a specific, nonsense geometrical figure (see Fig. 6.1). Subjects are provided with random series of digits (DSST) or geometric figures (SDMT) and have to write down as many corresponding symbols (DSST) or numbers (SDMT) as possible in a given amount of time. At least in the initial phase (before the transformation rules may be incidentally learned), subjects have to continuously shift attentional focus between table and stimulus rows to look up the correct assignment.

Meanwhile, some experimental paradigms assess the adaptive *zooming* (i.e., broadening and narrowing) of attentional focus, for example, by assessing the ability to attend to local and global stimulus features in so-called *Navon figures* (Navon 1977; see also Miyake et al. 2000). Here, the spatial arrangement of a group of small stimuli forms the global impression of a larger stimulus (e.g., several *A* and *K* letters that make up a large *X* letter; see Fig. 6.1). A series of exercise-related studies (e.g., Pesce et al. 2007) utilized this kind of stimuli: Subjects had to decide whether the presented stimuli contained a predefined target letter, which could be present either at the local level (i.e., as one of the small letters) or at the global level (i.e., as the large letter). Critically, the attentional focus was systematically manipulated by visual warning cues that indicated the probable location of the upcoming target letter.

In one condition, a *large* square cued the probable appearance of a *global* target stimulus, while *small* squares at a specific spatial position cued the probable appearance of a *local* target letter in this position. Thus, the physical size of the cue stimulus automatically zooms the attentional focus to the probable target location. In contrast, the other task condition put a stronger emphasis on "top-down" attentional control: Here, the *large* square cued the probable appearance of a *local* target, and the *small* square cued the appearance of a *global* target, which means that the automatic tendency to adapt the attentional zoom according to the physical size of the cue has to be overridden by voluntary control.

Finally, some paradigms measure *divided attention*, that is, the ability to distribute the available attentional resources, or move the attentional focus, over different stimuli or mental operations (van Zomeren and Brouwer 1994). These tasks are based on the assumption that the structural and energetic capacities of the information processing system are limited, which means that task situations that involve the parallel execution of several cognitive operations can induce interference, as the different processes may compete for the same processing resources. Divided attention is usually tested in *dual-task situations*, for example, by asking subjects to concurrently detect the appearance of target stimuli in two different streams of stimuli (van Zomeren and Brouwer 1994; Lezak et al. 2004). Another popular instrument is the *Paced Auditory Serial Addition Task* (PASAT: Gronwall 1977; Lezak et al. 2004): Here, random sequences of digits are presented, and subjects are instructed to continuously add the current digit to the digit that was presented immediately before (e.g., 5-7-3 $\rightarrow 5+7=$ *12* and $7+3=$ *10*). Additionally, task difficulty is manipulated by changing the tempo of stimulus presentation.

Divided attention is especially relevant for studies that examine cognitive function during acute exercise, as varying requirements of ongoing motor control (e.g., for running, as compared to cycling) may produce different levels of interference with the concurrent processing of the cognitive task (Lambourne and Tomporowski 2010). Critically, interference can eventually resolve in situations where overtraining automates the execution of one task component and leaves the redundant attentional resources for the execution of the concurrent task. As a consequence, the acute effects of an exercise bout may vary for inexperienced as compared to skilled athletes, but also depending on familiarity with the presented cognitive task: Such background differences in task proficiency may contribute to the variable findings of studies which examined cognitive performance during acute exercise (see Lambourne and Tomporowski 2010, for a more detailed discussion).

6.2.5 Executive Control Functions

The concept of executive control functions is an umbrella term for a class of "higher level" cognitive functions that are thought to regulate subsidiary sensory, cognitive, emotional, and motor processes in a supervisory (or "top-down") manner. They enable the planning, execution, and monitoring of complex goal-directed

behavior, especially in novel situations where no automated behavioral scheme is available, or where available behavioral schemes must be adapted to cope with changing situational demands (Gazzaley and D'Esposito 2007; Jurado and Rosselli 2007; Strauss et al. 2006).

The notion of executive control functions was already briefly introduced in previous sections: For example, the idea of supervisory control is especially salient in the "central executive" concept of Baddeley's working memory model (Baddeley 2003), which explains why working memory is often referred to as an executive control function (Miyake et al. 2000; see also: McMorris et al. 2011). Moreover, supervisory control processes are frequently used to explain the voluntary "top-down" regulation of attentional resources, especially in focused or divided attention tasks (van Zomeren and Brouwer 1994). While performance in many of the above-mentioned task paradigms is probably influenced by executive control, they mainly emphasize the subsidiary cognitive domains (i.e., attention and memory). Therefore, the following section will present some task paradigms that aim to operationalize executive control function more directly.

Traditionally, the concept of executive control is closely linked with the prefrontal cortex (PFC: Strauss et al. 2006; Stuss 2007): This region shows extensive synaptic connections (both excitatory and inhibitory) with a broad range of cortical and subcortical structures, which enables the PFC to both amplify *and* suppress neural activity in these associated brain circuits in a "top-down" fashion. From this neuroanatomical perspective, the PFC should be able to modulate a broad range of sensory, cognitive, emotional, and motor processes (Gazzaley and D'Esposito 2007; Miller and Cohen 2001). While the association between the frontal lobes and executive control functions as a psychological *construct* is generally accepted, there are some methodological complexities which have to be considered when measuring this psychological construct with so-called executive control or frontal lobe function *tasks* (for detailed discussions, see Jurado and Rosselli 2007; Stuss 2007): For example, many of the traditional tests are *sensitive*, but not *specific* to frontal lobe dysfunction, as damage in non-frontal (e.g., parietal) brain regions can also impair task performance, probably by interfering with those subordinate processes that are controlled by executive control functions. Thus, performance in these task cannot automatically be interpreted as an indicator of frontal lobe (dys)function (Stuss 2007; Strauss et al. 2006).

Moreover, traditional paradigms usually concentrate on the regulation of *cognitive* processes (i.e., cognitive control), and are mainly sensitive to *dorsolateral* (DLPFC) and *dorsomedial prefrontal* (DMPFC) damage: In contrast, patients with *orbital* (OFC) or *ventromedial* prefrontal (VMPFC) damage are often not affected in cognitive control, but show prominent impairments in behavioral and emotional self-regulation (Stuss 2007). This indicates that the ventral prefrontal regions show a different functional specialization, although it has to be acknowledged that there is still a paucity of standardized tests which can quantify these deficits reliably (Zald and Andreotti 2010). In practice, scientists need to be aware that none of the available tasks that aim to measure executive control functions actually provides a *global* indicator for frontal lobe function.

Unfortunately, the specific characteristics of the executive control mechanisms remain elusive (Jurado and Rosselli 2007; Etnier and Chang 2009). While some theories propose a unitary control mechanism (e.g., active maintenance of task-relevant information: Miller and Cohen 2001), many researchers prefer a functional system with distinct processes that cooperate flexibly to regulate behavior (e.g., Miyake et al. 2000; Stuss 2007). Unfortunately, there is no comprehensive taxonomy for these processes: Rather, there are a variety of alternative classifications, for example, volition, planning, purposeful action, and effective performance (Lezak et al. 2004); planning, scheduling, inhibition, and working memory (Colcombe and Kramer 2003); or shifting, updating, and inhibition (Miyake et al. 2000). In addition, successful performance in many of the classical frontal lobe/executive control tasks is probably not determined by one, but several of these subprocesses: Depending on the theoretical background (and the specific behavioral parameters that are derived from task performance), different studies will sometimes make varying assumptions about the executive control function which is predominantly captured by a given task. In practical terms, this means that researchers are advised to scrutinize the executive control processes that are actually operationalized by using a given task paradigm (see also Tomporowski 2009).

Recently, executive control functions have become a prominent topic in exercise-related cognitive studies (Colcombe and Kramer 2003; Etnier and Chang 2009; McMorris et al. 2011). In particular, there has been a paradigmatic shift in studies investigating the *acute* effects on cognition. While traditional "cognitive-energetic" models concentrated on the acute effects of exercise-induced arousal on elementary information processing capacities (see Sect. 6.2.4.1), there are recent theoretical and empirical considerations which suggest that arousal may also influence executive control, probably via changes in brain DA and NE neurotransmission that modulate neural signaling in those frontal brain networks (Lambourne and Tomporowski 2010; McMorris et al. 2011). Another influential model, the reticular-activating hypofrontality (RAH) model (formerly known as "transient hypofrontality hypothesis": Dietrich and Audiffren 2011), assumes that the need to allocate the limited metabolic (and computational) brain resources to motor control processes triggers a time-limited downregulation of PFC brain activity during acute bouts of exercise. This "hypofrontality" is predicted to interfere specifically with tasks that depend on explicit (i.e., controlled or executive) cognitive processing. Concurrently, there is a strong interest in the *chronic* effects of physical exercise on executive control functions, especially in older populations (Etnier 2009). This interest is fueled by findings from behavioral intervention studies (Kramer et al. 1999; Colcombe and Kramer 2003, but see Etnier and Chang 2009; Smith et al. 2010, for critical comments), as well as an increasing number of structural (e.g., Colcombe et al. 2006; see also Chaps. 17 and 20), and functional neuroimaging studies (e.g., Colcombe et al. 2004; Themanson et al. 2006; see also Chaps. 18 and 19).

The following sections will provide a short review of popular executive control tasks, with a special emphasis on paradigms that were already used in the sports- and exercise-related literature (for comprehensive reviews of the general test literature, see Lezak et al. 2004; Strauss et al. 2006). We will concentrate on two of those

executive control functions which are most frequently discussed: *set shifting* (or *cognitive flexibility*) and *inhibition*. As exercise-related applications for many of these tasks are discussed elsewhere in this book, we will mainly concentrate on general descriptions of some prototypical task formats.

6.2.5.1 Set Shifting and Cognitive Flexibility

A basic aspect of goal-directed behavior is the ability to establish and maintain task sets, that is, internal representations of rules or behavioral schemata that associate specific stimuli (or stimulus categories) with specific response options (Robbins 2007). While the ability to establish and maintain task sets is important (especially in the face of distracting stimuli), situational changes or the confrontation with multitasking situations often makes it necessary to adapt behavioral strategies according to modified situational demands, or switch between different goals. Neuropsychological data suggest that the frontal lobe and connected basal ganglia circuits are critical for accomplishing this flexibility (Robbins 2007).

Probably, the *Wisconsin Card Sorting Test* (WCST: Grant and Berg 1948), which has already been used to measure exercise-induced effects in a number of studies (e.g., Dietrich and Sparling 2004; Smiley-Oyen et al. 2008; Del Giorno et al. 2010), is the neuropsychological task that has been most closely linked to frontal lobe function (Etnier and Chang 2009; Jurado and Rosselli 2007). In this task, four stimulus cards are presented as target stimuli. These cards differ from one another on three stimulus attributes (see Fig. 6.2): (a) *number of stimuli* (1, 2, 3, or 4), (b) *color* (red, yellow, green, or blue), and (c) *shape* (cross, triangle, star, or square). Participants receive a second set of cards that show different combinations of the three stimulus dimensions (e.g., one blue square, three green triangles) and are instructed to assign these probe cards to the target stimulus card that shows the best match with regard to a critical stimulus attribute (which may be same shape, same number, or same color). Critically, the relevant attribute is not known in advance but must be inferred from "right" or "wrong" feedback that the experimenter gives after each sorting attempt. Once the correct stimulus dimension is discovered, this sorting rule (or task set) has to be maintained until the experimenter switches the relevant stimulus dimension (e.g., color → number), which is done without an explicit warning. From this point, subjects receive negative feedback for applying the previously established sorting rule. To adapt to the changed feedback contingencies, and avoid perseverative responding, subjects have to inhibit the established task set and use the feedback to switch to the correct task set.

The complex task structure of the WCST has certain drawbacks with regard to the functional interpretation of task performance. While the ability to shift to the relevant task set is clearly relevant, the task compounds this cognitive process with an additional learning component, as the correct stimulus–response mapping has to be inferred from feedback (Robbins 2007). Meanwhile, there are task paradigms where such learning aspects play a more limited role. A classic example is the *Trail-Making Test Part B* (TMT-B; Fig. 6.1), where subjects have to connect circles containing

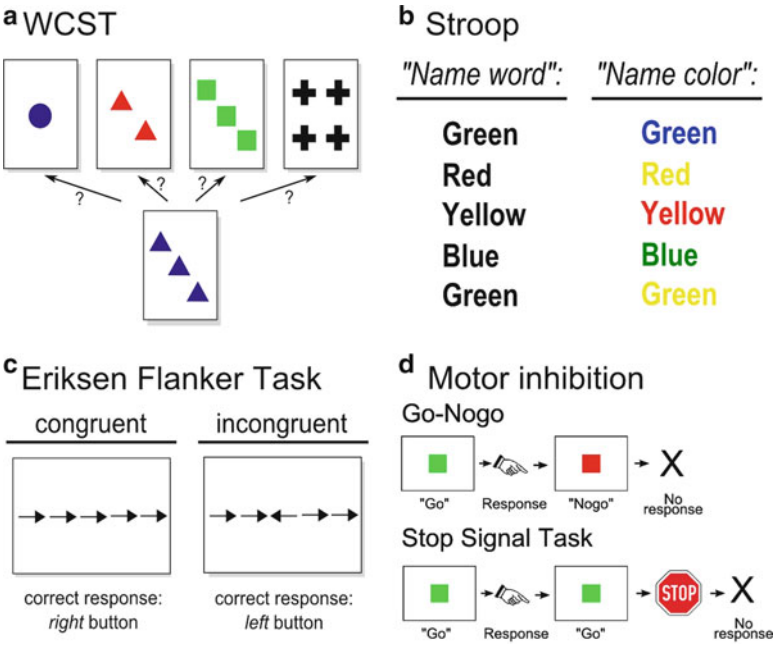

Fig. 6.2 Examples for executive control function tasks. Schematic description of task characteristics. See text for details. *WCST* Wisconsin Card Sorting Test

letters or numbers in alphabetical and numerical order, but in an alternating fashion (i.e., 1—A—2—B—3—C…). This means that the active task set must be continuously switched from letters to numbers, and back again. Another variant are *task-switching paradigms* (Monsell 2003), which have gained popularity in recent exercise-related studies (e.g., Coles and Tomporowski 2008; Kramer et al. 1999), including event-related potential (ERP) neuroimaging studies (e.g., Themanson et al. 2006; for further details, see also Chap. 18). Subjects are trained to discriminate stimuli (e.g., letter–number pairs, such as *5F*) with regard to a specific stimulus attribute, but critically, there are alternative (usually two) response criteria that are related to different stimulus features (e.g., "*Criterion A*: Is the number odd or even?" versus "*Criterion B*: Is the letter a consonant or vowel?"). Behaviorally, this alternation between task sets is associated with a slowing of reaction times (and higher error rates), so-called switch costs, which is usually thought to reflect a rapid task set reconfiguration by a controlling process. Thus, smaller switch costs can be interpreted as an indicator for an increased efficiency of cognitive control.

6.2.5.2 Inhibition

The concept of inhibitory functions refers to psychological processes that provide *active* suppression of other psychological processes, ranging from the sensory and

attentional processing of incoming stimuli, to internal (cognitive and affective) states, and to the execution of motor programs (Gazzaley and D'Esposito 2007, but see Aron 2007, for a critical view). Inhibitory functions have been implicated in various psychological tests, including WCST or task-switching tasks (McMorris et al. 2011; Aron 2007; Miyake et al. 2000; Etnier and Chang 2009), but there is a number of prototypical task formats that will be reviewed in the following section.

The *Stroop Color Word Interference Test* is probably the most classic measure of inhibition. While there are many different variants (reviewed by Lezak et al. 2004), the typical paradigm consists of at least two task conditions (see Fig. 6.2). In the control condition, a list of color words (e.g., red, blue, green, yellow) is presented (typically in neutral black ink), and subjects are instructed to read this word content as fast as possible. In the target condition, the *word content* differs systematically from the *printing color* (e.g., red printed in yellow). Critically, subjects are instructed to name the print color as fast as possible, while inhibiting the prepotent tendency to read the incongruent word content. Typically, this interference between color and word content slows response times and increases error probability. Accordingly, a high degree of interference, as indexed by the differences in speed and error rates between target and control condition(s), is interpreted as a behavioral indicator of inhibitory dysfunction.

Similar task demands can be found in *flanker task paradigms* (Eriksen and Eriksen 1974). Subjects are instructed to make a discriminative response to a stimulus that appears in the center of the screen, for example, the direction of an arrowhead pointing to either the left or the right (e.g., Colcombe et al. 2004; Themanson et al. 2008; see Fig. 6.2). Critically, the stimulus is surrounded by distractor stimuli (*flankers*) that can be either response-congruent to the target stimulus (e.g., →→→→→) or response-incongruent (e.g., →→←→→). Thus, attention must be focused on the target stimulus (and corresponding) response option, while inhibiting the processing of the flanker stimuli. Similar to the Stroop paradigm, this conflict typically slows down reaction times and/or increases the error probability for incongruent as compared to congruent trials. Flanker tasks are quite popular of the general functional neuroimaging literature, and there are already several neuroimaging applications in exercise-related studies, including fMRI (Colcombe et al. 2004) and especially event-related-potential (ERP) studies (e.g., Themanson et al. 2008; see also Chap. 18).

Finally, many neuroscientific studies use *go/nogo* and *stop signal tasks* (Fig. 6.2) to measure the active suppression of motor responses (Aron 2007; Robbins 2007). In go/nogo paradigms, subjects have to respond as fast as possible to one class of stimuli ("go" trials), while withdrawing to initiate a response to another class of stimuli ("nogo" trials). Typically, the number of go trials exceeds the number of "nogo" trials in order to establish a prepotent response tendency that has to be inhibited in the "nogo" trials: Thus, the probability of commission errors (i.e., motor responses in "nogo" trials) is a key dependent variable. In contrast, during stop signal tasks, subjects have to react to go stimuli, but in a fraction of trials, a stop signal is presented at a variable time point after the presentation of the go stimuli that signals the need to suppress an already-initiated motor response. If the stop signal appears shortly after the go signal, inhibition is likely to be successful, but if the

stop signal appears immediately before the execution of the go response, inhibition will probably fail. By varying this delay systematically, it is possible to infer the minimum time that is typically required to suppress the motor response successfully (so-called stop signal reaction time). Motor inhibition tasks are still rarely used in exercise-related studies: While there is still little evidence for behavioral effects in go/nogo tasks (Smiley-Oyen et al. 2008), there are some positive findings from behavioral studies using stop signal tasks (e.g., Kramer et al. 1999). This may justify further applications, especially in the context of functional neuroimaging, where go/no go and stop signal tasks are frequently used (for a recent meta-analysis, see: Swick et al. 2011). In fact, an initial EEG application of a go/nogo paradigm in the context of acute physical exercise is available (Kamijo et al. 2004).

6.2.6 Global Cognitive Function

Another variable that is potentially relevant for exercise-related research is global cognitive functioning. In a broader sense, this category encompasses a variety of test instruments which aim to provide a general indicator for the cognitive functioning level of an individual, including neuropsychological test batteries (which combine a range of domain specific subtests, e.g., for memory, attention, language), dementia screening inventories, and, most notably, intelligence tests (Strauss et al. 2006).

There are several intelligence tests available, for example, the *WAIS* (Wechsler 2008), or the *Kaufman Brief Test of Intelligence* (Kaufman and Kaufman 1990). These different instruments are based on different theoretical ideas about the underlying structure of intelligence (e.g., the number and nature of measured intelligence factors) that we will not discuss in detail (for a short overview, see Strauss et al. 2006). A recurring theme in intelligence theory and testing is the distinction between *fluid intelligence*, *which* is strongly related to analytic abilities (e.g., problem solving and reasoning) that afford the competency to find new solutions for unknown task situations, and *crystallized intelligence*, which relates to culturally acquired abilities, such as vocabulary, and semantic knowledge. Usually, both aspects are correlated, and as crystallized intelligence measures appear relatively resilient against aging and diseases (as compared to fluid intelligence), neuropsychologists often use these scores to derive an estimate for premorbid global cognitive function, which is especially relevant for assessments in clinical populations. Notably, these estimations are sometimes not directly based on intelligence tests (e.g., the *WAIS Vocabulary* subtest) but inferred from academic achievement tests, such as the *National Adult Reading Test* (Lezak et al. 2004; Strauss et al. 2006).

Turning to exercise-related studies, there are several reasons for using global cognitive measures: First of all, it is generally possible to use these scores as dependent variables, for example, to test whether physical exercise shows any acute (Dietrich and Sparling 2004) or chronic (e.g., Aberg et al. 2009) associations with IQ measures. Meanwhile, such global measures may lack sensitivity to detect subtle cognitive changes (especially crystallized intelligence measures which, as discussed

above, are thought to be rather insensitive to changes in brain physiology). Therefore, some authors prefer the assessment of specific cognitive functions, for example, executive control (e.g., Tomporowski et al. 2008). In fact, there seems to be a substantial overlap between executive control and fluid intelligence tasks (Jurado and Rosselli 2007; Strauss et al. 2006).

Meanwhile, there are other methodological considerations: Many of the above-mentioned tests (e.g., learning and memory tasks, such as the RAVLT) show correlations with education and intelligence scores (Strauss et al. 2006): This means that there may be a need to control this factor as a potential covariate, especially in the context of cross-sectional comparisons between groups (e.g., individuals with varying fitness levels) which may systematically differ regarding this background variable.

On the other hand, global cognitive measures may be relevant as a potential moderator variable for the influence of physical exercise on specific cognitive functions: For example, IQ measures are often discussed as an indicator for individual "cognitive reserve" capacities, which are thought to protect against (or at least delay) the detrimental effects of brain insults, such as neurodegenerative processes (Stern 2009). Thus, subjects with higher levels of cognitive ability may be more proficient in developing strategies that help them cope with adverse conditions. On the other hand, as these subjects already perform closer to ceiling level, they may have fewer opportunities to draw additional profit from beneficial interventions (Etnier et al. 2006; Etnier 2009). Consistent with the latter idea, Sibley and Beilock (2007) reported a beneficial effect of acute exercise on a working memory span task, but only for those subjects who showed a low baseline performance in this task.

6.2.7 Caveats and Trends

In recent years, the methodological approaches which are used to investigate the cognitive effects of physical exercise have experienced substantial refinements, and the ongoing development of task paradigms, especially in the field of cognitive neuroscience, will probably result in further improvements.

On the other hand, there are still some practical challenges that need to be considered in study design. A prominent aspect is the timescale of the measured cognitive effects. From a methodological perspective, cognitive assessments *during* the execution of acute exercise bouts are probably associated with the most distinct practical obstacles: For example, it may be necessary to adapt the whole test apparatus (e.g., stimulus display, response buttons) to the situational demands of the exercise regimen. Meanwhile, the motor control requirements of acute physical exercise may still interfere with the parallel execution of a psychological task (i.e., tax divided attention by inducing an implicit dual-task situation; Sect. 6.2.4.2). Notably, this detrimental effect may cease with increasing practice, given that the execution of one (or both) tasks becomes automatic: This could explain observations from a recent meta-analysis (Lambourne and Tomporowski 2010), which

indicated that cognitive performance measures show a slight decline during the first 20 min, but not in later phases of acute exercise treatments, while post-exercise measurements even show improvements (which may reflect a carryover of exercise-induced arousal increases into the immediate post-exercise phase). This suggests that the observed behavioral outcome will be influenced by both task selection and type of exercise intervention (Lambourne and Tomporowski 2010).

6.3 Affective Functions

Affective responses to physical exercise have been investigated in a large number of scientific studies. Beyond such phenomena as the runner's high (i.e., a state of euphoria while running), which are relevant only for a minority of athletes, the specific conditions that make physical exercise bouts pleasurable (or aversive) are also important from a public health point of view. For instance, interventions that support the motivation to engage in physical activity may help reduce the prevalence of sedentary lifestyles in Western industrial societies, and the negative health consequences associated with them (Ekkekakis et al. 2005b). In fact, mood enhancement is reported as a result of both acute (Reed and Ones 2006) and chronic (Reed and Buck 2009) exercise, and there are studies that indicate that the initial affective response to a moderate exercise bout predicts regular participation in exercise interventions (Williams et al. 2008). Moreover, the affective impact of physical exercise is also relevant from a clinical perspective, since an increasing number of studies confirm that moderate physical exercise has a beneficial effect on clinical symptoms of anxiety (Wipfli et al. 2008) and depression (Bartholomew and Ciccolo 2008).

This section will review affect-related measurement techniques that are potentially relevant for exercise-related studies. After providing a short outline of important affective phenomena, and relevant psychological theories of affective functions, we will present a number of methodological approaches which are commonly used to operationalize affect. In practice, affective reactions are predominantly measured by asking participants for their subjective affective experiences ("feelings"): Accordingly, affect-related rating scales and questionnaires will play a prominent role in this review. Meanwhile, affective states are not restricted to subjective experience, but can include bodily, motivational, and behavioral responses. Therefore, we provide a brief overview of psychophysiological and behavioral assessment techniques which are commonly used in affective neuroscience. The discussion will conclude with comments on methodological caveats and future prospects.

6.3.1 General Background

Affect is a psychological concept with several related meanings. In general, affects are feeling states that can be characterized as pleasant or unpleasant (i.e., positive or

negative) and reflect the subjective perception of what happens in the organism (Parkinson et al. 1996; Gray and Watson 2007). Notably, the term "affect" is used to refer to a variety of affect-related phenomena, for example mood, emotion, temperament, preference, or attitude (Gray and Watson 2007; Smith and Crabbe 2000; Scherer and Peper 2001).

While these affect-related constructs are interrelated, they can be differentiated by specific characteristics, such as intensity, duration, and rapidity of response patterns (Scherer and Peper 2001; Davidson 1998). For instance, *mood* refers to a prolonged affective feeling of an individual that often develops slowly, does not necessarily depend on a specific antecedent event (or may cumulate over several events, respectively), and typically lasts much longer (minutes, hours, or days) than *emotions*, which are acute, intense responses that are triggered by, and time-locked to, specific antecedent events. By contrast, *temperament* and *affect-related personality traits* (e.g., anxiousness, neuroticism) do not describe an immediate affective state, but refer to a stable disposition (or vulnerability) to experience specific emotional and mood states, which is assumed to vary between individuals (e.g., anxious people are more likely to react with anxiety than others). We emphasize these conceptual differences, because it was suggested that the interchangeable use of the term "affect" has been a steady cause of confusion, both in the general (Scherer and Peper 2001) and exercise-related affect literature (Smith and Crabbe 2000).

During the last decades, a number of theories discussed the relationship between exercise and affect. Many of the earlier models proposed that exercise modulates affect by influencing basic physiological mechanisms, such as monoamine or endorphin neurotransmission (Daley 2002), but made a few assumptions about the brain structures and psychological processes that are modulated by these physiological changes. Inspired by theoretical advances in affective neuroscience, recent accounts have started to formulate more specific predictions, and akin to the exercise-related cognitive literature, the regulatory functions of the frontal lobes often play a prominent role in these models (see also Chap. 21): For example, the *dual-mode theory* (DMT) (Ekkekakis et al. 2005b) assumes that exercise-induced affect changes result from evolutionarily adaptive signaling pathways which show a hierarchical organization, with fast and automatic subcortical mechanisms that are regulated by slower cognitive processes on the cortical (e.g., frontal) level. The key aspect of DMT is that cognitive appraisals influence affective processing in low, moderate, and—most importantly—heavy physical activity, which means that the same exercise intensity can cause different affective reactions, depending on the individual cognitive appraisal. Only during severe exercise, aversive bodily signals become overwhelming, and bypass "top-down" cognitive regulation to signal immediate threat to health or survival. Yet, the DMT suggests that heavy and severe exercise may also trigger opponent (possibly: opioidergic) processes with a positive valence that counteract these aversive reactions, which could explain affective rebound phenomena (i.e., a reversal from displeasure to pleasure) immediately after termination of severe exercise bouts. A different account is provided by the *reticular-activating hypofrontality* model (Dietrich and Audiffren 2011): This model proposes that transient hypofrontality effects during the course of intense physical exercise mediate anxiolytic and

antidepressant effect by changing the functional balance between the DLPFC and VMPFC, which is known to be implicated in mood disorders (Elliott et al. 2011).

6.3.2 *Subjective Measures*

The predominant approach to measure affective responses in humans is the assessment of their subjective affective experience (Bradley and Lang 2007). As this subjective experience is only accessible to introspection, individuals have to self-report evaluations of their subjective feelings, usually by rating the appropriateness of word labels that characterize emotional states (Gray and Watson 2007). In exercise-related studies, such ratings are typically used to assess exercise-induced *mood* changes. A short overview of affective self-report instruments that are frequently used in exercise-related studies is provided in Table 6.2: Since there are general overviews available (e.g., Reed and Ones 2006; Reed and Buck 2009; Ekkekakis 2008; see also: Ekkekakis and Petruzzello 1999), we will focus on a selection of popular measures.

As pointed out in previous reviews (e.g., Ekkekakis 2008; Bradley and Lang 2007; Gray and Watson 2007), the available self-report instruments make varying theoretical assumptions about the nature and organization of the affective states that they intend to measure (for a comprehensive review of neuropsychological theories of emotion, see Scherer and Peper 2001). We will broadly distinguish *dimensional* affect measures (e.g., for the positive or negative hedonic valence, or for the arousal level experienced during an affective state), and instruments that focus on *discrete emotions* (e.g., anxiety, fear, anger). Within these categories, we will further differentiate *general* measures (that were developed outside the realm of sports sciences) and *exercise-specific* measures.

6.3.2.1 Dimensional Measures

Dimensional models of affect assume that emotional states vary with regard to general common attributes which are conceptualized as a continuum, such as valence (i.e., the hedonic value, ranging from unpleasant to pleasant), arousal (ranging from low to high), or positive and negative affect (Gray and Watson 2007; Bradley and Lang 2007). Some models suggest that the subjective perception of these affect dimensions reflects the functional organization of underlying motivational systems on the brain level, e.g., in terms of approach/avoidance or appetitive/defensive systems (Davidson 1998; Bradley and Lang 2007).

Typically, these affect dimensions are measured with multi-item questionnaires, such as the *Positive and Negative Affect Scale* (PANAS: Watson et al. 1988). The PANAS contains ten positive affect-related adjectives (e.g., proud, enthusiastic) and ten negative adjectives (e.g., jittery, distressed) to measure positive affect and negative affect dimensions, respectively. Participants rate each adjective according to what they were currently feeling from 1 (*not at all—slightly*) to 5 (*extremely*).

Table 6.2 Affective self-report measures and exercise-related applications

Author	N	Sex	Exercise mode	Exercise duration	Neuronal measure	Questionnaire
Barnes et al. (2010)	30	MI	Cycling	30 min	None	PANAS, STAI, BDI
Bartholomew et al. (2005)	40	MI	Walking	30 min	None	POMS, SEES
Bixby et al (2001)	27	MI	Cycling	30 min	EEG	PANAS
Boecker et al. (2008)	10	M	Running	115 min	PET	VAMS
Dishman et al. (2010)	36	MI	Cycling	To exhaustion	EEG	POMS
Ekkekakis et al. (1999)	69	MI	Running	30 min	None	AD ACL, STAI
Fumoto et al. (2010)	10	MI	Cycling	15 min	NIRS	POMS
Hall et al. (2010)	30	MI	Running	To exhaustion	EEG	AD ACL
Moraes et al. (2011)	29	NR	Cycling	20 min	EEG (loreta)	POMS, STAI
Oda et al. (1999)	8	M	Aqua aerobics	50 min	EEG	POMS
Petruzzello et al. (2001)	69	MI	Running	30 min	EEG	AD ACL
Schneider et al. (2009a)	101	MI	Cycling	30 min	EEG	FS
Schneider et al. (2009b)	24	MI	Running	21–60 min	EEG	Mood meter
Steptoe et al. (1993)	72	M	Cycling	25 min	none	POMS
Vogt et al. (2010)	18	MI	Walking	45–60 min	EEG	Mood meter
Woo et al. (2009)	16	F	Running	15, 30, 45 min	EEG	POMS

M males, *F* females, *MI* mixed, *NR* not reported

PANAS positive and negative affect schedule, *POMS* profile of mood state, *AD ACL* activation deactivation adjective checklist, *VAMS* visual analogue mood scale, *FS* feeling scale, *SEES* subjective exercise experience scale, *STAI* state-trait anxiety inventory, *BDI* Beck depression inventory, *EEG* electroencephalography, *PET* position emission tomography, *NIRS* near-infrared spectroscopy

The questionnaire is frequently used in exercise and sport psychology (e.g., Barnes et al. 2010), including neuroimaging applications (Bixby et al. 2001).

The *Activation-Deactivation Adjective Checklist* (AD ACL: Thayer 1989) is a self-report measure that contains 20 items. There are five adjectives for each of the four subscales *Energy*, *Tiredness*, *Tension*, and *Calmness*, which represent the high and low poles of two orthogonal and bipolar activation dimensions: *Energetic arousal* (Energy—Tiredness) and *Tense Arousal* (Tension—Calmness). Each item is rated on a 4-point Likert scale (ranging from "1—definitely not feel" to "4—definitely feel"). Although not originally developed for this purpose, it was suggested that the AD ACL can be interpreted in terms of a two-dimensional "affective circumplex" model that represents the similarities and differences between affect states by arranging these states around the perimeter of a circle, with experientially similar states located in close proximity (Gray and Watson 2007; Ekkekakis 2008): The structure of this circumplex can be characterized by two orthogonal bipolar dimensions: valence and arousal (see Ekkekakis et al. 2005a, for a detailed discussion of psychometric properties and exercise-related applications of the AD ACL). In a recent study that examined the dose-dependent effects of different exercise intensities on mood states, resting frontal EEG asymmetry was predictive for affective responses after exercise, as measured by the AD ACL (Hall et al. 2010).

While the above-mentioned tests contain multiple items to measure the intended dimension, there are also less complex instruments. For example, the *affect grid* (Russell et al. 1989), which has also been applied in sport and exercise science (Hardy et al. 2001), uses a single rating in a two-dimensional coordinate space to measure hedonic tone (ranging from unpleasant-pleasant) and arousal (ranging from sleepiness-high arousal). The *Feeling Scale* (Hardy and Rejeski 1989) is a single-item scale that measures valence on a bipolar 11-point scale, ranging from −5 (very bad) to +5 (very good), and has already been used in exercise-related EEG studies (Schneider et al. 2009a). While most of these dimensional rating scales use verbal and numerical anchor descriptors, it should be noted that there are also nonverbal approaches, such as the *Self-Assessment Manikin* (SAM: Lang et al. 2008), which uses cartoon characters to symbolize the referenced feeling states on the three dimensions: valence, arousal, and dominance (for an exercise-related example, see Tian and Smith 2011).

Recently, there have been attempts to develop scales that assess emotional responses in the specific context of exercise and sport psychology, such as the *Exercise-Induced Feeling Inventory* (EFI: Gauvin and Rejeski 1993). The EFI has four subscales of *Positive Engagement*, *Revitalization*, *Tranquility*, and *Physical Exhaustion*. While the instrument has had positive reviews and empirical applications (e.g., Szabo and Bak 1999; Vlachopoulos et al. 1996), it should be noted that the validity of the different subscales has been questioned (Ekkekakis and Petruzzello 1999).

6.3.2.2 Discrete Emotions

A number of emotion theories are based on the idea that there is a number of distinct emotion qualities, or categories, that are not only associated with distinct feeling

states, but also with stereotyped response patterns, which are probably hard-wired in specific brain circuits: For example, fear responses are linked with a network including amygdala, hypothalamus, and periaqueductal gray (Panksepp 1988). While there are some prototypical examples, such as the basic emotions *happiness*, *sadness*, *fear*, *anger*, *disgust*, and *surprise*, there is no generally accepted taxonomy for these discrete emotional qualities, and as a consequence, a broad range of alternative scales with varying contents is in practical use.

A questionnaire that is frequently used to show exercise-induced changes in discrete mood states is the *Profile of Mood States* (POMS: McNair et al. 1971). In the long form, the scale contains 65 adjectives, which have to be rated on a 5-point Likert scale. The adjectives are assigned to six subscales, five with a negative content (*tension-anxiety*, *depression-dejection*, *anger-hostility*, *fatigue-inertia*, and *confusion-bewilderment*), and one with a positive content (*vigor-activity*). Meanwhile, please note that some studies (e.g., Woo et al. 2009) also integrate the different subscales to generate a summary "total mood disturbance" score (TMD = [(tension + depression + anger + fatigue + confusion)—vigor]), which in fact means that the POMS is converted into a dimensional, negative valence scale. Studies using the POMS to measure mood changes have been successful in showing that, for instance, *acute* mood changes are beneficial at low exercise intensity levels (Steptoe and Cox 1988). Further, studies have shown that moderate exercise intensities (Davranche et al. 2006) change mood more compared to high intensities (Steptoe et al. 1993), indicating an inverted U-curve relation between exercise intensity and mood. Consistent with the prominent role of the POMS in the sports literature, some exercise-related studies have also used the POMS in neuroimaging studies, for instance, to correlate acute changes in mood and EEG activity (Fumoto et al. 2010; Oda et al. 1999; Vogt et al. 2010). Finally, POMS scores were used in many studies which investigated the chronic effects of exercise in different exercise programs and populations (Reed and Buck 2009).

A practical disadvantage of the POMS is the considerable number of test items: Therefore, there have been attempts to develop shortened versions of the POMS for exercise-related applications (discussed in Leunes and Burger 2000): In some cases, each of the six subscales is reduced to one single item (e.g., Anderson and Brice 2011). A complementary approach is the use of visual analogue scales, such as *Visual Analogue Mood Scales* (VAMS: e.g., Stern et al. 1997), which have already been applied in exercise-related studies (e.g., Bixby et al. 2001): Instead of using multiple items to aggregate ratings for a given affective state, participants are directly asked to rate the current appropriateness of a affective state (e.g., sadness, tension, anger, fear, fatigue) by marking the corresponding position on a continuous horizontal line, with written anchors at either end point to define the possible extremes (e.g., "not at all sad" to "very sad").

While the POMS or VAMS capture a variety of distinct affective states, other measures concentrate on specific affective experiences. A classical example, which may be especially relevant for exercise-related studies in psychiatric populations, is the *Beck Depression Inventory* (BDI: Beck et al. 1961), which aims to measure the severity of depressive mood symptoms with 21 multiple-choice items. Another

important example (which is frequently studied in exercise research) is anxiety. A common instrument for the measurement of anxiety is the *State-Trait Anxiety Inventory* (STAI: Spielberger et al. 1970). The STAI contains 40 items in total, using 20 items for trait (e.g., "I lack self-confidence") and 20 items for state (e.g., "I feel upset") anxiety. Within sport and exercise psychology, the *Competitive State Anxiety Inventory* (CSAI: Martens et al. 1990) is frequently used, with a recent development including questions on how often negative feelings occur and whether these feelings have a negative or positive effect on performance (Martinent et al. 2010).

Whereas anxiety is an emotional state for which both general and exercise-specific questionnaires have been developed, the same cannot be said for many other emotion categories. There have been some exercise-specific scales developed for other emotions (e.g., Elbe et al. 2005), but in most cases, researchers have to rely on general affect questionnaires.

6.3.3 Objective Measures

Affective (and especially: emotional) responses are not limited to the subjective experience of an affective feeling, but can include other forms of expression. Although this assumption is implicit to many theories of affect, it is especially emphasized by c*omponential models* of emotion (e.g., Scherer and Peper 2001). These models conceptualize emotions as a complex pattern of responses that unfold dynamically and over multiple modalities. These modalities include *cognitive appraisals* (e.g., subjective evaluations of the significance of an affective event, and the expected ability to cope with these events), *physiological responses* (bodily symptoms: e.g., neuroendocrine responses and autonomic changes), *motivational changes* (action tendencies, in terms of approach, defense, or withdrawal), *motor expressions* (facial and vocal expression), and, of course, *subjective feelings* (emotional experience, as measured by subjective rating scales). In fact, there is a long-standing debate whether subjective emotional feelings may primarily reflect the interoceptive experience of these bodily changes (Scherer and Peper 2001; Bradley and Lang 2007; Kreibig 2010).

Emotion researchers have developed a variety of psychophysiological assessment techniques that are used to derive objective measures for these response modalities, some of which will be introduced in the following section. If possible, we will refer to exercise-related applications (see also Smith and Crabbe 2000; Smith and Cook 2005).

6.3.3.1 Standardized Elicitation of Affective Responses in the Laboratory

Typically, psychophysiological laboratory studies do not observe spontaneous fluctuations of the affective state of study participants, but measure affective responses in standardized settings, for example by presenting stimuli that aim to

provoke emotional reactions (e.g., verbal, pictorial, or acoustic stimuli with emotional content), or by instructing participants to imagine emotionally arousing situations (Bradley and Lang 2007). One of the most prevalent approaches is the use of material from the *International Affective Picture System* (IAPS: Lang et al. 2008), a collection of scenic photographs with appetitive, aversive, or neutral contents. For each of these pictures, normative SAM ratings for three affective dimensions (valence, arousal, and dominance) are available, which allows researchers to deliberately select stimuli based on their affective properties. Another popular approach is the presentation of faces with emotional expressions (e.g., anger, fear, disgust), which are usually taken from standardized picture series, such as the classic *Pictures of Facial Affect* set (POFA: Ekman and Friesen 1976).

While the above-mentioned stimulus types mainly have a conditioned affective value (i.e., are learned), it is also possible to use innate, unconditioned stimuli (e.g., painful heat or electroshocks: Bradley and Lang 2007; see also Chap. 7). A related approach that is commonly used in exercise-related studies to induce negative mood states (Hamer et al. 2006) is the performance of cognitively demanding tasks under stressful conditions (e.g., delivering a public speech, mental arithmetic under time pressure).

6.3.3.2 Autonomic Responses

A classical approach to assessing emotional responses on an objective level is the collection of physiological responses, for instance, changes in neuroendocrine, electrodermal, respiratory, cardiovascular, skeletal muscular, or gastrointestinal activity (Bradley and Lang 2007; Gray et al. 2009; Kreibig 2010).

A prominent technique is the observation of electrodermal activity, for example, emotion-induced changes in *galvanic skin resistance* (GSR). GSR shows an exclusive link with sympathetic nervous system activity, because the sympathetic innervations of sweat glands influence electric skin conductance, which can be measured with surface electrodes (Bradley and Lang 2007; for technical details, see Smith and Cook 2005; see also Chap. 7). GSR increases after presentation of affective stimuli were shown to be a good indicator of emotional arousal, although it has to be noted that GSR is not sensitive to emotional valence (i.e., increases for both positive and negative arousing events: Bradley and Lang 2007; Smith and Crabbe 2000). In general, exercise-related applications of GSR measures are rare, and provide mixed results (e.g., Steptoe et al. 1990; Rodrigues et al. 2007). Yet, it must be acknowledged that the acquisition of GSR responses is technically challenging, especially during or immediately after acute exercise bouts, where increased sweating reduces skin resistance tonically (although it may still be possible to detect phasic responses: Smith and Cook 2005).

Moreover, there is a variety of cardiovascular response modalities, such as *blood pressure* (see also Chap. 7) and *heart rate* (HR). For example, emotional stimuli have been shown to modulate the temporal pattern of HR decelerations and accelerations that are typically triggered by stimulus processing (see review in Bradley

and Lang 2007). There are a number of exercise-related applications, primarily studies that examined cardiovascular responses to psychological (e.g., public speaking, mental arithmetics) or physical stressors (e.g., painful stimulation). While there is evidence that acute bouts of exercise reduce blood pressure responses to psychosocial stressors (at least for durations >30 min at 50% $\dot{V}O_2$max: Hamer et al. 2006), recent meta-analytic analyses (Jackson and Dishman 2006) have questioned the assumption that cardiorespiratory fitness mitigates cardiovascular responses to psychosocial stressors, suggesting that many of the positive findings in the available literature may be explainable by methodological flaws. Another relevant parameter is *heart rate variability* (HRV), i.e., the variability of beat-to-beat intervals, which reflects the relative sympathetic-vagal balance of an organism (Malik 1996). While the HRV is strongly driven by respiratory rhythms (respiratory sinus arrhythmia), emotional arousal can modulate HRV parameters (Kreibig 2010; Appelhans and Luecken 2006), and there are some exercise-related studies that used HRV to obtain unobtrusive measures of pre-competitive arousal in athletes (Murray and Raedeke 2008; Laborde et al. 2011). Moreover, there is accumulating evidence that certain psychiatric populations (e.g., panic disorder patients) show trait-like HRV reductions (i.e., a reduced ability to adapt affective responses to the situational context) that may reflect a more general impairment of emotional regulation processes, possibly via PFC mechanisms: Thus, low HRF has been discussed as a potential biomarker, or even endophenotype, for a broad range of dysfunctions in affective (but also physical and cognitive) regulation (Thayer and Lane 2009). Again, it is tempting to speculate whether HRV changes might qualify as an objective indicator for the affective benefits of regular physical exercise in these patient populations.

6.3.3.3 Motor and Motivational Responses

Obviously, the most salient motor expressions of affect are emotional face expressions. In fact, the unique pattern of facial muscle activities that are characteristic for basic emotions (e.g., fear and disgust) provides an important social signal that we use intuitively to make inferences about the current emotional experience of others. There are several observer-based coding systems that aim to formalize this intuitive analysis with standardized coding systems, for example, the *Facial Action Coding System* (FACS: Ekman and Friesen 1978), which decomposes facial expressions into predefined facial movement elements. Additionally, it is possible to measure the underlying activity of specific facial muscles (e.g., the corrugator supercilii, zygomaticus major, and orbicularis oculi muscle) with *facial EMG*, which offers the possibility to detect subtle changes that are not detectable for an observer (Bradley and Lang 2007; Smith and Crabbe 2000). Yet, exercise-related applications are rare (Fillingim et al. 1992), precluding meaningful conclusions for this kind of paradigm.

The acquisition of facial EMG is also relevant for measuring the acoustic startle eyeblink reflex, a defensive reflex that can be used to investigate the motivational state of an individual (Smith and Crabbe 2000; Bradley and Lang 2007). In typical

experimental procedures, this reflex is tested by presenting loud bursts of white noise, and measuring the amplitude and latency of EMG responses from the orbicularis oculi muscles. The intensity of the acoustic startle eyeblink reflex is known to be modulated by the current affective state of an individual, e.g., while viewing positive or aversive IAPS pictures (see Bradley and Lang 2007, for an overview). Theoretically, exercise-induced mood changes may influence the situation-specific appraisal of such affective stimuli, and, thus, the *affective modulation of the startle response*. Actually, there have been some applications in the context of acute exercise studies (e.g., Smith and O'Connor 2003; see also Smith and Cook 2005), but to date, no reliable changes in affective startle modulation were observed, making this paradigm a less promising candidate for future studies, at least in the context of acute exercise studies. Meanwhile, clinical studies indicate that patients with mood disturbances show a dysfunctional affective modulation of startle responses (e.g., blunted affective modulation in depressives: Mneimne et al. 2008). Therefore, it is interesting to speculate whether this kind of paradigm could provide a biomarker for the mood-enhancing effects of regular physical exercise in these patient populations.

6.3.3.4 Modulation of Cognitive Processes by Affect

In recent years, considerable progress has been made to create experimental settings that assess the effects of affective states on cognitive processing (see Elliott et al. 2011, for review). In these "affective cognition" paradigms, affective stimuli are presented in the context of a primary cognitive task. It is implicitly assumed that the motivational significance of affective stimuli influences cognitive processing by automatically guiding attentional resources toward (or away from) the emotionally significant stimuli. Depending on the specific task context, these attentional biases can either facilitate, or interfere with cognitive performance, which is reflected by a modulation of response speed or accuracy for affective, as compared to neutral stimuli.

One relevant example is the *Emotional Stroop* task, where participants have to name the print color of emotional and neutral words (analogous to traditional Stroop paradigms). Another typical variant is the *attentional (or "dot") probe paradigm*. Here, participants briefly view pairs of stimuli which appear in different spatial locations and have different affective value (e.g., left: positive; right: neutral). Afterward, a probe stimulus appears at one of the two stimulus locations, and participants are instructed to respond to this stimulus as fast as possible (e.g., discriminate: Is the letter a *b* or a *p*?). Assuming that the affective stimuli attract (or divert) the attentional focus, response latencies for probes that replace emotional and neutral stimuli, respectively, should differ, i.e., show an *attentional bias*. Still, there are few applications in exercise-related studies: While Barnes et al. (2010) observed no attentional bias effects *after* an acute bout of moderate exercise, a recent study by Tian and Smith (2011) suggests that modulating effects may indeed be present, at least *during* moderate exercise. They predicted that moderate exercise would induce a positive affective state that induces an attentional bias toward pleasant faces, but away from unpleasant faces, while high intensity exercise was expected to induce a

negative affect state that would have the opposite effect on attentional bias scores. Although no effects were observed during high intensity exercise, the predicted bias changes emerged during the moderate exercise condition, which may reflect a positive affective shift during this condition. Nevertheless, further research is needed to corroborate these initial findings.

6.3.4 Caveats and Trends

Given the various distinctions between affect-related constructs (e.g., emotion, mood, temperament) and the different theoretical models of affective function, this section could give only a rather selective review of general methodological avenues. To complete this general state-of-the-art review of psychological affect measures, and their application in exercise-related studies, a number of caveats and possible trends should be considered.

Exercise-related studies predominantly use self-report rating scales that are either based on dimensional or discrete (i.e., categorical) affect models, and ongoing debate ensues regarding the most adequate measurement approach. Ekkekakis (2008) notes that there is an inherent risk in using scales for discrete emotional states, as these scales may only capture specific kinds of affective reaction, while potentially missing other affective reactions that may also be sensitive to the influence of physical exercise. This does not generally question the assessment of specific affective states (e.g., anxiety, euphoria) in exercise-related studies, but Ekkekakis (2008) recommends clarification of the rationale for the selection of specific affective states in exercise studies. In general, this implies that scale selection should be guided by a specific idea about the nature of the expected affective changes: For instance, should "feeling better" be defined as anxiety *reduction* or positive mood *induction* (Yeung 1996; Reed and Ones 2006; Wipfli et al. 2008)? These two forms of affective change do not necessarily coincide (Barnes et al. 2010).

In addition, it is disputable whether a change of affect should be measured by comparing pre- and posttest ratings on an *absolute* scale, or by using a *comparative* scale, where subjects provide a *post hoc* evaluation of changes from pre- to posttest. Which of these two strategies represents a better description of the subjects' response is a matter of debate (see: Carlsson 1983 for review). There is evidence that retrospective evaluations of affective states may be vulnerable to memory bias effects (Anderson and Brice 2011).

This draws attention to another crucial study design issue: *When* and *how often* should we test the affective state? This is important because affect responses may not increase or decrease linearly over time, and therefore, *post*-exercise assessments do not necessarily reflect the mood state *during* exercise: For instance, the observation of positive affect after exercise may reflect a post-exercise rebound after experiencing acute mood decline during exercise (Ekkekakis et al. 2005b; Reed and Ones 2006). A simple but costly strategy is to assess affect during exercise and relate it to baseline before and after exercise.

Here we are confronted with another obstacle: Many of the above-mentioned questionnaires use multiple items to measure the affective variable of interest. While this approach can increase the reliability of the measurement, multiple-item questionnaires naturally carry the risk of test fatigue, especially in situations where the assessment is repeated at multiple time points, for instance, over the course of an acute exercise bout. In this situation, single-item scales may provide the only viable alternative. Yet, it should be kept in mind that single-item scales may be more prone to the influences of measurement errors (Leunes and Burger 2000).

Another risk of repeated affect measurements over multiple time points is the unintended generation of demand and social desirability effects in participants who understand the role of emotions in the given study and therefore may alter their reported affective response, voluntarily or involuntarily (Anderson and Brice 2011; for a detailed discussion of expectancy effects, see also Morgan 1997). This may be especially salient for single-item rating scales where the measures construct can already be inferred from the presented scale description.

To avoid (or at least: reduce) this kind of artifacts, it would be a desirable strategy to run objective, unobtrusive affect measures (Smith and Cook 2005). Still, there are comparably few applications of these methodologies in exercise psychology, and this may (at least to some extend) be explained by the fact that these measurement approaches can also entail important obstacles. In general, the collection of psychophysiological data is often associated with considerable technical and personal efforts, which may not always be affordable in practice. Moreover, the specificity of the measured responses is often debatable: For example, some parameters (e.g., SCR, HR) are only sensitive to emotional *arousal*, but not to emotional *valence* (Smith and Crabbe 2000; Bradley and Lang 2007; Scherer and Peper 2001). Moreover, these responses are not specific to emotion, but can also reflect nonemotional mechanisms, for example, orienting responses or attentional effort (Smith and Crabbe 2000; Smith and Cook 2005). In particular, studies examining affective responses *during* acute exercise are confronted with the problem that physical activity itself induces physiological responses (e.g., increased heart rate, muscular tension, sweating) which can overshadow the subtle changes triggered by affective reactions (Bradley and Lang 2007; Smith and Cook 2005). This problem is less compelling for studies that investigate the chronic effects of regular exercise during rest. Yet, it should be considered that changes in physical fitness may influence physiological responsiveness in general (especially for the cardiovascular system), which could also have an impact on affect-related responses in these modalities. Moreover, it should be noted that the covariation between subjective and objective affect measures is far from perfect. In general, a synchronized co-activation of the different response levels should primarily be expected during acute emotions, and even here, we can often not expect strong correlations, because the specific response patterns (e.g., timing, and intensity) for the different affect components can show substantial variation, depending on factors such as stimulus characteristics, emotional state, and interindividual differences (Scherer and Peper 2001). Therefore, it seems advisable not to *replace* subjective ratings by objective measures, but to *combine* the different observation

levels to achieve multivariate measurements (Bradley and Lang 2007; Scherer and Peper 2001), which can be analyzed for emotion-specific consistencies in response patterns (e.g., Stephens et al. 2010).

Another aspect that should be considered is the possibility that the relationship between exercise and affect may not be uniform, but moderated by individual background characteristics, for example personality traits (e.g., anxiousness, extraversion, sensation seeking), attitudes (e.g., self-efficacy), or preferences (Ekkekakis and Petruzzello 1999). As personality traits describe the fact that individuals can generally show a stronger (of weaker) tendency to react with certain affective states, and it is plausible that these dispositions can moderate the affective effects of physical exercise. For instance, exercise effects on mood differ depending on whether specific preferences have been met (Brümmer et al. 2011; Schneider et al. 2009b; see also Chap. 21). Moreover, the anxiolytic effect of acute exercise may be more significant in participants with higher trait anxiety levels (e.g., Barnes et al. 2010). It is too early to provide taxonomies of different affective styles and personality variables that moderate the exercise–emotion relationship, but recent efforts are promising (Rhodes and Smith 2006; Schneider et al. 2009a).

Finally, the exercise–affect relation is often examined in isolation, as is the exercise–cognition relation. However, it is evident from previous psychological research that affect and cognition are interrelated, and therefore, further gains are expected in a more complex exercise–emotion–cognition relation. Some recent studies have examined these more complex associations, strengthening the complex relationship empirically. For instance, a recent study (Tomporowski and Ganio 2006) found that an acute bout of aerobic exercise not only influenced subsequent executive control in a task-switching paradigm, but concurrently changed the emotional reactivity to the demands of tasks. While participants generally reported that they experienced a stronger mental demand (as measured via the *NASA Task Load Index*) during the processing of a short-term memory task, as compared to task processing in a task-switching paradigm, both tasks were perceived as less frustrating after exercise, as compared to after rest (Tomporowski and Ganio 2006).

6.4 General Considerations

This chapter aimed to give an illustrative overview of psychological assessment techniques, with a special emphasis on functional domains that appear to be most relevant for current exercise research. There are many additional tests and measurement techniques that could be equally relevant but were not discussed in detail. For a more detailed picture, we have to refer to supplemental literature. For example, Lezak et al. (2004) and Strauss et al. (2006) provide excellent reviews of standardized test procedures for the neuropsychological assessment of cognitive functions, while Coan and Allen (2007) and Bradley and Lang (2007) present a broad variety of measurement techniques that are important in emotion research. This chapter will conclude with general considerations about practical issues that may be

relevant for the selection of psychological assessment techniques in exercise-related research, especially for future neuroimaging studies.

6.4.1 Which Task Is Appropriate?

Given the multitude of psychological test instruments that are available, the selection of the most appropriate task for a specific research question can be challenging. There are no "gold standards", and the available exercise-related studies use a broad range of different instruments to operationalize cognitive and affective functions. Accordingly, recent meta-analyses point out that this diversity complicates the qualitative and quantitative synthesis of the available psychological data (Colcombe and Kramer 2003; Tomporowski 2009; Lambourne and Tomporowski 2010).

From a methodological point of view, task selection should be based on theoretical assumptions about the psychological constructs that have to be measured, and thus, a critical question is whether the utilized instruments sufficiently capture the intended constructs, i.e., show sufficient *construct validity* (Ekkekakis 2008; Tomporowski 2009). As we have illustrated, contemporary psychology has fractionated the traditional psychological domains, such as "memory," "attention," and "emotion," into a variety of specialized functional components, which multiplies the possible number of mechanisms that could be targeted by the modulating effects of physical exercise. In practical terms, this implies that global hypotheses, such as "physical exercise influences memory", may often be too unspecific, and researchers must be aware that the specific tasks they choose to operationalize psychological function will probably only assess some relevant aspects of a targeted construct, but possibly miss other aspects. For example, traditional memory tests (e.g., the RAVLT) assess the influence of physical activity on *declarative* memory functions but allow no inferences about *nondeclarative* memory (in fact, physical exercise may even have opposite effects: Eich and Metcalfe 2009). Moreover, there is probably no single test instrument that can provide a comprehensive assessment of executive control (Etnier and Chang 2009). A similar situation can be found for the assessment of affective responses, where there have been criticisms that scales for discrete emotions may only sample specific aspects of affective experience (Ekkekakis 2008): An illustrative example is the POMS, where five out of six scales describe negative mood states, while only "vigor" can be interpreted in terms of positive mood states (Anderson and Brice 2011).

Yet, it must be acknowledged that our theoretical advances in conceptualizing cognitive and emotional functions are not necessarily reflected by the tasks that are available for their practical assessment, i.e., there is often no one-by-one correspondence between psychological constructs and behavioral tasks: For example, many of the above-mentioned cognitive tests, such as TMT, WCST, Stroop, and RAVLT, predate the development of modern cognitive theories, and, hence, are not specifically tailored for measuring specific cognitive function.

Probably, the best practical solution to deal with the above-mentioned problems is the application of a broader test battery (e.g., for executive control functions: Miyake et al. 2000; Etnier and Chang 2009), and, especially in the affective domain, the use of multiple, subjective and objective measurement techniques. On the one hand, this approach would allow an exploratory approach in situations where no specific hypotheses about the relevant psychological processes are available. On the other hand, the use of tasks with overlapping functional demands allows us to make comparisons between tasks that draw on similar psychological processes (e.g., inhibition, declarative memory), and should therefore share a vulnerability to exercise-induced effects that modulate the respective processes. Of course, there is often insufficient time for broad batteries, especially in studies that investigate transient acute exercise effects, which may dissipate before the test battery is completed. Thus, a careful, theory-driven selection of tasks that are likely to tap into the psychological process(es) of interest remains a key methodological issue (Etnier and Chang 2009; Strauss et al. 2006).

6.4.2 The Relationship Between Brain and Behavior

In this chapter, cognitive and emotional test instruments were implicitly discussed as behavioral markers for underlying changes on the brain level. Actually, there is a long tradition in clinical neuropsychology to use psychological tests as localizer tasks, that is, to make inferences about *where* the brain shows functional alterations. In exercise sciences, there are currently two brain regions that seem to be especially relevant for this logic: the frontal lobe and the hippocampus. Actually, the fact that recent neuroimaging studies find exercise-related differences in these brain regions (e.g., see also Chaps. 17 and 19) adds plausibility to this assumption.

Yet, we should always be aware of the alternative possibility that observed behavioral differences are not (or at least not only) mediated by physiological mechanisms, but may also be influenced by nonbiological factors (Spirduso et al. 2008). For example, it has been suggested that the antidepressant effects of exercise are mediated by enhanced feelings of self-efficacy (as a consequence of experiencing mastery over the exercise regimen), or by distracting attention from ongoing ruminations (Barnes et al. 2010; Daley 2002).

6.4.3 Translational Research

While neuroimaging studies of physical exercise in human subjects have gained popularity in recent years (e.g., Colcombe et al. 2004; Themanson et al. 2006; Erickson et al. 2009), many of our current insights into the brain mechanisms of physical exercise were gained in animal studies (Cotman et al. 2007; Etnier 2009; Sect. 1, this volume). An obvious advantage of animal studies is the opportunity to

derive direct measurements of brain physiology via invasive techniques, which are usually not available in human studies. Meanwhile, the integration of these different approaches can be challenging, as not only the physiological measurement techniques, but also behavioral paradigms are not always complementary, which can hamper the generalizability of results across species. This lack of complementary testing procedures is most obvious for paradigms that draw on verbal responses (e.g., certain memory tests, verbal IQ measures, and questionnaires for subjective emotional experience), which are naturally not applicable in animal research.

Meanwhile, there are an increasing number of test instruments that have been adapted to both human and animal research (e.g., go/nogo, stop signal task), or were even explicitly designed to maximize cross-species comparability, for example, the *Cambridge Neuropsychological Test Automated Battery* (CANTAB®: Cambridge Cognition, Cambridge, UK). Recent methodological advances in translational neuroscientific research are promising, and it is likely that exercise-related research will profit from future developments in this field.

6.4.4 Transfer from Behavioral to Neuroimaging Studies

Currently, the majority of studies that investigate the psychological effects of physical exercise are still based on behavioral assessments. After establishing a link between exercise and the outcomes of specific psychological tests, it is an obvious idea to use neuroimaging techniques to search for physiological processes that are correlated with these behavioral changes.

Straightforward solutions are possible in situations where behavioral parameters from conventional "paper and pencil" tests can be correlated with parameters of brain function that are assumed to be rather stable, for example, brain structure volumes (Chaddock et al. 2010), resting-state functional connectivity in fMRI data series (Voss et al. 2010), or resting brain regional blood flow (Pereira et al. 2007), because it is possible to collect the psychological tests and physiological measurements at different time points and places (although close temporal proximity between the two measurements generally remains desirable).

The situation is different for functional activation studies, where behavioral task paradigms are used to evoke cognitive or affective processes and observe the corresponding, time-locked brain responses in the neuroimaging data. Here, behavioral assessments and neuroimaging need to be synchronized, and the form of cognitive or affective stimulation has to be adapted to the prerequisites of the imaging technique. While several of the above-mentioned behavioral tasks have been adapted to neuroimaging experiments, and although there are already exercise-related neuroimaging applications for some of these paradigms, for example, for flanker tasks (Colcombe et al. 2004; Themanson et al. 2008), and task-switching paradigms (Themanson et al. 2006), several technical and design issues have to be considered, especially in fMRI experiments. These requirements will often complicate a simple transfer from behavioral to neuroimaging studies.

For example, subject motion during the acquisition of the neuroimaging data is a critical issue, since many of these techniques afford participants to be immobilized as much as possible. This prerequisite does not only limit the acquisition of fMRI data during acute exercise, but also complicate the adaptation of many neuropsychological "paper and pencil" tests, where task performance often depends on oral or complex motor responses (e.g., writing, manual manipulation of objects). Typically, this problem is solved by minimizing the motor requirements of the task, for example, by limiting subject responses to button presses or the manipulation of a joystick. Yet, it has to be kept in mind that such modifications can occasionally alter the specific quality of the task. Motor constraints are also limiting the online assessment of emotional experience. Multi-item questionnaires for subjective emotional experiences, which are prominent in behavioral studies, are generally difficult to implement in the scanner environment. Typically, subjective ratings are restricted to short, unidimensional ratings (e.g., for valence, or arousal). For example, Goldin et al. (2005) asked participants to evaluate emotion intensity continuously by using a rating dial that regulated the height of bar graph.

Functional neuroimaging investigations of affective experience have to cope with additional drawbacks: There is an ongoing discussion whether the explicit instruction to make conscious reflections about the subjective affective experience can influence the pattern of brain activations that are elicited by emotional states (Taylor et al. 2003). Therefore, implicit measurements of affective reactions, for example by the measurement of psychophysiological responses, may provide important supplementary information. While special technical solutions are needed to transfer psychophysiological measurement techniques (e.g., for GSR, HRV, EMG) to the MR environment, they become more and more prevalent in fMRI research (for a comprehensive review, see Gray et al. 2009; see also Chap. 7). Although it must be acknowledged that there are still few exercise-related studies that used these measurement techniques successfully, future studies in this field may profit from these refinements. Another methodology that could be relevant is the use of affective cognition paradigms, which have already been adapted in several fMRI experiments with healthy and psychiatric populations (Elliott et al. 2011). Again, the available behavioral data from exercise-related studies (e.g., Barnes et al. 2010; Tian and Smith 2011) are too scarce (and ambiguous) to formulate clear recommendations.

Another practical problem which should be considered while adapting behavioral tests to an fMRI environment is scan duration: Functional neuroimaging experiments are often much longer than complementary behavioral tests because a large number of observations are needed to derive reliable brain activation patterns. These longer task durations may not always be tolerated by participants, and may also narrow possibilities to measure transient post-exercise effects (which may already dissipate during the experiment).

Finally, functional imaging experiments typically compare brain activations during "active" task conditions with brain activations during "control" task conditions in order to isolate those brain activations that are genuine to the cognitive or affective process of interest, while cancelling out activations due to irrelevant sensory, cognitive,

or motor processes. In practice, the search for an appropriate control condition can be a reasonable challenge, especially in situations where the transformation of complex tasks is intended (e.g., the WCST), where several processing steps may need to be fractionated by comparing different "active" and "control" conditions: Therefore, it often seems impracticable to adhere to the original behavioral tasks (Frith et al. 2004). In any case, a thorough understanding of the cognitive (or affective) processes that are assumed to be participating in task completion remains an important prerequisite for designing efficient neuroimaging experiments.

6.5 Conclusion

While the advent of modern neuroimaging technologies has brought fascinating opportunities to gain direct insights into the physiology of the human brain, psychological assessment techniques continue to play an important role, because they provide complementary outcome measures that allow inferences about the functional significance of the neuroimaging data, and because psychological background variables (e.g., global cognitive function, personality traits) may be relevant as potential confounds, or moderator variables. This holds also true for neuroimaging studies that aim to investigate the influence of physical exercise on brain function. While this research field is still developing, there are promising perspectives: For example, the assessment of executive control functions will probably continue to play a prominent role, and there is a growing interest in behavioral tasks that are sensitive to hippocampal memory functions. Meanwhile, the measurement of affective responses is mainly based on subjective affect ratings, with comparably few applications of objective measurement techniques. Future exercise-related studies will probably profit from the ongoing development of advanced behavioral paradigms in cognitive and affective neurosciences. These methodological refinements will help to improve our understanding of the brain mechanisms that mediate the modulating effects of physical exercise on psychological function.

References

Aberg MA, Pedersen NL, Toren K, Svartengren M, Backstrand B, Johnsson T, Cooper-Kuhn CM, Aberg ND, Nilsson M, Kuhn HG (2009) Cardiovascular fitness is associated with cognition in young adulthood. Proc Natl Acad Sci USA 106:20906–20911

Anderson RJ, Brice S (2011) The mood-enhancing benefits of exercise: memory biases augment the effect. Psychol Sport Exerc 12:79–82

Appelhans BM, Luecken LJ (2006) Heart rate variability as an index of regulated emotional responding. Rev Gen Psychol 10:229–240

Aron AR (2007) The neural basis of inhibition in cognitive control. Neuroscientist 13:214–228

Atkinson RC, Shiffrin RM (1968) Human memory: a proposed system and its control processes. In: Spence KW, Spence JT (eds) The psychology of learning and motivation, vol 2. Academic, New York, pp 89–195

Audiffren M (2009) Acute exercise and psychological functions: a cognitive-energetic approach. In: McMorris T, Tomporowski PD, Audiffren M (eds) Exercise and cognitive function. Wiley, Chichester, pp 1–39

Baddeley AD (2003) Working memory: looking back and looking forward. Nat Rev Neurosci 4:829–839

Baddeley AD, Hitch G (1974) Working memory. In: Bower GH (ed) The psychology of learning and motivation: advances in research and theory, vol 8. Academic, New York, pp 47–89

Barnes RT, Coombes SA, Armstrong NB, Higgins TJ, Janelle CM (2010) Evaluating attentional and affective changes following an acute exercise bout using a modified dot-probe protocol. J Sports Sci 28:1065–1076

Bartholomew JB, Ciccolo JT (2008) Exercise, depression and cognition. In: Spirduso W, Poon LW, Chodzko-Zajko W (eds) Exercise and Its mediating effects on cognition. Human Kinetics, Champaign, IL, pp 33–46

Bartholomew JB, Morrison D, Ciccolo JT (2005) Effects of acute exercise on mood and well-being in patients with major depressive disorder. Med Sci Sports Exerc 37:2032–2037

Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J (1961) An inventory for measuring depression. Arch Gen Psychiatry 4:561–571

Bird CM, Burgess N (2008) The hippocampus and memory: insights from spatial processing. Nat Rev Neurosci 9:182–194

Bixby WR, Spalding TW, Hatfield BD (2001) Temporal dynamics and dimensional specificity of the affective response to exercise of varying intensity: differing pathways to a common outcome. J Sport Exerc Psychol 23:171–190

Boecker H, Sprenger T, Spilker ME, Henriksen G, Koppenhoefer M, Wagner KJ, Valet M, Berthele A, Tolle TR (2008) The runner's high: opioidergic mechanisms in the human brain. Cereb Cortex 18:2523–2531

Bradley MM, Lang PJ (2007) Emotion and motivation. In: Cacioppo JT, Tassinari LG, Bengtson GG (eds) Handbook of psychophysiology, 3rd edn. Cambridge University Press, New York, pp 581–607

Brümmer V, Schneider S, Abel T, Vogt T, Strüder HK (2011) Brain cortical activity is influenced by exercise mode and intensity. Med Sci Sports Exerc 43:1863–1872

Carlsson AM (1983) Assessment of chronic pain. I. Aspects of the reliability and validity of the visual analogue scale. Pain 16:87–101

Chaddock L, Erickson KI, Prakash RS, Kim JS, Voss MW, VanPatter M, Pontifex MB, Raine LB, Konkel A, Hillman CH, Cohen NJ, Kramer AF (2010) A neuroimaging investigation of the association between aerobic fitness, hippocampal volume, and memory performance in preadolescent children. Brain Res 1358:172–183

Chaddock L, Hillman CH, Buck SM, Cohen NJ (2011) Aerobic fitness and executive control of relational memory in preadolescent children. Med Sci Sports Exerc 43:344–349

Coan JA, Allen JJB (2007) Handbook of emotion elicitation and assessment. Oxford University Press, New York

Colcombe SJ, Erickson KI, Scalf PE, Kim JS, Prakash R, McAuley E, Elavsky S, Marquez DX, Hu L, Kramer AF (2006) Aerobic exercise training increases brain volume in aging humans. J Gerontol A Biol Sci Med Sci 61A:1166–1170

Colcombe SJ, Kramer AF (2003) Fitness effects on the cognitive function of older adults: a meta-analytic study. Psychol Sci 14:125–130

Colcombe SJ, Kramer AF, Erickson KI, Scalf P, McAuley E, Cohen NJ, Webb A, Jerome GJ, Marquez DX, Elavsky S (2004) Cardiovascular fitness, cortical plasticity, and aging. Proc Natl Acad Sci USA 101:3316–3321

Coles K, Tomporowski PD (2008) Effects of acute exercise on executive processing, short-term and long-term memory. J Sports Sci 26:333–344

Cotman CW, Berchtold NC, Christie L-A (2007) Exercise builds brain health: key roles of growth factor cascades and inflammation. Trends Neurosci 30:464–472

Daley AJ (2002) Exercise therapy and mental health in clinical populations: is exercise therapy a worthwhile intervention? Adv Psychiatr Treat 8:262–270

Davidson RJ (1998) Affective style and affective disorders: perspectives from affective neuroscience. Cognition Emotion 12:307–330
Davranche K, Audiffren M (2009) A chronometric and electromyographic approach to the effect of exercise on reaction time. In: McMorris T, Tomporowski PD, Audiffren M (eds) Exercise and cognitive function. Wiley, Chichester, pp 153–159
Davranche K, Audiffren M, Denjean A (2006) A distributional analysis of the effect of physical exercise on a choice reaction time task. J Sports Sci 24:323–329
Del Giorno JM, Hall EE, O'Leary KC, Bixby WR, Miller PC (2010) Cognitive function during acute exercise: a test of the transient hypofrontality theory. J Sport Exerc Psychol 32:312–323
Dietrich A, Audiffren M (2011) The reticular-activating hypofrontality (RAH) model of acute exercise. Neurosci Biobehav Rev 35:1305–1325
Dietrich A, Sparling PB (2004) Endurance exercise selectively impairs prefrontal-dependent cognition. Brain Cogn 55:516–524
Dishman RK, Thom NJ, Puetz TW, O'Connor PJ, Clementz BA (2010) Effects of cycling exercise on vigor, fatigue, and electroencephalographic activity among young adults who report persistent fatigue. Psychophysiology 47:1066–1074
Eich TS, Metcalfe J (2009) Effects of the stress of marathon running on implicit and explicit memory. Psychon Bull Rev 16:475–479
Ekkekakis P (2008) Affect circumplex redux: the discussion on its utility as a measurement framework in exercise psychology continues. Int Rev Sport Exerc Psychol 1:139–159
Ekkekakis P, Hall EE, Petruzzello SJ (1999) Measuring state anxiety in the context of acute exercise using the State Anxiety Inventory: an attempt to resolve the brouhaha. J Sport Exerc Psychol 21:205–222
Ekkekakis P, Hall EE, Petruzzello SJ (2005a) Evaluation of the circumplex structure of the activation deactivation adjective check list before and after a short walk. Psychol Sport Exerc 6:83–101
Ekkekakis P, Hall EE, Petruzzello SJ (2005b) Variation and homogeneity in affective responses to physical activity of varying intensities: an alternative perspective on dose-response based on evolutionary considerations. J Sports Sci 23:477–500
Ekkekakis P, Petruzzello SJ (1999) Acute aerobic exercise and affect: current status, problems and prospects regarding dose–response. Sports Med 28:337–374
Ekman P, Friesen WV (1976) Pictures of facial affect. Consulting Psychologists Press, Palo Alto, C. A
Ekman P, Friesen WV (1978) Facial action coding system: a technique for the measurement of facial movement. Consulting Psychologists Press, Palo Alto
Elbe A-M, Szymanski B, Beckmann J (2005) The development of volition in young elite athletes. Psychol Sport Exerc 6:559–569
Elliott R, Zahn R, Deakin JFW, Anderson IM (2011) Affective cognition and its disruption in mood disorders. Neuropsychopharmacology 36:153–182
Erickson KI, Prakash RS, Voss MW, Chaddock L, Hu L, Morris KS, White SM, Wójcicki TR, McAuley E, Kramer AF (2009) Aerobic fitness is associated with hippocampal volume in elderly humans. Hippocampus 19:1030–1039
Eriksen BA, Eriksen CW (1974) Effects of noise letters on the identification of a target letter in a nonsearch task. Percept Psychophys 16:143–149
Etnier JL (2009) Chronic exercise and cognition in older adults. In: McMorris T, Tomporowski PD, Audiffren M (eds) Exercise and cognitive function. Wiley, Chichester, pp 227–247
Etnier JL, Chang YK (2009) The effect of physical activity on executive function: a brief commentary on definitions, measurement issues, and the current state of the literature. J Sport Exerc Psychol 31:469–483
Etnier JL, Nowell PM, Landers DM, Sibley BA (2006) A meta-regression to examine the relationship between aerobic fitness and cognitive performance. Brain Res Rev 52:119–130
Fillingim RB, Roth DL, Cook EW 3rd (1992) The effects of aerobic exercise on cardiovascular, facial EMG, and self-report responses to emotional imagery. Psychosom Med 54:109–120

Foerde K (2010) Implicit learning and memory: psychological and neural aspects. In: Koob GF, Le Moal M, Thompson RF (Eds) Encyclopedia of behavioral neuroscience. Elsevier Academic, pp 84–93

Frith CD, Gallagher H, Maguire E (2004) Mechanisms of control. In: Richard SJF, Karl JF, Christopher DF, Raymond JD, Cathy JP, Semir Z, John TA, William DP (eds) Human brain function, 2nd edn. Academic, Burlington, pp 329–362

Fumoto M, Oshima T, Kamiya K, Kikuchi H, Seki Y, Nakatani Y, Yu X, Sekiyama T, Sato-Suzuki I, Arita H (2010) Ventral prefrontal cortex and serotonergic system activation during pedaling exercise induces negative mood improvement and increased alpha band in EEG. Behav Brain Res 213:1–9

Gauvin L, Rejeski WJ (1993) The exercise-Induced feeling inventory: development and initial validation. J Sport Exerc Psychol 15:403–423

Gazzaley A, D'Esposito M (2007) Unifying prefrontal cortex function: executive control, neural networks and top-down modulation. In: Miller B, Cummings J (eds) The human frontal lobes: functions and disorders, 2nd edn. Guilford, New York, pp 187–206

Goldin PR, Hutcherson CAC, Ochsner KN, Glover GH, Gabrieli JDE, Gross JJ (2005) The neural bases of amusement and sadness: a comparison of block contrast and subject-specific emotion intensity regression approaches. Neuroimage 27:26–36

Graf P, Schacter DL (1985) Implicit and explicit memory for new associations in normal and amnesic subjects. J Exp Psychol Learn Mem Cogn 11:501–518

Grant DA, Berg EA (1948) A behavioural analysis of degree of reinforcement and ease of shifting to new responses in a Weigl-type card-sorting problem. J Exp Psychol Gen 38:404–411

Gray EK, Watson D (2007) Assessing positive and negative affect via self-report. In: Coan JA, Allen JJB (eds) Handbook of emotion elicitation and assessment. Oxford University Press, New York, pp 171–183

Gray MA, Minati L, Harrison NA, Gianaros PJ, Napadow V, Critchley HD (2009) Physiological recordings: basic concepts and implementation during functional magnetic resonance imaging. Neuroimage 47:1105–1115

Gronwall DM (1977) Paced auditory serial-addition task: a measure of recovery from concussion. Percept Mot Skills 44:367–373

Hall EE, Ekkekakis P, Petruzzello SJ (2010) Predicting affective responses to exercise using resting EEG frontal asymmetry: does intensity matter? Biol Psychol 83:201–206

Hamer M, Taylor A, Steptoe A (2006) The effect of acute aerobic exercise on stress related blood pressure responses: a systematic review and meta-analysis. Biol Psychol 71:183–190

Hardy CJ, Rejeski WJ (1989) Not what, but how one feels: the measurement of affect during exercise. J Sport Exerc Psychol 11:304–317

Hardy J, Hall CR, Alexander MR (2001) Exploring self-talk and affective states in sport. J Sports Sci 19:469–475

Hillman CH, Erickson KI, Kramer AF (2008) Be smart, exercise your heart: exercise effects on brain and cognition. Nat Rev Neurosci 9:58–65

Jackson EM, Dishman RK (2006) Cardiorespiratory fitness and laboratory stress: a meta-regression analysis. Psychophysiology 43:57–72

Jurado MB, Rosselli M (2007) The elusive nature of executive functions: a review of our current understanding. Neuropsychol Rev 17:213–233

Kamijo K, Nishihira Y, Hatta A, Kaneda T, Wasaka T, Kida T, Kuroiwa K (2004) Differential influences of exercise intensity on information processing in the central nervous system. Eur J Appl Physiol 92:305–311

Kaufman AS, Kaufman NL (1990) Kaufman brief intelligence test: manual. American Guidance Service, Circle Pines, MN

Kramer AF, Hahn S, Cohen NJ, Banich MT, McAuley E, Harrison CR, Chason J, Vakil E, Bardell L, Boileau RA, Colcombe A (1999) Ageing, fitness and neurocognitive function. Nature 400:418–419

Kreibig SD (2010) Autonomic nervous system activity in emotion: a review. Biol Psychol 84:394–421

Laborde S, Brüll A, Weber J, Anders LS (2011) Trait emotional intelligence in sports: a protective role against stress through heart rate variability? Personal Indiv Diff 51:23–27
Lambourne K, Tomporowski P (2010) The effect of exercise-induced arousal on cognitive task performance: a meta-regression analysis. Brain Res 1341:12–24
Lang PJ, Bradley MM, Cuthbert BN (2008) International affective picture system (IAPS): affective ratings of pictures and instruction manual. Technical Report A-8. The Centre for Research in Psychophysiology, University of Florida, Gainesville, FL
Leunes A, Burger J (2000) Profile of mood states research in sport and exercise psychology: past, present, and future. J Appl Sport Psychol 12:5–15
Lezak MD, Howieson DB, Loring DW (2004) Neuropsychological assessment, 4th edn. Oxford University Press, New York
Malik M (1996) Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Eur Heart J 17:354–381
Martens R, Burton D, Vealey RS, Bump LA, Smith DE (1990) Development and validation of the Competitive State Anxiety Inventory-2 (CSAI-2). In: Martens R, Vealey RS, Burton D (eds) Competitive anxiety in sport. Human Kinetics, Champaign, IL, pp 193–208
Martinent G, Ferrand C, Guillet E, Gautheur S (2010) Validation of the French version of the Competitive State Anxiety Inventory-2 Revised (CSAI-2R) including frequency and direction scales. Psychol Sport Exerc 11:51–57
McMorris T (2008) Exercise and cognition: towards an inter-disciplinary model. Open Sports Med J 2:60–68
McMorris T, Sproule J, Turner A, Hale BJ (2011) Acute, intermediate intensity exercise, and speed and accuracy in working memory tasks: a meta-analytical comparison of effects. Physiol Behav 102:421–428
McNair D, Lorr M, Droppelman L (1971) Profile of mood states. Educational and Industrial Testing Service, San Diego, CA
Miller EK, Cohen JD (2001) An integrative theory of prefrontal cortex function. Annu Rev Neurosci 24:167–202
Miyake A, Friedman NP, Emerson MJ, Witzki AH, Howerter A, Wager TD (2000) The unity and diversity of executive functions and their contributions to complex "Frontal Lobe" tasks: a latent variable analysis. Cogn Psychol 41:49–100
Mneimne M, McDermut W, Powers AS (2008) Affective ratings and startle modulation in people with nonclinical depression. Emotion 8:552–559
Monsell S (2003) Task switching. Trends Cogn Sci 7:134–140
Moraes H, Deslandes A, Silveira H, Ribeiro P, Cagy M, Piedade R, Pompeu F, Laks J (2011) The effect of acute effort on EEG in healthy young and elderly subjects. Eur J Appl Physiol 111:67–75
Morgan WP (1997) Methodological considerations. In: Morgan WP (ed) Physical activity and mental health. Taylor & Francis, Washington, DC, pp 3–32
Murray NP, Raedeke TD (2008) Heart rate variability as an indicator of pre-competitive arousal. Int J Sport Psychol 39:346–355
Nadel L, Hardt O (2011) Update on memory systems and processes. Neuropsychopharmacology 36:251–273
Navon D (1977) Forest before trees: the precedence of global features in visual perception. Cogn Psychol 9:353–383
Oda S, Matsumoto T, Nakagawa K, Moriya K (1999) Relaxation effects in humans of underwater exercise of moderate intensity. Eur J Appl Physiol Occup Physiol 80:253–259
Panksepp J (1988) Brain emotional circuits and psychopathologies. In: Clynes M, Panksepp J (eds) Emotions and psychopathology. Plenum, New York, pp 37–76
Parkinson B, Totterdell P, Briner RB, Reynolds S (1996) Changing moods: the psychology of mood and mood regulation. Longman, London
Pereira AC, Huddleston DE, Brickman AM, Sosunov AA, Hen R, McKhann GM, Sloan R, Gage FH, Brown TR, Small SA (2007) An in vivo correlate of exercise-induced neurogenesis in the adult dentate gyrus. Proc Natl Acad Sci USA 104:5638–5643

Pesce C, Tessitore A, Casella R, Pirritano M, Capranica L (2007) Focusing of visual attention at rest and during physical exercise in soccer players. J Sports Sci 25:1259–1270
Petruzzello SJ, Hall EE, Ekkekakis P (2001) Regional brain activation as a biological marker of affective responsivity to acute exercise: influence of fitness. Psychophysiology 38:99–106
Pontifex MB, Hillman CH, Fernhall B, Thompson KM, Valentini TA (2009) The effect of acute aerobic and resistance exercise on working memory. Med Sci Sports Exerc 41:927–934
Reed J, Buck S (2009) The effect of regular aerobic exercise on positive-activated affect: a meta-analysis. Psychol Sport Exerc 10:581–594
Reed J, Ones DS (2006) The effect of acute aerobic exercise on positive activated affect: a meta-analysis. Psychol Sport Exerc 7:477–514
Rhodes RE, Smith NE (2006) Personality correlates of physical activity: a review and meta-analysis. Br J Sports Med 40:958–965
Robbins TW (2007) Shifting and stopping: fronto-striatal substrates, neurochemical modulation and clinical implications. Phil Transact R Soc Lond B Biol Sci 362:917–932
Rodrigues AVS, Martinez EC, Duarte AFA, Ribeiro LCS (2007) Aerobic fitness and its influence in the mental stress response in army personnel. Revista Brasileira de Medicina do Esporte 13:113–117
Russell JA, Weiss A, Mendelsohn GA (1989) Affect grid: a single-item scale of pleasure and arousal. J Pers Soc Psychol 57:493–502
Scherer KR, Peper M (2001) Psychological theories of emotion and neuropsychological research. In: Boller F, Grafman J, Gainotti G (eds) Handbook of neuropsychology, vol 5, Emotional behavior and its disorders. Elsevier, Amsterdam, pp 17–48
Schneider M, Graham D, Grant A, King P, Cooper D (2009a) Regional brain activation and affective response to physical activity among healthy adolescents. Biol Psychol 82:246–252
Schneider S, Brümmer V, Abel T, Askew CD, Strüder HK (2009b) Changes in brain cortical activity measured by EEG are related to individual exercise preferences. Physiol Behav 98: 447–452
Shohamy D, Myers CE, Kalanithi J, Gluck MA (2008) Basal ganglia and dopamine contributions to probabilistic category learning. Neurosci Biobehav Rev 32:219–236
Sibley BA, Beilock SL (2007) Exercise and working memory: an individual differences investigation. J Sport Exerc Psychol 29:783–791
Smiley-Oyen AL, Lowry KA, Francois SJ, Kohut ML, Ekkekakis P (2008) Exercise, fitness, and neurocognitive function in older adults: the "selective improvement" and "cardiovascular fitness" hypotheses. Ann Behav Med 36:280–291
Smith A (1982) Symbol digit modalities test: manual (revised). Western Psychological Services, Los Angeles
Smith JC, Cook DB (2005) Methodology in psychophysiological studies: applications in physical activity. Int J Sport Exerc Psychol 3:534–553
Smith JC, Crabbe JB (2000) Emotion and exercise. Int J Sport Psychol 31:156–174
Smith JC, O'Connor PJ (2003) Physical activity does not disturb the measurement of startle and corrugator responses during affective picture viewing. Biol Psychol 63:293–310
Smith PJ, Blumenthal JA, Hoffman BM, Cooper H, Strauman TA, Welsh-Bohmer K, Browndyke JN, Sherwood A (2010) Aerobic exercise and neurocognitive performance: a meta-analytic review of randomized controlled trials. Psychosom Med 72:239–252
Spielberger CD, Gorsuch RL, Lushene RE (1970) Manual for the state-trait anxiety inventory. Consulting Psychologists Press, Palo Alto, CA
Spirduso WW, Poon LW, Chodzko-Zajko W (2008) Using resources and reserves in an exercise-cognition model. In: Spirduso WW, Poon LW, Chodzko-Zajko W (eds) Exercise and its mediating effects on cognition. Human Kinetics, Champaign, IL, US, pp 3–11
Squire LR (2004) Memory systems of the brain: a brief history and current perspective. Neurobiol Learn Mem 82:171–177
Stephens CL, Christie IC, Friedman BH (2010) Autonomic specificity of basic emotions: evidence from pattern classification and cluster analysis. Biol Psychol 84:463–473
Steptoe A, Cox S (1988) Acute effects of aerobic exercise on mood. Health Psychol 7:329–340

Steptoe A, Kearsley N, Walters N (1993) Acute mood responses to maximal and submaximal exercise in active and inactive men. Psychol Health 8:89–99
Steptoe A, Moses J, Mathews A, Edwards S (1990) Aerobic fitness, physical activity, and psychophysiological reactions to mental tasks. Psychophysiology 27:264–274
Stern RA, Arruda JE, Hooper CR, Wolfner GD, Morey CE (1997) Visual analogue mood scales to measure internal mood state in neurologically impaired patients: description and initial validity evidence. Aphasiology 11:59–71
Stern Y (2009) Cognitive reserve. Neuropsychologia 47:2015–2028
Strauss E, Sherman EMS, Spreen O (2006) A compendium of neuropsychological tests: administration, norms, and commentary, 3rd edn. Oxford University Press, New York
Stroth S, Hille K, Spitzer M, Reinhardt R (2009) Aerobic endurance exercise benefits memory and affect in young adults. Neuropsychol Rehabil 19:223–243
Stroth S, Reinhardt RK, Thöne J, Hille K, Schneider M, Härtel S, Weidemann W, Bös K, Spitzer M (2010) Impact of aerobic exercise training on cognitive functions and affect associated to the COMT polymorphism in young adults. Neurobiol Learn Mem 94:364–372
Stuss DT (2007) New approaches to prefrontal lobe testing. In: Miller BL, Cummings JL (eds) The human frontal lobes: functions and disorders, 2nd edn. Guilford, New York
Swick D, Ashley V, Turken U (2011) Are the neural correlates of stopping and not going identical? Quantitative meta-analysis of two response inhibition tasks. Neuroimage 56:1655–1665
Szabo A, Bak M (1999) Exercise-induced affect during training and competition in collegiate soccer players. European Yearbook of Sport Psychology 3:91–104
Taylor SF, Phan KL, Decker LR, Liberzon I (2003) Subjective rating of emotionally salient stimuli modulates neural activity. Neuroimage 18:650–659
Thayer JF, Lane RD (2009) Claude Bernard and the heart-brain connection: further elaboration of a model of neurovisceral integration. Neurosci Biobehav Rev 33:81–88
Thayer RE (1989) The biopsychology of mood and arousal. Oxford University Press, New York
Themanson JR, Hillman CH (2006) Cardiorespiratory fitness and acute aerobic exercise effects on neuroelectric and behavioral measures of action monitoring. Neuroscience 141:757–767
Themanson JR, Hillman CH, Curtin JJ (2006) Age and physical activity influences on action monitoring during task switching. Neurobiol Aging 27:1335–1345
Themanson JR, Pontifex MB, Hillman CH (2008) Fitness and action monitoring: evidence for improved cognitive flexibility in young adults. Neuroscience 157:319–328
Tian Q, Smith JC (2011) Attentional bias to emotional stimuli is altered during moderate- but not high-intensity exercise. Emotion 11:1415–1424
Tomporowski PD (2009) Methodological issues: research approaches, research design, and task selection. In: McMorris T, Tomporowski PD, Audiffren M (eds) Exercise and cognitive function. Wiley, Chichester, pp 91–113
Tomporowski PD, Davis CL, Miller PH, Naglieri JA (2008) Exercise and children's intelligence, cognition, and academic achievement. Educ Psychol Rev 20:111–131
Tomporowski PD, Ganio MS (2006) Short-term effects of aerobic exercise on executive processing, memory, and emotional reactivity. Int J Sport Exerc Psychol 4:57–72
van Zomeren AH, Brouwer WH (1994) Clinical neuropsychology of attention. Oxford University Press, New York
Vlachopoulos S, Biddle SJH, Fox K (1996) A social cognitive investigation into the mechanisms of affect generation in children's physical activity. J Sport Exerc Psychol 18:174–193
Vogt T, Schneider S, Brümmer V, Strüder HK (2010) Frontal EEG asymmetry: the effects of sustained walking in the elderly. Neurosci Lett 485:134–137
Voss MW, Prakash RS, Erickson KI, Basak C, Chaddock L, Kim JS, Alves H, Heo S, Szabo AN, White SM, Wojcicki TR, Mailey EL, Gothe N, Olson EA, McAuley E, Kramer AF (2010) Plasticity of brain networks in a randomized intervention trial of exercise training in older adults. Front Aging Neurosci 2:32
Watson D, Clark LA, Tellegen A (1988) Development and validation of brief measures of positive and negative affect: the PANAS scales. J Pers Soc Psychol 54:1063–1070

Wechsler D (2008) Wechsler adult intelligence scale-fourth edition (WAIS-IV). Pearson, San Antonio, TX

Wechsler D (2009) Wechsler memory scales, 4th edn. Pearson, San Antonio, TX

Williams DM, Dunsiger S, Ciccolo JT, Lewis BA, Albrecht AE, Marcus BH (2008) Acute affective response to a moderate-intensity exercise stimulus predicts physical activity participation 6 and 12 months later. Psychol Sport Exerc 9:231–245

Williamson JD, Espeland M, Kritchevsky SB, Newman AB, King AC, Pahor M, Guralnik JM, Pruitt LA, Miller ME (2009) Changes in cognitive function in a randomized trial of physical activity: Results of the Lifestyle Interventions and Independence for Elders Pilot Study. J Gerontol A Biol Sci Med Sci 64A:688–694

Winter B, Breitenstein C, Mooren FC, Voelker K, Fobker M, Lechtermann A, Krueger K, Fromme A, Korsukewitz C, Flöel A, Knecht S (2007) High impact running improves learning. Neurobiol Learn Mem 87:597–609

Wipfli BM, Rethorst CD, Landers DM (2008) The anxiolytic effects of exercise: a meta-analysis of randomized trials and dose-response analysis. J Sport Exerc Psychol 30:392–410

Woo M, Kim S, Kim J, Petruzzello SJ, Hatfield BD (2009) Examining the exercise-affect dose-response relationship: does duration influence frontal EEG asymmetry? Int J Psychophysiol 72:166–172

Yeung RR (1996) The acute effects of exercise on mood state. J Psychosom Res 40:123–141

Zald DH, Andreotti C (2010) Neuropsychological assessment of the orbital and ventromedial prefrontal cortex. Neuropsychologia 48:3377–3391

Chapter 7
Assessing Somatosensory Profiles and Autonomic Nervous System Responses in Physical Exercise Studies

Michael Valet, Till Sprenger, Lukas Scheef, and Henning Boecker

Abstract The aim of this chapter is to summarize methods for assessing effects of physical exercise on somatosensory and autonomic nervous system responses. The focus will be laid on extended methods for evaluating thermal and pain processing ("Quantitative Sensory Testing"; QST), which may be modulated by exercise. Additionally, methods for measuring blood pressure (BP), heart rate (HR), heart rate variability (HRV), and skin conductance (SC) in the MRI scanner will be reviewed, as the autonomic nervous system is involved in both exercise and pain. Implementing these methods in the context of human neuroimaging experiments has important implications for the conduction, analysis, and interpretation of exercise studies.

7.1 Introduction

It is a common observation that participants in marathon races—despite injuries like blisters or stress fractures—are able to finish these strenuous competitions without major pain interference. Also, the incidence of "silent" myocardial ischemia is

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raised in athletes (Sheps et al. 1987) and phenomena of "reduced pain perception" have been associated with raised "opioidergic tone" during and after exercise, blunting the alerting symptoms of pain. Early findings of antinociceptive effects mediated by exercise go back to the late 1970s (Black et al. 1979). Since then, a number of studies—spanning over the past three decades—have provided evidence that endurance (Koltyn 2000) and resistance (Focht and Koltyn 2009; Koltyn 2000; Koltyn and Arbogast 1998) training impacts on pain perception: Pain detection thresholds are elevated in athletes, as compared to untrained individuals (Droste et al. 1991; Janal et al. 1984; Koltyn 2000), and the perception of a variety of painful stimuli (Koltyn 2000), including heat pain stimulation (Janal et al. 1984), electrical stimulation (Kemppainen et al. 1990; Olausson et al. 1986), and pressure stimulation (Hoffman et al. 2005), was found to be reduced by exercise. Systematic investigations have been performed mainly in cycling and running determining the levels of exercise (in relation to aerobic capacity) needed to induce hypoalgesia (Koltyn 2002). It was shown that hypoalgesia is induced more consistently after high-intensity exercise with at least 200 W workload or at least 75% of maximal oxygen uptake over 30 min, as compared to lower or self-selected intensities, or shorter-lasting exercise (Koltyn 2002).

The exact mechanisms underlying antinociceptive effects of exercise are not known. Since the discovery of endogenous opioids in the mid-1970s (Farrell 1985), release of endogenous opioid peptides during exercise has been considered to be a key mechanism of exercise-induced pain control (Boecker et al. 2008; Goldfarb and Jamurtas 1997). This interpretation is supported by pharmacological work in rats, showing that pain threshold elevations induced by exercise can be reversed by the opioid receptor antagonist Naloxone (Shyu et al. 1982) and, likewise, that the antinociceptive effects of exogenously administered opioids can be effectively attenuated by exercise challenges. This phenomenon is referred to as "cross-tolerance" (Kanarek et al. 1998; Mathes and Kanarek 2001) and, notably, can be elicited directly (Mathes and Kanarek 2006) by morphine administration into the periaqueductal gray (PAG), a key area of the descending antinociceptive pathway known to mediate opioidergic antinociceptive effects (Sandkuhler 1996). It has to be pointed out that participation of other (non-opioid) pathways, including the endocannabinoid system (Dietrich and McDaniel 2004), has to be considered as well. Moreover, Hoffmann et al. showed that a serotonin synthesis blocker suppresses the analgesic effects of skeletal muscle stimulation (Hoffmann et al. 1990) and, as shown by Kemppainen et al. (1990), corticotropin plays a role in elevating pain thresholds after exercise. In this latter study, dexamethasone was applied to subjects before exercising on a cycle ergometer. It was found that dexamethasone attenuates exercise-related pain threshold elevations. NMDA-induced analgesia has also been reported in mice (Marek et al. 1992), but also other non-pharmacological factors like distraction (Bushnell et al. 1985; Johnson and Petrie 1997) may all contribute to the behavioral findings of blunted pain responses.

Independent of the underlying causal mechanisms, the effects of exercise on pain systems need to be measured precisely and extensively using dedicated and validated techniques: Pain thresholds (i.e., the point at which stimuli are reported to be

painful) and pain tolerances (i.e., the point at which noxious stimuli cannot be tolerated any more) can be assessed with different methods of pain stimulation, such as electrical, heat, cold, ischemic, and pressure stimulation. However, the suitability of certain pain stimulation methods such as the cold pressor test (i.e., immersing a hand to the wrist in a bath of ice water and assessing pain perception with pain intensity ratings or tolerance time) or the application of noxious cold or heat stimuli with a thermode (e.g., Medoc TSA II) in the context of exercise-induced hypoalgesia has been questioned (Droste and Greenlee 1992; Padawer and Levine 1992; Pertovaara and Kemppainen 1992; Ruble et al. 2005). Most consistent results in exercise studies have been found when using painful pressure or electrical stimuli (Koltyn 2002). Recently, a multimodal approach with various experimental pain modalities has been suggested outside the specific context of exercise for assessing pain thresholds and responses, and was substantiated by investigating different pain modalities with noxious electrical, heat, cold, pressure, and reflex-inducing receptive field stimuli in a healthy population of 272 subjects (Neziri et al. 2011). As different polymodal nociceptors and peripheral somatosensory fiber systems (A-delta-fibers, C-fibers) are involved in the transduction and transmission of pain (see below), the combination of these different stimulation procedures may allow to comprehensively address the complexity of nociception and the individual pain experience in future studies of exercise.

Besides altered pain thresholds, studies on physical exercise also evidenced changes in thermal detection thresholds and reduced thermal sensitivity, which persisted for approximately 15–30 min following exercise (Kemppainen et al. 1985). However, other authors have not been able to identify changes of thermoception after exercise (Ruble et al. 2005); therefore, it is important to sufficiently quantify changes of the somatosensory system when conducting experiments. In the following, we will summarize methods for assessing exercise-induced effects on pain processing in the neuroimaging context after an introduction into the principal peripheral nerve fiber systems involved in the transmission of pain (and other somatosensory input):

7.2 Peripheral Nerve Fiber Systems

The transmission of somatosensory information from skin receptors to the central nervous system is realized by different nerve fiber systems. Each peripheral fiber system mediates different sensory information, of which the A-beta-, A-delta-, and C-fiber systems are described in more detail.

7.2.1 A-Beta-Fibers

The A-beta-fiber system consists of large caliber myelinated fibers (6–12 μm diameter) with a nerve conduction velocity of about 50–60 m/s and is usually

involved in the processing of tactile stimuli, such as touch, vibration, and proprioception (Treede 2011). The clinical investigation of the A-beta-fiber system is usually the domain of nerve conduction studies (NCS) and somatosensory-evoked potentials (SSEP), which are electrophysiological methods commonly used in clinical neurological routine to detect demyelination or axonal damage. However, the usage of these methods is limited to defined body regions and pathological states can only be detected if nerves are damaged to a significant degree. More subtle changes or early stages of damage may be evidenced using a simple Rydel–Seiffer tuning fork (vibration testing) or von Frey filaments (as part of Quantitative Sensory Testing (QST); for a detailed description, see below). Testing the vibration perception is a very sensitive parameter to detect alterations of the A-beta-fiber system (Perkins and Bril 2003). The Rydel–Seiffer tuning fork has been shown to possess a similar sensitivity as more complex devices for the testing of vibration thresholds (Pestronk et al. 2004). The use of simple tools such as von Frey filaments, calibrated monofilaments reflecting different stimulus intensities, allows to detect alterations of the sense of touch (Perkins and Bril 2003). While the tuning fork tests deeper A-beta-fibers, von Frey filaments test the superficial system. The phenomenon that moving innocuous touch stimuli are perceived as painful is called dynamic mechanical allodynia (DMA). It can be detected using devices such as cotton wisps (force of ~3 mN), cotton wool tips (~100 mN), or brushes (~200–400 mN). Under physiological conditions, the A-beta-fiber system is not involved in the transmission of nociceptive signals; however—through reorganization processes within the central nervous system (CNS) at the spinal and/or cerebral level—the activation of the A-beta-fiber system may be perceived as painful. DMA is therefore a pathological sign of sensitization of the nociceptive transmission in the CNS.

7.2.2 A-Delta-Fibers

The A-delta-fiber system with nerve conduction velocities around 30 m/s consists of myelinated small-caliber fibers (1–5 μm). The system of A-delta-fibers together with unmyelinated C-fibers (conduction velocity 0.5–2 m/s, 0.2–1.5 μm diameter) is usually termed “small fiber system”. A-delta and C-fibers (see below) can be found in the skin, muscles, and visceral organs. These fibers represent about 70% of the peripheral nervous system and are involved in mechanoception, thermoception, nociception, viscероception, and autonomic nervous system responses. The terminal ends of the A-delta-fiber system mediate detection of coldness (transduction by cold receptors), detection of punctate stimuli (mechanoceptors), and together with C-fibers, transmission of nociceptive cold, heat, punctate, pinch, and pressure pain stimuli. The pathological condition of cold or pressure hyperalgesia is not fully understood, both peripheral involvement of A-Delta- and C-fibers, and central disinhibition processes are possible.

7.2.3 C-Fibers

The C-fiber system is involved in the transmission of warm/heat and nociceptive stimuli. Thermoception is encoded by a mixed proportional-differential response of the cold receptors of A-delta-fibers and the heat receptors of C-fibers (Handwerker et al. 1982). This means that the CNS encodes the temperature sensation by activity differences of both receptor types. The temperature zone between 30 and 35°C is usually encoded as "indifferent" in the brain. C-fibers are thought to be involved in signaling different pathological conditions. One is heat hyperalgesia, most frequently appearing after UV-sunburn or acute tissue damage, occasionally in neuropathic pain conditions, such as postherpetic neuralgia. The detection of heat hyperalgesia in affected skin points toward a peripheral sensitization of nociceptors. Another condition is termed paradoxical heat sensation, a sensation of warmth elicited by application of a cold stimulus. It may occur occasionally in asymptomatic subjects (especially in the elderly), but more importantly in patients with neuropathic pain conditions. Physiologically, cooling down the skin stimulates both the A-delta- and the C-fiber system. A malfunctioning of the cold sensing A-delta-fiber system may lead to disinhibition processes at a spinal or supraspinal level, so that the C-fiber input is preferentially processed evoking a paradoxical heat sensation in response to the cooling (Susser et al. 1999).

7.3 Quantitative Sensory Testing

QST is a validated and standardized tool for psychophysiological evaluation of the somatosensory system (Dyck et al. 1993; Geber et al. 2011; Rolke et al. 2006a, b). QST measures the individual perception of experimental sensory stimuli of defined intensities. The basic idea of QST is to address a broad spectrum of submodalities of the somatosensory system, such as thermal and tactile sensations, including nociception, and the sensation of deep tissues. Patterns of functional losses or gains allow to create "somatosensory profiles" and to draw conclusions on underlying (patho-) physiological mechanisms. In the context of exercise, QST may be a suitable tool for quantifying short-term and long-term changes of sensory perception before and after exercise, or changes related to repeated bouts of exercise. In most QST protocols, a wide range of instruments investigating different peripheral fiber systems are applied (see Fig. 7.1). The QST protocol of the German Research Network on Neuropathic Pain (DFNS) allows to study all fiber systems comprehensively (Rolke et al. 2006a). This protocol comprises two testing batteries (thermal and mechanical part) measuring a total of 13 sensory parameters (see Fig. 7.2). The thermal part determines thermal detection thresholds for the perception of cold and warm stimuli, the discrimination ability of alternating cold and warm stimuli (thermal sensory limen), paradoxical heat sensations (see above), as well as thermal pain thresholds in

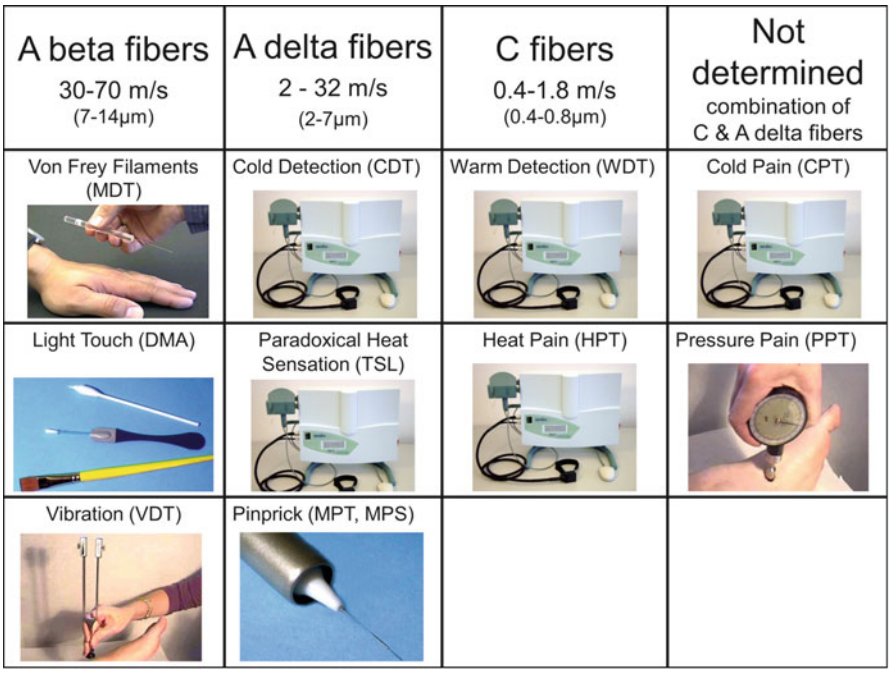

Fig. 7.1 QST instruments for the evaluation of different fiber systems (modified from Rolke et al. 2006a, b)

response to cold and hot stimuli. The mechanical part determines mechanical detection thresholds for touch and vibration, the mechanical pain sensitivity including thresholds for pinprick and blunt pressure, stimulus/response-functions for pinprick sensitivity, dynamic mechanical allodynia, and the temporal summation in response to repetitive noxious pinprick stimuli ("wind-up"). Almost all parameters test the superficial sensory system, whereas blunt pressure tests the deep pain sensitivity of muscles and deep tissue.

The QST protocol is able to evaluate both a gain and a loss of sensory function. For the standardized QST protocol, reference values have been determined in 180 healthy male and female controls (age range: 20–60 years) in a multicenter study (Rolke et al. 2006b). In this study, QST data of six body regions (face, hand, and foot, both sides each) were analyzed regarding the influence of age, gender, body side, and body region. Effect sizes for body region, age, and gender differences were calculated for each QST parameter allowing comparisons across parameters. The sensitivity of absolute vs. relative QST reference values was compared for side-to-side and across body areas. The reference values help to identify abnormal conditions in individuals, or to monitor changes of the somatosensory profile due to exercise or pharmacological intervention. The reference values may be used to

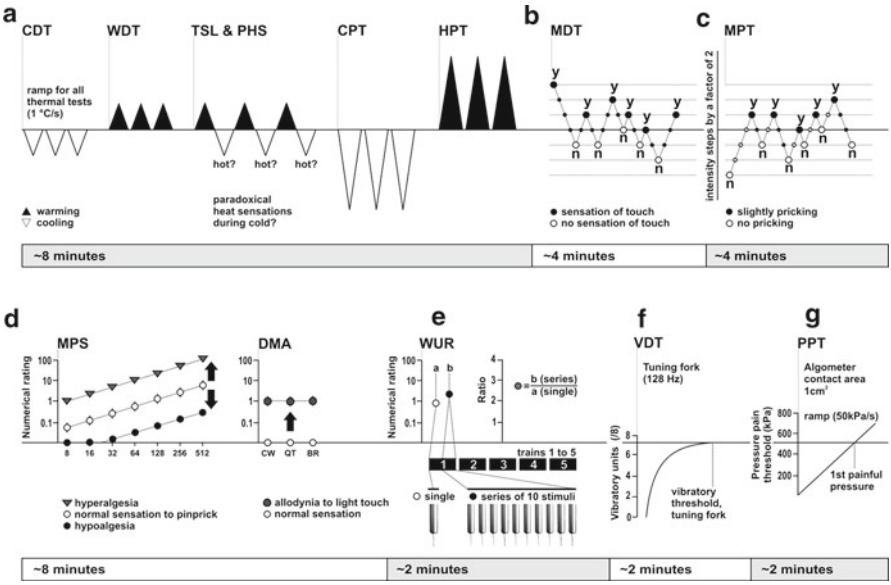

Fig. 7.2 The standardized QST protocol assesses 13 parameters in seven test procedures (**a**–**g**). All procedures are presented including a time frame for testing over one area. (**a**) Thermal testing comprises detection and pain thresholds for cold, warm, or hot stimuli (C- and A-delta-fiber-mediated): cold detection threshold (CDT); warm detection threshold (WDT); number of paradoxical heat sensations (PHS) during the thermal sensory limen procedure (TSL) for alternating warm and cold stimuli; cold pain threshold (CPT); heat pain threshold (HPT). (**b**) Mechanical detection threshold (MDT) tests for A-beta-fiber function using von Frey-filaments. (**c**) Mechanical pain threshold (MPT) tests for A-delta-fiber-mediated hyper- or hypoalgesia to pinprick stimuli. (**d**) Stimulus–response-functions: mechanical pain sensitivity (MPS) for pinprick stimuli, and dynamic mechanical allodynia (DMA) assess A-delta-mediated sensitivity to sharp stimuli (pinprick), and also A-beta-fiber-mediated pain sensitivity to stroking light touch (*CW* cotton wisp, *QT* cotton wool tip, *BR* brush). (**e**) Wind-up ratio (WUR) compares the numerical ratings within five trains of a single pinprick stimulus (a) with a series (b) of 10 repetitive pinprick stimuli to calculate WUR as the ratio: b/a. (**f**) Vibration detection threshold (VDT) tests for A-beta-fiber function using a Rydel–Seiffer 64 Hz tuning fork. (**g**) Pressure pain threshold (PPT) is the only test for deep pain sensitivity, most probably mediated by muscle C- and A-delta-fibers (slightly modified from Rolke et al. 2006b, with permission from Elsevier)

generate standardized reports for the detection of pathological sensory signs in test persons (see Fig. 7.3). In addition, *z*-score profiles can be compiled to allow a visual interpretation of QST findings (Fig. 7.4). The *z*-score profile represents deviations of single QST parameters from the normative data and is calculated with the formula $Z = (\text{individual QST parameter value of test person} - \text{mean QST parameter value of controls}) / \text{standard deviation of controls}$.

Regarding the reliability of QST, another recently published multicenter study demonstrated a high test–retest (TR-R) and interobserver (IO-R) reliability in

Most affected area: right hand – palmar_hypothenar (skin temp. 22.80 C)
Contralateral / other area: left hand – palmar_hypothenar (skin temp. 23.70 C)

	Most affected area	Contralateral / other area	Findings (Area compared to normative data)	Side-to-Side comparison
CDT (deviation from baseline 32 C)	–8.23 C	–2.80 C	Most affected area: **hypoesthesia** Contralateral / other area: **normal value**	**Hypoesthesia** compared to the contralateral area
WDT (deviation from baseline 32 C)	11.87 C	2.33 C	Most affected area: **hypoesthesia** Contralateral / other area: **normal value**	**Hypoesthesia** compared to the contralateral area
TSL	17.03 C	4.80 C	Most affected area: **hypoesthesia** Contralateral / other area: **normal value**	**Hypoesthesia** compared to the contralateral area
CPT (absolute value)	21.30 C	4.53 C	Most affected area: **normal value** Contralateral / other area: **normal value**	**Hyperalgesia** compared to the contralateral area
HPT (absolute value)	40.83 C	42.70 C	Most affected area: **normal value** Contralateral / other area: **normal value**	No abnormal side-to-side difference
PPT	226 kPa	484 kPa	Most affected area: **hyperalgesia** Contralateral / other area: **normal value**	**Hyperalgesia** compared to the contralateral area
MPT	5.66 mN	78.79 mN	Most affected area: **hyperalgesia** Contralateral / other area: **normal value**	**Hyperalgesia** compared to the contralateral area
MPS	100.00	0.13	Most affected area: **hyperalgesia** Contralateral / other area: **normal value**	**Hyperalgesia** compared to the contralateral area
WUR	-	3.20	Most affected area: **not evaluable** Contralateral / other area: **normal value**	Not evaluable
MDT	19.698 mN	2.828 mN	Most affected area: **hypoesthesia** Contralateral / other area: **normal value**	**Hypoesthesia** compared to the contralateral area
VDT	6.17/8	7.33 /8	Most affected area: **hypoesthesia** Contralateral / other area: **normal value**	**Hypoesthesia** compared to the contralateral area
DMA	41.93	0.00	Most affected area: **dynamic mechanical allodynia** Contralateral / other area: **normal value**	
PHS	0 /3	0 /3	Most affected area: **normal value** Contralateral / other area: **normal value**	

Fig. 7.3 Example of a QST report, from the QST lab of the Department of Neurology, Technische Universität München, Munich Germany. Abbreviations: see legend Fig. 7.2

patients with lesions of the somatosensory system (Geber et al. 2011). QST of 13 sensory parameters was performed at the clinically most affected site and at a control area, which was affected to a lesser degree or entirely unaffected. Measurements were conducted during a morning and an afternoon session on two consecutive days by paired examiners (4 × QST per patient; $n = 60$). All examiners were trained in certified QST centers to the same QST protocol according to the DFNS guidelines (see http://www.certkom.com/ for certified QST centers) and were equipped with a comprehensive handbook with standardized instructions. For both TR-R and IO-R, high correlations ($r = 0.80$–0.93) were found. The reliabilities were significantly better in the affected area (TR-R: $r = 0.86$; IO-R: $r = 0.83$) than in the unaffected control area (TR-R: $r = 0.79$; IO-R: $r = 0.71$), suggesting that disease-related systematic variance increases the reliability of QST. The study concluded that standardized QST performed by trained examiners is a valuable experimental and diagnostic instrument with good test–retest and interobserver reliability.

QST will be a very useful tool for future investigations of exercise-induced changes of the somatosensory system, such as hypoalgesia. Furthermore, the diagnostic properties of QST allow to confirm that subjects/athletes recruited for experimental studies possess an intact somatosensory system. Test persons should have a normal reflex status of the upper and lower extremities as well as normal QST values for warmth and cold, mechanical, and vibration detection thresholds. Such a screening procedure of experimental participants ensures that no occult small or large-fiber polyneuropathy is overseen, which may interact with sensory changes induced by exercise.

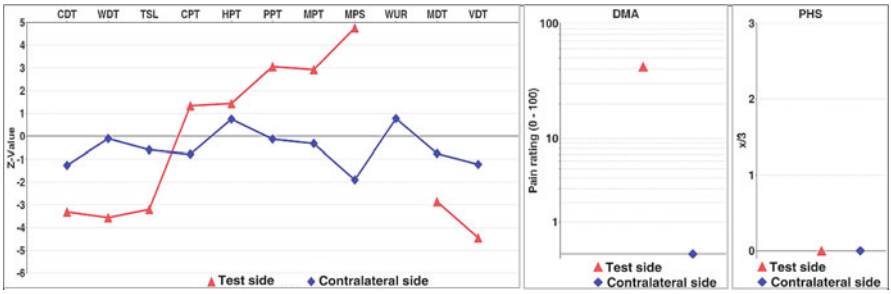

Fig. 7.4 *Z*-score profile of a subject who reported intermittent dysaesthesia in the innervation area of the ulnar nerve (skin over hypothenar). The individual QST data are compared to normative data matched for age and gender. Deviations of individual QST parameters from the mean of the normative data are shown as *z*-scores. *Z*-scores outside the 95% confidence interval (*z*-score >1.96 and <−1.96) are considered abnormal. Compared to the normative data, a positive *z*-score indicates a gain of function and a negative *z*-score a loss of function. On the test side (*red line*, *triangles*) impaired thermal and mechanical perception is detected. The *z*-scores for the cold detection threshold (CDT, A-delta-fiber-mediated), warm detection threshold (WDT, C-fiber-mediated) and thermal sensory discrimination ability (TSL, A-delta- and C-fiber-mediated) indicate a loss of function compared to the normative data and compared to the intra-individual contralateral side. The mechanical tests detected a loss of function with impaired mechanical and vibration detection thresholds (MDT, VDT, A-beta-fiber-mediated). Signs of a gain of function were found for pain pressure threshold (PPT), mechanical pain threshold (MPT), mechanical pain sensitivity (MPS), and dynamic mechanical allodynia (DMA). The parameters MPS and DMA point toward central sensitization. The Wind-up Ratio (WUR) for the test side is missing because it could not be evaluated. Abbreviations: see legend Fig. 7.2

7.4 Measuring Autonomic Nervous System Responses in Exercise Studies

In the following, we will summarize methods that allow measuring autonomic responses, notably blood pressure, heart rate/heart rate variability, and electrodermal activity, which are typically affected by exercise and painful stimuli (Andreassi 2007). Therefore, it is pivotal to measure the associated autonomic responses in imaging studies of exercise, and, most notably in exercise studies focusing specifically on the antinociceptive effects elicited by exercise.

Blood pressure (BP) is typically elevated during exercise; however, little research has been conducted examining the relationship between BP, exercise, and hypoalgesia. A few studies in this field indicate that there is an interaction between pain modulatory and cardiovascular systems. Animal studies using hypertensive rats observed elevated nociceptive thresholds when using tail flick, hot plate, or flinch-jump paradigms for noxious stimulation (France 1999). Human studies with induction of elevated BP by pharmacological interventions with norfenefrine or caffeine also observed alterations in pain perception (Ghione 1996). It is believed that the interaction originates from brainstem nuclei such as the PAG, which play an important role in the control and modulation of both the cardiovascular and the pain processing system (Koltyn and Umeda 2006). The pain modulating system

may be triggered by the activation of baroreceptors, which are usually involved in the regulation of BP. Because BP is elevated during exercise, it is plausible that baroreceptor activation interferes with brain regions, such as the amygdala, hypothalamus, PAG, parabrachial region, and reticular zone of the ventrolateral medulla, thereby regulating autonomic responses necessary for adaptation and survival (Dworkin et al. 1994).

The few existing studies examining the relationship between BP and pain perception generally demonstrate that hypertensive subjects with increased BP over a prolonged time after exercise exhibit higher pain thresholds (i.e., hypoalgesia) to experimental noxious stimulation than normotensive controls (France 1999; Ghione 1996). However, two recent studies did not observe any dose–response relationship between BP levels and hypoalgesia, although isometric exercise produced hypoalgesia (Umeda et al. 2009, 2010). To conclude, although the evidence of a close relationship between hypoalgesia and blood pressure is limited, we believe that blood pressure should be monitored as a potential covariate of interest in neuroimaging experiments studying the effects of exercise. Methodically, BP could be intermittently assessed with a standard upper arm cuff or continuously using a servo-plethysmo-manometer for the finger. The use of a finger cuff has been evaluated several times and a high consistency of BP values between finger and intra-arterial BP monitoring was shown (Parati et al. 1989).

In the same line, it is strongly recommended to measure heart rate (HR) during imaging studies on exercise and to derive heart rate variability (HRV). It is important to rule out significant HR differences in postexercise bout situations, when comparing with pre-exercise rest situations. Heart rate may also be considered as a covariate for between-group statistical analyses of imaging data (see also Chap. 12), as trained athletes have very low resting heart rates. The HRV, which is considered as an index of autonomic regulation of the heart, is also amenable easily with commercially available HR recording devices. Physiologically, HRV is considered to represent the autonomic system influence on the HR, where HRV "provides information about the ability of the nervous system to organize an affective homeostatic response in accordance with the situational demands" (Appelhans and Luecken 2008). In this paper, the authors derived HRV indices based on spectral analysis in two distinct frequency bands. This procedure was suggested by Pumprla and colleagues: "HRV in the high-frequency (HF) band (0.15–0.40 Hz) reflects respiratory sinus arrhythmia, the parasympathetically driven oscillation in heart rate associated with breathing. In distinction, low frequency (LF) HRV (0.04–0.15 Hz) is influenced by both parasympathetic and sympathetic influences" (Pumprla et al. 2002). As a rule of thumb, higher values of HRV are considered to represent efficient cardiac autonomic control (Lewis and Short 2010), and HRV is normally large in healthy young individuals, whereas it becomes more regular and tends to show less variability with progressing age or disease (Lewis and Short 2010). For a detailed recent review on HRV, including effects of exercise, recovery, and overtraining, we refer to Lewis and Short (2010). Pain effects on HRV are the focus of the article by Appelhans and Luecken, referenced above.

Another widely applied method for measuring autonomic responses during imaging is to acquire task-associated changes of electrodermal activity (EDA), which is of particular interest in the context of emotional paradigms. In fact, emotion, cognition, and attention are highly associated with changes of the sympathetic tone. The measurement of EDA, incorporating slow shifts of basal skin conductance levels (SCL; average prestimulus level) and more rapid transient skin conductance responses (SCR; e.g., elicited by external stimuli or internal emotional events), helps to identify the influence of task-related arousal, inferred from autonomic nervous system activity, on brain activation. As pointed out before, there is good evidence that both exercise (Critchley et al. 2000) and pain (Leone et al. 2006) affect the autonomic nervous system. Recording the EDA provides complementary information that can be used to improve the data analysis, particularly when behavioral or task effects are difficult to model a priori (Macintosh et al. 2007) or—as shown in the context of pain imaging studies—to guide and improve the analysis of fMRI and EEG pain data (Mobascher et al. 2009). It has been suggested that the hypothalamus and specific brainstem areas are involved in the homeostatic control of sympathetic arousal via descending connections to the spinal cord (Critchley et al. 2011). Higher order regions like the ventromedial prefrontal cortex, the midgenual and subgenual anterior cingulate cortex, the insular cortex, and the amygdala have been found to influence or interact with EDA. These regions are also involved in the processing of emotions, cognition, attention, and motivational behavior, all of which play a central role in the endurance, motivation, and well-being of exercise.

EDA has been studied in relation to fitness measures: in a laboratory setting, volunteers were engaged in speeded mental tasks designed to induce psychosocial stress; trained subjects showed faster autonomic recovery after the stressor than untrained subjects (Keller and Seraganian 1984). In a longitudinal setup, 60 subjects were "randomly assigned to 10-week aerobic exercise, meditation, or music appreciation programs"; participants assigned to the exercise program showed faster recovery in the electrodermal response, together with improved fitness (Keller and Seraganian 1984). In another study, EDA responses to a cognitive stressor (Stroop Color-Word-Naming Task) were studied after exhaustive physical exercise in two groups differing in their physical control activity (Moya-Albiol et al. 2001). Elite sportsmen showed lower heart rates and skin conductance levels during the cognitive task, and greater heart rate recovery than physically active subjects. Hence, there are indications that EDA should be measured in exercise studies, as EDA reflects differences in autonomic responses depending on physical fitness states, and as such, has to be considered as a valuable tool in neuroimaging studies of exercise.

For measuring autonomic nervous system responses no specific make or model can be recommended for neuroimaging experiments, as there are numerous MR-compatible and commercially available electrocardiogram, BP, oxygenation, or SCR monitoring devices. MRI-compatible Ag–AgCl surface electrodes are used for EDA recordings and may be applied between the thenar and hypothenar eminences. Data are usually filtered using a low cutoff (10 s) and a high cutoff Filter (250 Hz). After visual inspection for artifacts, EDA data can be analyzed to determine amplitudes and sums of skin responses in relation to tasks/conditions of neuroimaging

experiments. More detailed information about mathematical models for the analysis of SCR and SCL can be found in works from Benedek et al. (Benedek and Kaernbach 2010a, b). The SCR may be defined as the peak-to-peak amplitude difference in skin conductance of the largest positive deflection. Raw skin conductance scores can be square root transformed and scaled to each subject's maximal response to account for interindividual SCR variability. Normalized SCR values can then be entered into the parametric modulations of fMRI models (see also Chap. 12) to account for the influence of the autonomic nervous system on brain activation (Dube et al. 2009).

7.5 Conclusions

We have summarized methods for assessing exercise-induced effects on pain and autonomic responses in the imaging context, namely QST for evaluating somatosensory (including pain) systems, and BP, HRV, and EDA for assessing the autonomic nervous system. These recordings have important implications for analysis and interpretation of exercise-related neuroimaging experiments.

References

Andreassi JL (2007) Psychophysiology. Human behavior and physiological response, 5th edn. Lawrence Erlbaum, London

Appelhans BM, Luecken LJ (2008) Heart rate variability and pain: associations of two interrelated homeostatic processes. Biol Psychol 77:174–182

Benedek M, Kaernbach C (2010a) A continuous measure of phasic electrodermal activity. J Neurosci Methods 190:80–91

Benedek M, Kaernbach C (2010b) Decomposition of skin conductance data by means of nonnegative deconvolution. Psychophysiology 47:647–658

Black J, Chesher GB, Starmer GA, Egger G (1979) Painlessness of the long-distance runner. Med J Aust 1:522–523

Boecker H, Henriksen G, Sprenger T, Miederer I, Willoch F, Valet M, Berthele A, Tolle TR (2008) Positron emission tomography ligand activation studies in the sports sciences: measuring neurochemistry in vivo. Methods 45:307–318

Bushnell MC, Duncan GH, Dubner R, Jones RL, Maixner W (1985) Attentional influences on noxious and innocuous cutaneous heat detection in humans and monkeys. J Neurosci 5:1103–1110

Critchley HD, Corfield DR, Chandler MP, Mathias CJ, Dolan RJ (2000) Cerebral correlates of autonomic cardiovascular arousal: a functional neuroimaging investigation in humans. J Physiol 523(Pt 1):259–270

Critchley HD, Nagai Y, Gray MA, Mathias CJ (2011) Dissecting axes of autonomic control in humans: insights from neuroimaging. Auton Neurosci 161:34–42

Dietrich A, McDaniel WF (2004) Endocannabinoids and exercise. Br J Sports Med 38:536–541

Droste C, Greenlee MW (1992) Comments on Padawer and Levine, PAIN, 48 (1992) 132–135. Pain 50:241, author reply 242–243

Droste C, Greenlee MW, Schreck M, Roskamm H (1991) Experimental pain thresholds and plasma beta-endorphin levels during exercise. Med Sci Sports Exerc 23:334–342

Dube AA, Duquette M, Roy M, Lepore F, Duncan G, Rainville P (2009) Brain activity associated with the electrodermal reactivity to acute heat pain. Neuroimage 45:169–180
Dworkin BR, Elbert T, Rau H, Birbaumer N, Pauli P, Droste C, Brunia CH (1994) Central effects of baroreceptor activation in humans: attenuation of skeletal reflexes and pain perception. Proc Natl Acad Sci USA 91:6329–6333
Dyck PJ et al. (1993) Quantitative sensory testing: a consensus report from the Peripheral Neuropathy Association. Neurology 43:1050–1052
Farrell PA (1985) Exercise and endorphins – male responses. Med Sci Sports Exerc 17:89–93
Focht BC, Koltyn KF (2009) Alterations in pain perception after resistance exercise performed in the morning and evening. J Strength Cond Res 23:891–897
France CR (1999) Decreased pain perception and risk for hypertension: considering a common physiological mechanism. Psychophysiology 36:683–692
Geber C, Klein T, Azad S, Birklein F, Gierthmuhlen J, Huge V, Lauchart M, Nitzsche D, Stengel M, Valet M, Baron R, Maier C, Tolle T, Treede RD (2011) Test-retest and interobserver reliability of quantitative sensory testing according to the protocol of the German Research Network on Neuropathic Pain (DFNS): a multi-centre study. Pain 152:548–556
Ghione S (1996) Hypertension-associated hypalgesia. Evidence in experimental animals and humans, pathophysiological mechanisms, and potential clinical consequences. Hypertension 28:494–504
Goldfarb AH, Jamurtas AZ (1997) Beta-endorphin response to exercise. An update. Sports Med 24:8–16
Handwerker HO, Keck FS, Neermann G (1982) Detection of temperature increases in the operating range of warm receptors and of nociceptors. Pain 14:11–20
Hoffman MD, Shepanski MA, MacKenzie SP, Clifford PS (2005) Experimentally induced pain perception is acutely reduced by aerobic exercise in people with chronic low back pain. J Rehabil Res Dev 42:183–189
Hoffmann P, Skarphedinsson JO, Delle M, Thoren P (1990) Electrical stimulation of the gastrocnemius muscle in the spontaneously hypertensive rat increases the pain threshold: role of different serotonergic receptors. Acta Physiol Scand 138:125–131
Janal MN, Colt EW, Clark WC, Glusman M (1984) Pain sensitivity, mood and plasma endocrine levels in man following long-distance running: effects of naloxone. Pain 19:13–25
Johnson MH, Petrie SM (1997) The effects of distraction on exercise and cold pressor tolerance for chronic low back pain sufferers. Pain 69:43–48
Kanarek RB, Gerstein AV, Wildman RP, Mathes WF, D'Anci KE (1998) Chronic running-wheel activity decreases sensitivity to morphine-induced analgesia in male and female rats. Pharmacol Biochem Behav 61:19–27
Keller S, Seraganian P (1984) Physical fitness level and autonomic reactivity to psychosocial stress. J Psychosom Res 28:279–287
Kemppainen P, Pertovaara A, Huopaniemi T, Johansson G, Karonen SL (1985) Modification of dental pain and cutaneous thermal sensitivity by physical exercise in man. Brain Res Mol Brain Res 360:33–40
Kemppainen P, Paalasmaa P, Pertovaara A, Alila A, Johansson G (1990) Dexamethasone attenuates exercise-induced dental analgesia in man. Brain Res 519:329–332
Koltyn KF (2000) Analgesia following exercise – a review. Sports Med 29:85–98
Koltyn KF (2002) Exercise-induced hypoalgesia and intensity of exercise. Sports Med 32:477–487
Koltyn KF, Arbogast RW (1998) Perception of pain after resistance exercise. Br J Sports Med 32:20–24
Koltyn KF, Umeda M (2006) Exercise, hypoalgesia and blood pressure. Sports Med 36:207–214
Leone M, Proietti Cecchini A, Mea E, Tullo V, Curone M, Bussone G (2006) Neuroimaging and pain: a window on the autonomic nervous system. Neurol Sci 27(Suppl 2):S134–S137
Lewis MJ, Short AL (2010) Exercise and cardiac regulation: what can electrocardiographic time series tell us? Scand J Med Sci Sports 20:794–804
Macintosh BJ, Mraz R, McIlroy WE, Graham SJ (2007) Brain activity during a motor learning task: an fMRI and skin conductance study. Hum Brain Mapp 28:1359–1367
Marek P, Mogil JS, Sternberg WF, Panocka I, Liebeskind JC (1992) N-methyl-D-aspartic acid (NMDA) receptor antagonist MK-801 blocks non-opioid stress-induced analgesia. II.

Comparison across three swim-stress paradigms in selectively bred mice. Brain Res 578: 197–203
Mathes WF, Kanarek RB (2001) Wheel running attenuates the antinociceptive properties of morphine and its metabolite, morphine-6-glucuronide, in rats. Physiol Behav 74:245–251
Mathes WF, Kanarek RB (2006) Chronic running wheel activity attenuates the antinociceptive actions of morphine and morphine-6-glucouronide administration into the periaqueductal gray in rats. Pharmacol Biochem Behav 83:578–584
Mobascher A, Brinkmeyer J, Warbrick T, Musso F, Wittsack HJ, Stoermer R, Saleh A, Schnitzler A, Winterer G (2009) Fluctuations in electrodermal activity reveal variations in single trial brain responses to painful laser stimuli – a fMRI/EEG study. Neuroimage 44:1081–1092
Moya-Albiol L, Salvador A, Costa R, Martinez-Sanchis S, Gonzalez-Bono E, Ricarte J, Arnedo M (2001) Psychophysiological responses to the Stroop Task after a maximal cycle ergometry in elite sportsmen and physically active subjects. Int J Psychophysiol 40:47–59
Neziri AY, Curatolo M, Nuesch E, Scaramozzino P, Andersen OK, Arendt-Nielsen L, Juni P (2011) Factor analysis of responses to thermal, electrical, and mechanical painful stimuli supports the importance of multi-modal pain assessment. Pain 152:1146–1155
Olausson B, Eriksson E, Ellmarker L, Rydenhag B, Shyu BC, Andersson SA (1986) Effects of naloxone on dental pain threshold following muscle exercise and low frequency transcutaneous nerve stimulation: a comparative study in man. Acta Physiol Scand 126:299–305
Padawer WJ, Levine FM (1992) Exercise-induced analgesia: fact or artifact? Pain 48:131–135
Parati G, Casadei R, Groppelli A, Di Rienzo M, Mancia G (1989) Comparison of finger and intra-arterial blood pressure monitoring at rest and during laboratory testing. Hypertension 13:647–655
Perkins BA, Bril V (2003) Diabetic neuropathy: a review emphasizing diagnostic methods. Clin Neurophysiol 114:1167–1175
Pertovaara A, Kemppainen P (1992) Comments on Padawer and Levine, PAIN, 48 (1992) 132-135. Pain 50:239–240, author reply 242–233
Pestronk A, Florence J, Levine T, Al-Lozi MT, Lopate G, Miller T, Ramneantu I, Waheed W, Stambuk M (2004) Sensory exam with a quantitative tuning fork: rapid, sensitive and predictive of SNAP amplitude. Neurology 62:461–464
Pumprla J, Howorka K, Groves D, Chester M, Nolan J (2002) Functional assessment of heart rate variability: physiological basis and practical applications. Int J Cardiol 84(1):1–14. Review
Rolke R, Baron R, Maier C, Tolle TR, Treede RD, Beyer A, Binder A, Birbaumer N, Birklein F, Botefur IC, Braune S, Flor H, Huge V, Klug R, Landwehrmeyer GB, Magerl W, Maihofner C, Rolko C, Schaub C, Scherens A, Sprenger T, Valet M, Wasserka B (2006a) Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. Pain 123:231–243
Rolke R, Magerl W, Campbell K, Schalber C, Caspari S, Birklein F, Treede R (2006b) Quantitative sensory testing: a comprehensive protocol for clinical trials. Eur J Pain 10:77–88
Ruble SB, Hoffman MD, Shepanski MA, Valic Z, Buckwalter JB, Clifford PS (2005) Thermal pain perception after aerobic exercise. Arch Phys Med Rehabil 86:1019–1023
Sandkuhler J (1996) The organization and function of endogenous antinociceptive systems. Prog Neurobiol 50:49–81
Sheps DS, Adams KF, Hinderliter A, Price C, Bissette J, Orlando G, Margolis B, Koch G (1987) Endorphins Are Related to Pain Perception in Coronary-Artery Disease. Am J Cardiol 59:523–527
Shyu BC, Andersson SA, Thoren P (1982) Endorphin mediated increase in pain threshold induced by long-lasting exercise in rats. Life Sci 30:833–840
Susser E, Sprecher E, Yarnitsky D (1999) Paradoxical heat sensation in healthy subjects: peripherally conducted by A delta or C fibres? Brain 122(Pt 2):239–246
Treede RD (2011) Das somatosensorische System. In: Schmidt RF, Lang F, Heckmann M (eds) Physiologie des Menschen. Springer, Heidelberg, pp 297–323
Umeda M, Newcomb LW, Koltyn KF (2009) Influence of blood pressure elevations by isometric exercise on pain perception in women. Int J Psychophysiol 74:45–52
Umeda M, Newcomb LW, Ellingson LD, Koltyn KF (2010) Examination of the dose-response relationship between pain perception and blood pressure elevations induced by isometric exercise in men and women. Biol Psychol 85:90–96

Chapter 8
Humoral Factors in Humans Participating in Different Types of Exercise and Training

Sandra Rojas Vega, Wildor Hollmann, and Heiko K. Strüder

Abstract This chapter provides an overview on some effects of qualitatively and quantitatively different types of exercise stimuli on the blood concentration of neurotrophic factors, the hormone prolactin, and amino acids in humans. The findings of the research described are discussed in respect to their functional implications for neurogenesis and neurotransmitter systems in the brain.

8.1 Introduction

Qualitative and quantitative selective exercise stimuli are essential components in modern sports medicine (Hollmann and Strüder 2009), however, knowledge about the correlation between different types of physical exercise and brain health is still limited. The mechanisms through which exercise promotes brain health in humans have also been associated with humoral factors (Hollmann et al. 2003; Hollmann and Strüder 2000). The following chapter addresses aspects of the influence of physical exercise on these factors with special attention being paid to important neurotrophic factors as well as the hormone prolactin (PRL)

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and their impact on neurogenesis (see also Chaps. 1 and 2) as well as amino acids and their influence on neurotransmitters. Methodological aspects of the applied exercise stimuli, such as the type (e.g., endurance exercise, strength), the mode (e.g., graded, continuous), the duration (e.g., acute, chronic), or the intensity (e.g., aerobic, anaerobic) of the exercise regime as well as the training status of the investigated subjects, will be considered.

8.2 Neurotrophic Factors

Since it was discovered that new neurons are produced in specific human brain regions throughout one's lifetime (Eriksson et al. 1998), the relationship between altered growth factor function leading to modified neurogenesis has received increasing attention during the last 2 decades. While it has already been well established that impairment of synthesis and function of growth factors is an important causative factor in the pathogenesis of neuropathies, it is now increasingly recognized that this impairment plays a major role in the etiology of neuropsychiatric disorders in humans such as dementias and depression (Duman et al. 2000; Kempermann et al. 2008).

8.2.1 Brain-Derived Neurotrophic Factor

The neurotrophic factor brain-derived neurotrophic factor (BDNF) is one of the key regulators for increasing adult neurogenesis. It is well established that BDNF enhances synaptic transmission as well as long-term potentiation (LTP) and stimulates synaptic protein synthesis. BDNF has also been shown to promote differentiation of neural stem cells into neurons and to play an important role in preventing the death of newly generated cells. BDNF also supports the survival of neurons during stressful conditions such as ischemic insults and trauma (Vaynman and Gomez-Pinilla 2005).

Thus, BDNF promotes brain plasticity and functional changes. As a consequence, it is assumed that the maintenance of cerebral BDNF levels is of utmost importance. It is known that the peripherally produced BDNF, being able to cross the blood–brain barrier (BBB) in both directions, can exert supporting trophic effects on the CNS (Pan et al. 1998).

The production of BDNF is regulated by neuronal activity (Zafra et al. 1992). In addition, physiological stimuli such as exercise appear to be regulators for the BDNF levels (Neeper et al. 1995; Seifert et al. 2010). The regulation of BDNF through different types of exercise opens up an interesting avenue for research on the role of BDNF as a mediator in neuroplasticity (Fig. 8.1).

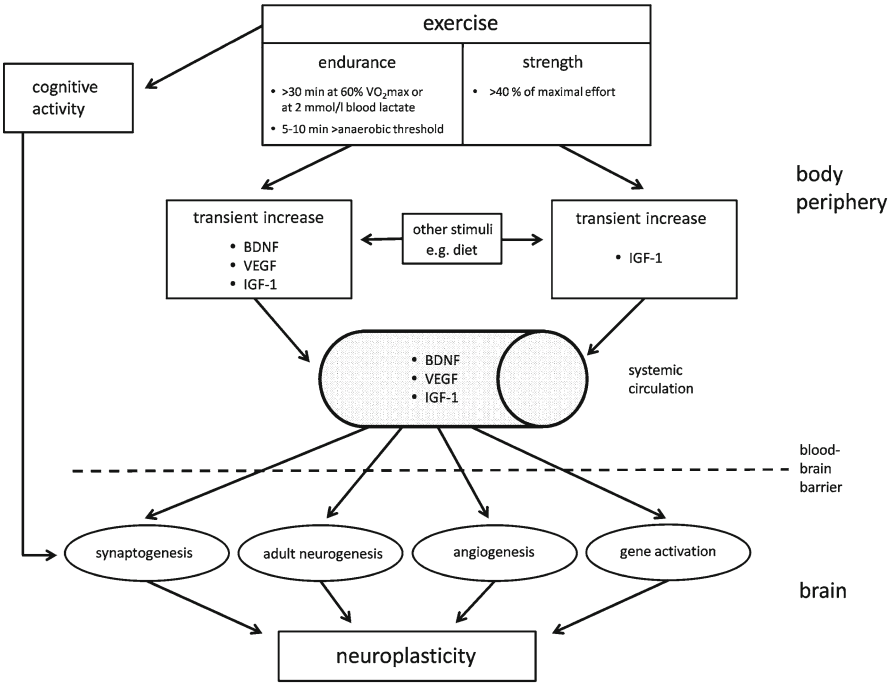

Fig. 8.1 Proposed mechanisms by which neuromuscular exercise affects neuroplasticity. The signaling of the organism's physical activity to the brain involves humoral but also directly neuronal modulation. Every physical activity already implies cognitive activity because activation in different brain regions, e.g., related to learning and memory, is required. The effects of exercise on neuroplasticity are mediated by the convergence and the synergy between growth factors like BDNF, IGF-1, and VEGF released during bouts of endurance exercise. Exercise can influence brain plasticity through the modulation of synaptogenesis, neurogenesis, and angiogenesis and also through activation of plasticity-related genes. *BDNF* brain-derived neurotrophic factor, *IGF-1* insulin-like growth factor 1, *VEGF* vascular endothelial growth factor

8.2.1.1 Effect of Acute and Chronic Exercise on Peripheral BDNF Levels

Acute Exercise

Different kinds of exercise regimes have been tested for their impact on the peripheral BDNF concentrations in humans. Incrementally graded exercise tests (GXT) are most usually used to test BDNF response. It was found that acute graded exercise elevates BDNF levels in a transient manner (Rojas Vega et al. 2006a; Ferris et al. 2007; Zoladz et al. 2008; Gustafsson et al. 2009; Laske et al. 2010).

The percentage increase depends on the exercise routines applied, with the associated differences in metabolic demands and the extent of effort. Rojas Vega et al. (2006a) reported that a GXT on a cycle ergometer up to exhaustion caused basal values to increase by approximately 40%. In a later study by Ferris et al. (2007), the peripheral BDNF levels during a GTX increased to a similar extent. In both studies the lactate concentration in the study participants upon reaching exhaustion was similar (approximately 10 mmol/L). Enhanced BDNF values after GXT were also reported for track or treadmill running (Winter et al. 2007; Laske et al. 2010), rowing (Gustafsson et al. 2009), and handcycling (Rojas Vega et al. 2008). After a graded submaximal cycling workout producing a lactate concentration of about 3 mmol/L, the increase in BDNF in women was found to be about 11% (Rojas Vega et al. 2012). The highest BDNF concentration was measured 5 min after completing the GXT session, with values returning to baseline levels within 10–15 min post exercise. All these studies using GXT suggest a link between BDNF elevations and exercise intensity.

Continuous high-intensity exercise of a few minutes duration caused an increase of BDNF levels of large variation. Some investigators report that high-intensity exercise increases BDNF concentrations in healthy subjects more effectively than low-intensity exercise (Rojas Vega et al. 2006a; Ferris et al. 2007; Castellano and White 2008; Gustafsson et al. 2009). According to studies so far, this was not the case, however, for diseased persons or persons with disabilities (Gold et al. 2003; Schulz et al. 2004; Rojas Vega et al. 2008; Gustafsson et al. 2009; Ströhle et al. 2010). Ferris et al. (2007) reported that an exercise intensity of 20% below the ventilatory threshold in healthy individuals caused no increase in BDNF levels, whereby at higher intensities (10% above the ventilatory threshold) increased BDNF blood concentrations were found. Winter et al. (2007) showed that short bouts of anaerobic exercise (two sprints over less than 3 min each with lactate levels above 10 mmol/L) increase BDNF levels to about 12% above baseline levels.

Exercise of longer lasting duration must be performed at an intensity low enough not to induce high lactate accumulation. No changes in BDNF concentrations were found in test persons after continuous cycling for 10 min; the corresponding lactate values were about 2 mmol/L (Rojas Vega et al. 2006a). An early study by Gold et al. (2003) reported that the BDNF levels were increased by 43% in multiple sclerosis patients as well as in healthy persons after 30 min cycling at 60% $\dot{V}O_2$max. Similarly, a study by Winter et al. (2007) showed that 40 min of low effort running (<2 mmol/L blood lactate) results in a transient increase of BDNF levels of about 15%. Other researchers reported elevated BDNF levels immediately after moderate endurance exercises such as cycling, stepping, and walking (Schulz et al. 2004; Tang et al. 2008; Ströhle et al. 2010).

Interestingly, all studies performed on subjects suffering from major depression, multiple sclerosis (MS), anorexia nervosa, or panic disorder exhibited lower values of basal BDNF compared to those in healthy untrained people (Gustafsson et al. 2009; Laske et al. 2010; Ströhle et al. 2010; Castellano and White 2008). This indicates either a reduced production of BDNF and therefore a reduced neuroprotection or an increased turnover of neurotrophins in the damaged CNS. Gold et al. (2003),

however, reported unchanged concentrations of BDNF in MS patients. Only one study investigated athletes with spinal cord injuries reporting that the intensity-dependent character of the BDNF response behaves inversely to that found in healthy individuals. This is because the BDNF levels here increased more due to acute exercise of a low to moderate intensity than to high-intensity prolonged exercise (Rojas Vega et al. 2008).

Only few studies used strength exercise as a stimulus for promoting BDNF release. The determination of exercise intensity is often done using the 1 repetition maximum (1RM) method. 1RM is the maximum amount of weight one can lift in a single repetition for a given exercise. Yarrow et al. (2010) examined 20 young men after strength exercises consisting of four sets with six repetitions at 52.5% of the 1RM and found a 32% increase in BDNF concentration. Rojas Vega et al. (2010) investigated the effect of different intensities of acute strength exercise on BDNF. Exercises at 40% and 110% of the maximum effort curve did not induce elevations in BDNF levels compared to pre-exercise values.

In summary, during acute exercise in humans the level of circulating BDNF is coupled to the intensity or duration as well as mode of the exertion. Acute endurance exercise at an intensity of 60% $\dot{V}O_2max$ or at a lactate concentration of about 2 mmol/L, respectively, increases BDNF in the blood if the duration is at least 30 min. Exercise bouts of short duration also seem to increase BDNF concentrations if the intensity of the bouts is high. Strength exercise does not seem to affect plasma BDNF concentrations.

Chronic Exercise

In addition to factors such as age, sex, body weight, nutrition, and circadian rhythm, the concentration of BDNF also seems to be influenced by the training status (Lommatzsch et al. 2005). Most studies (Currie et al. 2009; Nofuji et al. 2008; Chan et al. 2008; Flöel et al. 2010; Gold et al. 2003) reported lower basal BDNF levels in athletes than in untrained persons. These lower basal BDNF levels might be attributable to a higher clearance rate of BDNF, or a greater increase in plasma volume due to physical training and the resulting lower circulating BDNF in the periphery. Schiffer et al. (2009) and Schulz et al. (2004) did not detect any differences between BDNF concentrations before and after an aerobic training period in the study participants at rest. Schiffer et al. (2009) applied a training period with exercise two to three times a week at 60% $\dot{V}O_2max$. However, four to seven training sessions per week at a higher percentage of $\dot{V}O_2max$ resulted in greater exercise-induced levels of BDNF concentrations compared to before the training period (Baker et al. 2010). Thus, the frequency and intensity of training appear to influence the BDNF response to exercise, although further studies are needed to substantiate these results.

After strength training with untrained volunteers or recreational athletes, studies by Schiffer et al. (2009), Levinger et al. (2008), and Goekint et al. (2010) reported that basal levels of BDNF in test persons at rest remain unchanged, while

Yarrow et al. (2010) found changes in the responses to acute strength exercise. This study was conducted for 5 weeks with two groups using two exercises on strength-training devices with different intensities for each group. The studies by Schiffer et al. (2009), Levinger et al. (2008) and Goekint et al. (2010) applied a traditional training method using strength-training devices for a longer training period of 10–12 weeks. Training with a complete body workout was conducted three times per week.

In summary, based on the present data, no reliable conclusions can be drawn on the effect of strength training on the basal concentration of BDNF.

8.2.1.2 Factors Influencing BDNF Response to Exercise and the Functional Implications

The effect of lactate is one of the possible underlying mechanisms that could stimulate BDNF release after acute high-intensity exercise with considerable lactatemia. A recent study by Schiffer et al. (2011) investigating the influence of a lactate clamp on BDNF concentration with the study participants at rest showed an increase of peripheral BDNF concentrations. The sodium lactate infusion raised the lactate values to 10–15 mmol/L without acidosis but with alkalosis. The lactate concentrations reached were similar to those that occurred during exercise workouts which induced BDNF augmentation. Recently, it was also shown that buffering the decrease of pH during a maximal ramp test on a cycle ergometer does not reduce the exercise-induced BDNF increases (Rojas Vega et al. 2012). In this study, the infusion of bicarbonate attenuated the pH and base excess values, whereby the lactate values of 10 mmol/L remained unaffected. As the study by Schiffer et al. (2011), with test subjects at rest, led to alkalosis and the investigation by Rojas Vega et al. (2012) with subjects undergoing high-intensity exercise led to acidosis, it seems likely that the pH or base excess values do not play a decisive role in inducing BDNF release. Across both studies, the best correlations with BDNF concentrations were observed for lactate. These results suggest that lactate supports the release of BDNF at its major secretion area in the central nervous system during exercise. Interestingly, a portion of BDNF is released from the human brain during exercise (Rasmussen et al. 2009), however, peripheral sources can also contribute to increases of BDNF in the blood (Lommatzsch et al. 2005; Tang et al. 2008; Matthews et al. 2009). Because the actions of BDNF in the CNS can be due to the growth factor of central or peripheral origin, in this review we refer to its effects in the CNS without attributing a source.

The regulation of BDNF through exercise opens up an interesting perspective for the function of BDNF as a mediator in neuroplasticity in the CNS. The increase of the serum BDNF concentration as a result of exercise seems to be of importance for maintaining proper brain functions (Cotman and Berchtold 2002). A connection between peripheral BDNF, with its ability to cross the BBB, and the central action of BDNF is a necessary prerequisite for this effect. There is mounting

evidence that a deficiency in BDNF plays a critical role in the pathophysiology of mood disorders such as depression and neurodegenerative diseases, i.e., Alzheimer's and dementia (Kempermann et al. 2008).

8.2.2 Insulin-Like Growth Factor 1

Insulin-like growth factor 1 (IGF-1) is important for anabolic effects of exercise and training, i.e. muscle hypertrophy. It is also a potent neurotrophic factor promoting neuronal survival and differentiation (Leventhal et al. 1999). Peripheral IGF-1 has been demonstrated to play an important role in neurogenesis in the hippocampus (Aberg et al. 2000; Trejo et al. 2001). There is an abundant presence of receptors in the neuronal tissues of the CNS, while synthesis of IGF-1 protein from adult central neurons is very low, which suggests that the adult brain takes up IGF-1 from sources outside the brain (Bondy and Lee 1993). The biological process of circulating IGF-1 influences the CNS via a range of different paths. It is also assumed that peripheral IGF-1 is important for mediating effects of other growth factors in the CNS. For example, hippocampal expression of BDNF is enhanced in the presence of IGF-1 (Ding et al. 2006). Moreover, IGF-1 modulates a variety of homeostatic processes in the CNS, processes which are promoted by exercise and involve angiogenesis (Lopez-Lopez et al. 2004). A blocking of the peripheral IGF-1 resulted in a significant reduction in the production of new brain capillaries due to the inhibiting effects of the vascular endothelial growth factor (VEGF), a molecule prominently involved in promoting blood vessel growth.

8.2.2.1 Effect of Acute and Chronic Exercise on Peripheral IGF-1 Levels

It has been shown that (1) exercise stimulates the release of IGF-1 in the liver, resulting in an elevated brain uptake of IGF-1 (Carro et al. 2000), and (2) peripheral IGF-1, by crossing the BBB, increases the presence of IGF-1 mRNA in the hippocampus (Ding et al. 2006; Fig. 8.1). The relevance of this mechanism is underscored by the fact that the administration of peripheral antibody-IGF-1 blocks the exercise-induced neurogenesis in the dentate gyrus (Trejo et al. 2001). Restoring IGF-1 levels through an exogenous administration fosters functional recovery, thus helping to rectify learning deficits and promoting neurogenesis and neuroplasticity. The use of exogenous IGF-1 indicates that it is essential but not sufficient to mimic all the effects of exercise, which provide neurotrophic support and influence plasticity-related processes in the brain (Llorens-Martin et al. 2009). The action of exercise-induced IGF-1 augmentation on the brain in humans could be facilitated by changes in the transport proteins and by changes in the BBB permeability during exercise.

Acute Exercise

Several studies have reported increased levels of IGF-1 in humans after acute exercise (Bang et al. 1990; Cappon et al. 1994; Schwarz et al. 1996). After 10 min of cycle ergometer exercise at intensity above the lactate threshold, IGF-1 increased to 14% above the pre-exercise levels and remained elevated for 20 min after cessation of the exercise period (Cappon et al. 1994). Rojas Vega et al. (2012) have shown in women that 10 min of aerobic cycling increased circulating IGF-1 levels by 16%, and this augmentation was maintained for at least 10 min into the recovery phase. Schwarz et al. (1996) reported that the IGF-1 levels increase after low- and high-intensity continuous exercise periods. During a period of cycling for 10 min at levels below the anaerobic lactate threshold, the IGF-1 concentrations increased by 7%, while high-intensity exercise raised these levels by 13%. Consistent with these findings, Bang et al. (1990) reported an increase in IGF-1 concentration levels in healthy subjects of 26% after 10 min of exercise. Rojas Vega et al. (2008) also observed an increase of circulating IGF-1 levels of 7% in disabled athletes after 42 km of hand cycling at an intensity of 65% of $\dot{V}O_2$max. Hagberg et al. (1988), however, did not find an increase in IGF-1 in long-distance runners after a 60-min exercise period on the treadmill at an intensity of 70% of $\dot{V}O_2$max. However, only slightly increased levels of lactate were observed during exercise, indicating a low physiological stress for these athletes, probably causing these contrary findings.

A study by Rojas Vega et al. (2010) revealed that high- and low-intensity strength exercises increased the circulating levels of IGF-1. Although increases in IGF-1 were found for both exercise intensities, the two study intensities exhibited different post exercise responses. Specifically, only the low exercise intensity exhibited continuous IGF-1 augmentation during the 10-min recovery phase, an effect not found for the high-intensity condition. This response pattern may be related to an enhanced clearance of IGF-1 following high-intensity strength exercise. Interestingly, this study revealed that only low-intensity exercise was required to achieve a large increase of circulating IGF-1. Compared with studies applying a continuous low-intensity endurance exercise workout, low-intensity strength exercise elevated IGF-1 concentration to a much greater extent (28%). Further, Schwarz et al. (1996) indicated that high-intensity cycling produced an IGF-1 increase of 13%, which correlated with the values found after high-intensity strength exercise in a study by Rojas Vega et al. (2010).

Chronic Exercise

A number of cross-sectional analyses have shown that the presence of circulating IGF-I correlated with the level of fitness (Poehlman and Copeland 1990), although the results of different exercise training studies have given inconsistent values of basal IGF-I concentrations (i.e., unchanged (McCall et al. 1999), increased (Koziris et al. 1999), and decreased (Eliakim et al. 1998)). The variance in these findings

may result from differences in the extent and intensity of the training programs. The decreased basal IGF-1 concentrations after short-term (5 week) interval endurance training correlated with a negative energy balance during the training intervention (Eliakim et al. 1998). On the other hand, it seems that a high training volume is most effective for increasing basal IGF-1 levels, e.g., a high intensive cycling race lasting 3 weeks consisting of 21 stages over a distance of 3,518 km as well as a 4-month training program with a weekly workload of 500 km resulted in significant augmentations (Manetta et al. 2003; Chicharro et al. 2001).

Basal levels of IGF-1 were found to be unchanged after short-term strength training (<10 weeks) (McCall et al. 1999; Kraemer and Ratamess 2005; Izquierdo et al. 2006), whereas long-term strength training (>10 weeks) resulted in increases in the IGF-1 basal concentrations (Koziris et al. 1999; Borst et al. 2001 and Marx et al. 2001). However, some long-term studies also reported unchanged IGF-1 levels (Walker et al. 2004).

Schiffer et al. (2009) reported decreased basal IGF-1 levels after 12 weeks of intensive strength training where extensive scatter in basal IGF-1 concentration was found for different individuals. Finally, acute overreaching resulting from a high-volume strength training has been shown to reduce basal IGF-1 concentrations by 11% (Raastad et al. 2003), whereby the values returned to baseline levels when normal training was resumed. Considered together, these results indicate that chronic adaptations of basal IGF-1 levels after training may also be affected by the volume and intensity of the strength training (Kraemer and Ratamess 2005; Raastad et al. 2003). On the other hand, studies evaluating the effects of prolonged training on acute exercise-induced IGF-1 responses showed that the circulating IGF-1 level was unchanged after 12 weeks of strength training (McCall et al. 1999). In this study, however, the IGF-1 values were corrected for plasma volume decrease. This is a somewhat questionable procedure as the uncorrected concentration is what the tissue "senses" and which mediates the effects of exercise on the target tissues (Cappon et al. 1994).

8.2.2.2 Factors Influencing IGF-1 Response to Exercise and the Functional Implications

The majority of circulating IGF-1 is bound to binding proteins (BP). The biological effects of IGF on the nervous system are mediated by the type I of IGF receptors. The function of the binding protein is to regulate the IGF bioavailability by hindering degradation, by modulating the levels of free IGF and possibly, by delivering IGF to target tissues. The most abundant BP is IGFBP-3, which is synthesized in the liver, reaching its peak circulating levels during puberty and decreasing with increasing old age. Interestingly, there is a marked IGFBP-3 protease activity during pregnancy, which appears to play a key role in the higher circulating IGF-1 bioavailability. The pregnancy-associated cleavage patterns are thought to be responsible for the local release of bioactive IGF-1 in humans when subjected to high-intensity exercise.

Schwarz et al. (1996) showed that IGFBP-3 increases its proteolytic activity during heavy exercise simultaneously with a peak increase in IGF-1. Increases in circulating IGF-1 after exercise might also reflect increases in hepatic IGF-1 production, which is assumed to be unrelated to exercise-induced secretion of growth hormones (GH) (Bang et al. 1990; Schwarz et al. 1996), because the IGF-1 reaches peak levels before the GH levels peak. Furthermore, Bang et al. (1990) showed that exercise induced increases in IGF-1 levels not only in healthy people but also in persons with a pituitary insufficiency.

Only a few studies have examined the adaptation of circulating IGFBP-3 to strength training. Whereas Elloumi et al. (2005) and Borst et al. (2001) reported a reduction of basal IGFBP-3 after long-term strength training, a study by Izquierdo et al. (2006) showed an increase. Elloumi et al. (2005) proposed that the decreased IGFBP-3 together with the elevated levels of IGF-1 in the test person at rest is an indicator for overtraining. The study by Izquierdo et al. (2006) suggested that an increase in IGFBP-3 concomitant with decreased IGF-1 levels in the test person at rest might be a compensatory process in the body to preserve IGF-1 availability.

Nemet et al. (2004) found that the energy balance is a regulating parameter, insofar that training plus an energy intake deficit causes a reduction in IGF-I levels, whereas training plus energy intake excess results in increased IGF-I concentrations. These results are in line with results by Smith et al. (1987), which showed that acute exercise that produces a negative caloric balance also causes an IGF-1 decrease, analogue to an equivalent restriction in caloric intake without exercise.

The potential beneficial stimulus on the brain might be related to repeated exercise-induced elevations of IGF-1 during training programs. Endurance and strength training also seem to increase basal IGF-1 concentrations if volume and/or intensity of training are high. Low-intensity strength training already induces high IGF-1 augmentation. Thus, strength exercise of this particular intensity should be considered when defining exercise prescriptions aimed at benefiting brain health throughout a subject's life span.

8.2.3 Vascular Endothelial Growth Factor

It has been suggested that adult neurogenesis occurs within the so-called angiogenic niche (Hsieh and Eich 2010). Within this niche, endothelial cells are regulators for self-renewal of stem-like cells through the release of trophic factors. Thus, an alteration in the vascular microenvironment affects neurogenesis. VEGF is primarily a potent mitogen of endothelial cells (Leung et al. 1986). There is growing evidence, however, that VEGF also induces neurotrophic and neuroprotective effects (Ding et al. 2004). An artificially induced elevation of VEGF was shown to increase adult neural progenitor cell differentiation into neurons in the adult hippocampus (Fabel

et al. 2003), an effect associated with enhanced cognition (Cao et al. 2004). It has been shown in humans that exercise increases angiogenesis in the dentate gyrus (Pereira et al. 2007). Theoretically, this might improve access to growth factors in the brain. Angiogenesis is a vital adaptation to chronic exercise whereby the exercise-induced enhanced VEGF levels has been proposed as a stimulus for this process (Prior et al. 2004).

8.2.3.1 Effect of Acute and Chronic Exercise on Peripheral VEGF Levels

VEGF is produced by skeletal muscle cells and can be released into the blood circulation during exercise (Hiscock et al. 2003). A peripheral blockade of VEGF was shown to abolish exercise-induced neurogenesis, while the baseline levels of neurogenesis were not affected (Fabel et al. 2003). An association between neurogenesis and VEGF in humans has not yet been proven. Notwithstanding, an in vivo correlation between neurogenesis and angiogenesis was recently demonstrated in exercising humans (Pereira et al. 2007). This study found that exercise selectively affects angiogenesis in the hippocampus, which in turn correlated with the cardiopulmonary and cognitive function.

Acute Exercise

Several studies have shown that circulating VEGF is increased by acute exercise (e.g., Kraus et al. 2004; Rojas Vega et al. 2012). After 10 min of acute submaximal exercise at lactate concentration of about 3 mmol/L, the VEGF levels increased to 19% above those levels of the test person at rest (Rojas Vega et al. 2012). Submaximal exercise of longer duration induced an even higher increase of circulating VEGF (Kraus et al. 2004). The increased levels persisted from 20 min up to 2 h after cessation of exercise (Kraus et al. 2004; Rojas Vega et al. 2012). The transient nature of the VEGF response to a single exercise routine appears to be coupled to the increase of mRNA (Richardson et al. 1999) as well as the decrease of VEGF protein in the skeletal muscle immediately after exercise (Kraus et al. 2004). Thus, the disappearance of VEGF from skeletal muscle results in an increase in circulating VEGF. This effect is involved in the well-documented formation of new capillaries, because the VEGF induces mitogenesis in endothelial cells and therefore functions as an angiogenic factor.

Only few studies have examined the effect of strength exercise on VEGF concentrations. Jozsi et al. (2000) demonstrated that acute strength exercise (3×8 repetitions of five lower body exercises at 80% of the 1RM) enhances the increase of VEGF mRNA in human muscles. In accordance with these data, Richardson et al. (1999) reported that VEGF mRNA levels are augmented in human skeletal muscles after only 30 min of knee-extensor exercise at 50% of the 1RM. In this study, however, a GXT to exhaustion in advance was part of

the exercise workout, therefore making it impossible to separately quantify the effects of the two kinds of stimuli on VEGF. The effect of isokinetic strength exercises on VEGF concentrations was evaluated by Rojas Vega et al. (2010). Each test person was tested on 1 day at an exercise load equal to 40% and on another day at 110% of the averaged individual maximal effort curve, respectively. At both intensities, however, the strength exercise did not increase the levels of serum VEGF at any time during the trials.

Chronic Exercise

In endurance-trained people no differences were found in the basal circulating VEGF concentrations compared to sedentary people (Kraus et al. 2004). An investigation by Gustafsson et al. (2002), however, revealed a decrease in the basal VEGF values after a 10-day training program. The conflicting results of the studies might have stemmed from the initial physical condition of the subjects. The athletes in the study by Kraus and coworkers had completed a long training period (>6 month) and the training volume was high (6 days/week), while the subjects in the study by Gustafsson et al. (2002) were only subject to a training period of 10 days. Kraus et al. (2004) reported that acute exercise increased the VEGF levels at 0 and 2 h postexercise in endurance athletes but not at any time in sedentary individuals. There was no difference, however, in the VEGF levels between the two groups at any other point in time. An analysis of the individual peak postexercise VEGF levels revealed that exercise increased VEGF levels independent of the training status.

8.2.3.2 Factors Influencing the VEGF Response to Exercise and the Functional Implications

Factors such as the age and gender of subjects as well as a variety of medical/physical conditions can influence the response of VEGF levels to exercise. Breen et al. (1996) reported a greater increase in the levels of VEGF mRNA in rats, when exercised in a hypoxia environment. In contrast, an in vivo study by Kraemer and Ratamess (2005) found that VEGF gene expression is not sensitive to tissue hypoxia. The response of VEGF levels to acute exercise appears to be mediated by the reduction of intracellular partial pressure of oxygen (pO_2) occurring during the transition period from rest to exercise. The VEGF mRNA levels, however, were not enhanced when exercise was performed under hypoxia (Richardson et al. 1999). Apparently, there is an intracellular "pO_2-threshold" beyond which no enhanced angiogenic stimulus is produced. Submaximal and maximal exercise under normoxia appears to reach this threshold and therefore may induce a neuro-angiogenic stimulus. Furthermore, prolonged exercise during severe hypobaric–hypoxia (after a high altitude marathon run-up to 4,722 m) decreased VEGF serum concentrations (Gunga et al. 1999). In contrast, intensive swim training for 21 days at 1,886 m enhanced

VEGF serum levels, whereby it is difficult to distinguish between effects of altitude and those of exercise. Hypoxia per se, however, does not seem to play a decisive role in exercise-induced increases of circulating VEGF levels.

VEGF concentrations in pregnant women were not detectable with the subject at rest or after graded exercise up to a heart rate of 150 bpm (Rojas Vega et al. 2012). This may indicate that enzymatic (probably protease) activity occurs or is substantially increased in the blood circulation, which degrades the VEGF protein. This suggests that a possible degradation of peripheral VEGF during late gestation suppresses the action of this factor and is not influenced by exercise. Because it has been suggested that elevated levels of VEGF during pregnancy may be involved in the pathogenesis of preeclampsia, undetectable levels of VEGF after exercise may reflect an important physiological adaptation in pregnant women, which reduces the risk of the onset of preeclampsia.

Muscle VEGF protein, VEGF mRNA, and muscle vascularization with a person at rest is lower in the elderly than in young men and women. This age-related decline contrasts with the response to acute exercise. That is, after 45 min of cycle ergometer exercise at 50% of $\dot{V}O_2$max, the VEGF protein and VEGF mRNA levels increased, independent of age (Croley et al. 2005). This response to exercise suggests a compensatory mechanism with age for improving the diffusive capacity of the muscles (Charifi et al. 2004) and seems to be an important biological mechanism in promoting neuroangiogenesis, and thus protecting the brain from a decline in neurogenesis with age. VEGF may constitute the link between neurogenesis and angiogenesis in exercising humans, and mediate neurotrophic and neuroprotective properties. The optimal dose and duration of exercise for the promotion of angiogenesis through increases of circulating VEGF correspond to aerobic exercise lasting longer than 10 min, which is also typically recommended in exercise programs aimed at promoting health. More studies are required for strength exercises. It can be assumed, however, that acute strength exercise at an intensity of >50% of the individual maximal effort enhances the VEGF levels.

8.2.4 Analytical Aspects for the Neurotrophic Factors BDNF, IGF-1, and VEGF

Blood for measurements of neurotrophic factors may be obtained from veins or arteries. The specimen of choice is venous blood, which is usually taken from the brachial vein. Samples should be collected in venipuncture tubes which were prechilled in ice water. Either serum or plasma samples can be used. In the case of plasma, heparin or ethylenediaminetetraacetic acid (EDTA) is used as an anticoagulant. With the addition of anticoagulants to the blood, plasma can activate blood platelets and change the concentration of the constituents to be measured (Schneider et al. 1997).

Care is required when taking the blood sample, its preparation (especially the time frame until samples are frozen) and storage, because these methodological aspects influence the humoral values. Venous occlusion from the use of a tourniquet changes the concentration of the blood components, mainly peptides and proteins, when the stasis is more than 3 min (Young and Bermes 1986). After blood collection, venipuncture tubes must be immediately placed on ice until processed. Many proteins are thermally labile and serum or plasma should be stored and frozen immediately. When additive-free tubes (serum) are used, the time for blood clotting prior to serum extraction and the temperature at which blood clotting occurs must be taken into account to ensure complete clotting and platelet degranulation in the sample. Serum and plasma are obtained by centrifugation of the samples tubes for 10 min at 3,000 rpm and 4°C. Supernatants must be aliquoted and stored at −80°C until analysis. Possible interference of the specimen collection and storage has been well documented for BDNF. A study by Katoh-Semba et al. (2007) found that BDNF in serum is gradually released from platelets at 4°C, while it begins to degrade immediately at a room temperature of 26°C. Furthermore, Trajkovska et al. (2007) showed a decrease of BDNF concentration in blood stored at 4°C, which did not occur at −20°C, whereas the storage of blood serum at −20°C resulted in a reduction of BDNF concentration over time. These results suggest that BDNF storage in platelets hinders degradation for prolonged periods subsequent to extracting the blood. However, plasma samples also allow clotting if stored for prolonged periods after collection.

The concentrations of serum BDNF are approx. 200 times higher than those found for plasma BDNF, which indicates that BDNF is stored in the platelets. Platelets circulate for up to 11 days in peripheral blood, whereas BDNF protein circulates in plasma for less than an hour. Thus, platelet BDNF might be a long-term marker of varying plasma BDNF concentrations (Lommatzsch et al. 2005). However, a relationship between serum BDNF levels and BDNF concentrations in the CNS has been shown in several animal studies and also in clinical studies of patients with mood disorders (Karege et al. 2002, 2005; Lang et al. 2004; Shimizu et al. 2003). In these studies serum BDNF but not plasma BDNF correlated with the severity of depression. Consequently, serum samples are preferred for analysis of BDNF.

For the analytical procedure, the assay technique for serum or plasma BDNF, VEGF, and IGF-1 is the enzyme-linked immunosorbent assay ELISA. ELISA kits from several manufacturers are available (e.g., ChemiKine, Promega, R&D System, Phoenix pharmaceuticals). All measurements should be performed in duplicate and according to the instructions of the manufacturer.

8.3 Prolactin

Interestingly, is has been shown that PRL is the only hormone which augments neurogenesis in the subventricular zone (SVZ) by stimulating the proliferation of neural stem cells and their differentiation into neurons (Shingo et al. 2003). A reduced level of neurogenesis was found in mice with a deficiency of PRL receptors. Peripheral as well as a central infusion of PRL induced neurogenesis in the SVZ.

These findings suggest that alterations of PRL during exercise might also be associated with increased neurogenesis.

The level of PRL is known to increase in response to physical stress such as exhaustive exercise or sexual activity (Noel et al. 1972; Brisson et al. 1981; Exton et al. 2001). PRL is synthesized in lactotrophic cells in the anterior pituitary and secreted in episodes. This process is controlled by PRL releasing (PRFs) and inhibiting factors (PIFs). Pituitary PRL acts as hormone via classic endocrine pathways. PRL is also produced at numerous extrapituitary sites where it is regulated by local factors, and thus can act in a direct fashion as a growth factor, neurotransmitter, or immune-regulator in an autocrine or paracrine manner (Bole-Feysot et al. 1999; Ben-Jonathan and Hnasko 2001). Whereas the physiological function of PRL in reproduction processes and in the induction of maternal lactogenesis is well established, the role of PRL secretion in males still has to be clarified. The release of PRL in humans is subject to the action of dopamine (DA) as the main PIF (Ben-Jonathan and Hnasko 2001). Increased DA synthesis and metabolism were shown during and following exercise (Meeusen and de Meierleir 1995), suggesting that exercise-induced PRL release is not related to alterations in the dopaminergic system activity and PRFs, such as the thyrotropin-releasing hormone (TRH) or serotonin (5-HT), are responsible for the acute secretory activities.

5-HT is one of the most prominent excitatory neurotransmitters for stimulating PRL release (Reichlin 1998; Tuomisto and Manisto 1985). 5-HT neurons originating in the dorsal raphe nuclei project to the hypothalamus and induce PRL release from the anterior pituitary by activating central 5-HT_{1A} and/or $5\text{-HT}_{2A/2C}$ receptors (Van de Kar et al. 1996). Because the administration of tryptophan (TRP), 5-hydroxytryptophan (5-HTP), 5-HT, or 5-HT-releasing drugs increased secretion of PRL in rats, while the destruction of serotonergic neurons in dorsal raphe nuclei prevented PRL increase after 5-HT releasers were administered or it was induced by suckling (Van de Kar et al. 1996), the physiological role of 5-HT on PRL secretion has been used as a hormonal probe for 5-HT activity after exercise (Strüder and Weicker 2001). Similarly, based on the findings that 5-HT plays an important role for the PRL response to stress and considering that 5-HT is involved in the pathophysiology of mood and affective disorders, PRL has been used to characterize such alterations. A blunted PRL response to serotonergic challenges is an endocrine abnormality described in depressed patients (Mayberg et al. 2002).

8.3.1 Effect of Acute and Chronic Exercise on Peripheral PRL Levels

Acute Exercise

Different exercise workouts have been used to specify PRL response to exercise. Intense acute physical exercise is a strong stimulus for PRL secretion (De Meirleir et al. 1985a). No PRL increases were found after short-term exercise at 50% $\dot{V}O_2$max (Luger et al. 1992) or 65% $\dot{V}O_2$max (Strüder et al. 1998b).

Exercise performed at higher intensities (>70% $\dot{V}O_2$max) raised PRL after 30 min (Luger et al. 1992) as well as after 15 min at exercise intensity of 80% $\dot{V}O_2$max (Keizer et al. 1987). Increases of PRL levels were found already after two consecutive 400-m runs with 2 min rest in between (Rojas Vega 2001) and after 7.5 min of incremental cycling to exhaustion in athletes (Rojas Vega et al. 2006a). The effect of a single bout of high-intensity endurance exercise (treadmill running at about 100% $\dot{V}O_2$max) on the PRL concentration in 22 males was studied by Daly et al. (2005), whereby a sharp increase of PRL was found at the point of volitional fatigue. Elevated PRL concentrations were observed up to 60 min after cessation of exercise.

For PRL secretion during exercise, duration and intensity are of importance (Fig. 8.2). Low-intensity exercise usually induced a significant PRL increase when the duration of exercise was prolonged, e.g., cycling at a lactate concentration of about 2 mmol/L (Strüder et al. 1997) or after a marathon run (Tanaka et al. 1986). Strüder et al. (1997) excluded glucose availability as a trigger stimulus of PRL secretion during exercise as infusion of glucose alone or glucose with insulin during exercise did not affect its release. The authors proposed that exercise-induced hyperprolactinemia during prolonged exercise is rather related to the increase of the free tryptophan (TRP) to branched-chain amino acids (BCAA) ratio. This increase favors free TRP uptake at the competitive L-carrier of the blood–brain barrier which accounts for augmented 5-HT synthesis in the brain (Fig. 8.3).

Chronic Exercise

Studies investigating the effects of training on PRL secretion have shown inconsistent results. Specifically, Smallridge et al. (1985) reported that plasma PRL response after TRH challenge was enhanced after endurance training, suggesting that secretion of PRL is sensitive to the training level. In contrast to these results, studies by Strüder et al. (1998b) showed that the acute PRL response to 30 min of cycling did not differ between sedentary and endurance-trained elderly subjects. Neither basal plasma hormone concentration nor the response to TRH stimulation differed between both groups, suggesting that this specific PRL regulation mechanism was not altered by endurance training. On the other hand, Jakeman et al. (1994) used PRL as a hormone marker of the 5-HT function following oral administration of an acute dose of a 5-HT agonist and found a lower peak PRL concentration as well as a lower total release in endurance athletes compared with untrained subjects. This lower neuroendocrine response was suggested to be caused by a downregulation of central 5-HT receptor function.

Alternatively, an excessive increase in training volume over 4 weeks caused an elevation of the basal PRL level in young endurance athletes, while a moderate training over 3 weeks in recreational athletes led to lower basal PRL values (Strüder and Weicker 2001). Furthermore, Lehmann et al. (1992) reported that an increase in training volume, designed to induce an overtraining syndrome, did not lead to a change in the basal PRL concentration; the exercise-induced PRL level, however, was slightly decreased after absolving the training program.

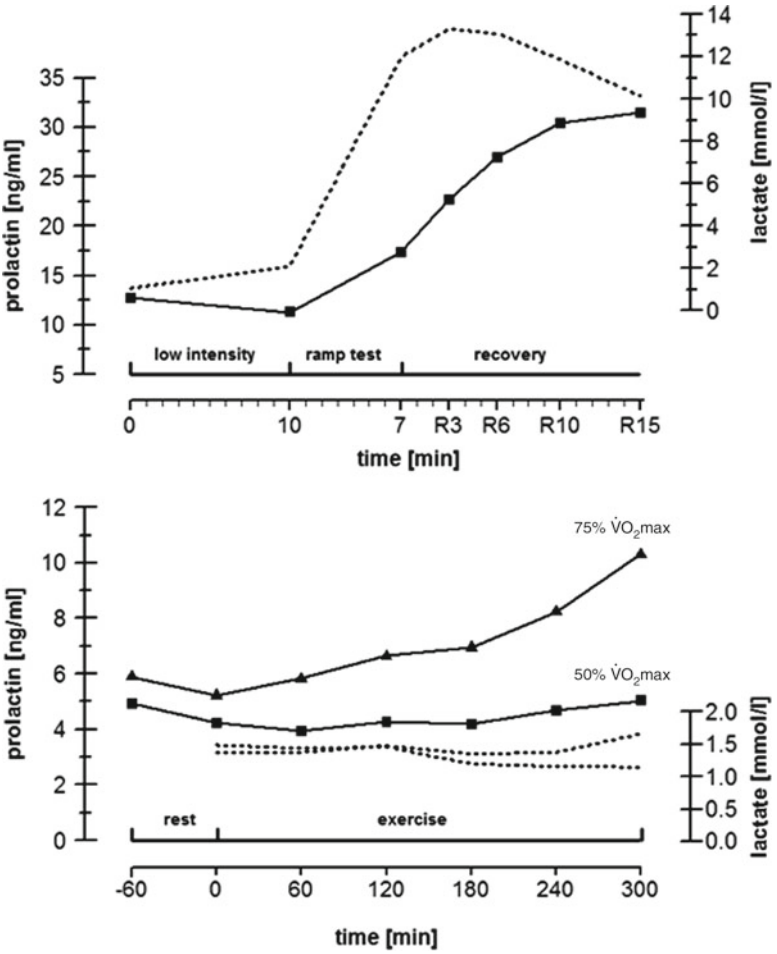

Fig. 8.2 Effects of exercise on prolactin (PRL). Exercise was performed in two different modalities: incremental exercise to exhaustion (*top*) or constant low- and moderate-intensity exercise of longer duration (button). Lactate values (*dotted lines*) at the end of incremental test (ramp test) are above the anaerobic threshold (AT) while lactate values at low/moderate-intensity exercise are below AT. The closed lines show the corresponding PRL concentration in the blood. Exercise exceeding the intensity of AT raises PRL levels. Exercise of long duration at moderate intensity stimulates PRL release. During 300 minutes of exercise at constant low or constant moderate intensity lactate values (*dotted lines*) do not differ between trials and are below the anaerobic threshold. Closed lines show the corresponding PRL concentrations at the respective exercise intensities. (Modified from Strüder et al. 1997; Rojas Vega et al. 2008)

Studies investigating the effects of chronic strength training (Häkkinen et al. 1985) or a single session of strength training (Bosco et al. 2000) on PRL levels did not reveal significant changes in the basal levels of the hormone. Similarly, Hickson et al. (1994) reported unchanged basal plasma PRL levels in males and females after 9 weeks of heavy strength training, despite the fact that PRL concentrations were assessed directly after acute bouts of very heavy strength exercises in males.

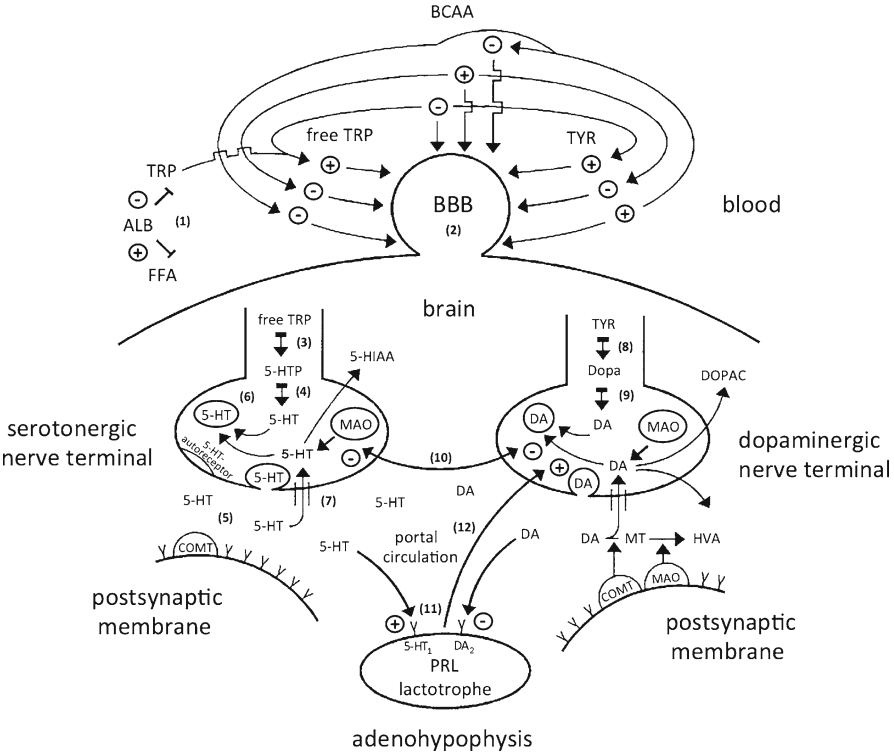

Fig. 8.3 Relation between the monoaminergic system and the lactotrope system of the adenohypophysis: During endurance exercise augmentation of plasma FFA induces an increment of free TRP due to displacement of TRP from ALB (1). Plasma free TRP, BCAA, and TYR compete for transport over the L-carrier at the BBB (2). Exercise-induced decline of BCAA favors the entry of free TRP and TYR into the brain. Administration of BCAA reduces free TRP and TYR transport into the brain while TYR administration reduces free TRP and BCAA transport over the BBB. In the brain free TRP is converted to 5-HTP by TRP-hydroxylase (3), the unsaturated rate-limiting enzyme in the synthesis of 5-HT. 5-HTP is decarboxylized to 5-HT (4). 5-HT can be released (5) or stored (6). 5-HT that is not stored in vesicle is degraded by MAO to 5-HIAA. The 5-HT transporter regulates the reuptake of 5-HT from the synaptic cleft (7). Paroxetin administration prevents reuptake of 5-HT into nerve terminals. TYR is transported into the neurons and converted to DOPA by TYR-hydroxylase (8), the largely saturated rate-limiting enzyme in DA synthesis. DOPA is decarboxylated to DA (9). Newly synthesized DA can be released or stored. Following the breakdown by COMT and/or MOA, DA is transformed into HVA and DOPAC. 5-HT and DA activity may inhibit each other (10). 5-HT and DA released at the outer layer of the medial eminence enters the portal circulation, where it may act directly on the mammotrophic substances of the anterior pituitary. 5-HT bound to 5-HT_1 receptors has stimulating influence while DA bound to DA_2 receptors inhibits PRL release (11). PRL, via short-loop feedback, elevates DA turnover (12). *ALB* albumin, *BBB* blood–brain barrier, *COMT* catechol-o-methyl transferase, *DOPA* dihydroxyphenylalanine, *DOPAC* 3,4-dihydroxyphenylacetic acid, *HVA* homovanillic acid, *MAO* monoamine oxidase, *5-HIAA* 5-hydroxyindoleacetic acid, *5-HTP* 5-hydroxytryptophan) (Modified from Strüder et al. 1998a)

8.3.2 *Factors Influencing the PRL Response to Exercise and the Functional Implications*

PRL exhibits a circadian rhythm with peak values in the early morning hours with circulating PRL levels lowest at midday. Approximately 14 pulses of PRL secretion per day occur in healthy men with an average inter-pulse interval of 95 min (Nokin et al. 1972). Thus, the time of blood sampling has to be considered when determining PRL responses to exercise. Furthermore, environmental inputs, internal milieu, and the reproductive state can modify the circadian pattern of PRL (Freeman et al. 2000) and therefore might modify the exercise-induced hormonal responses.

Basal PRL levels and responses to PRL releasing stimuli, such as exercise, are higher in women than men. PRL levels are basically unchanged throughout the menstrual cycle with only a slight increase in PRL during the luteal phase (Fujimoto et al. 1990). PRL responses to exercise, however, are greater in the mid-luteal phase than in the early follicular phase of the menstrual cycle. Abundant evidence is available to suggest that basal PRL concentration and PRL release during exercise and following maximal and submaximal exercise are reduced in runners with amenorrhea despite high lactate levels (De Souza et al. 1991). Similar to pregnancy, a blunted response to 10 min moderate exercise has been recently reported (Rojas Vega et al. 2012). In this study it was shown that despite the fact that the ability to perform strenuous exercise during pregnancy is not reduced, the achieved maternal lactate concentrations were low during exercise. Thus, one possible explanation for this apparent inconsistent response of PRL may be that when exercise is of short duration only acidosis induces PRL augmentations in humans.

An accumulation of H^+, produced by an increase in lactate concentration, glucose availability, and oxygen availability have been suggested as PRFs during exercise. At high exercise intensities the anaerobic lactic contribution seems to be an important trigger for inducing PRL augmentation (De Meirleir et al. 1985a). The underlying mechanism might be mediated by 5-HT, since this neurotransmitter plays a crucial role in central chemosensitivity (Rojas Vega et al. 2006b). Extensive evidence is available which shows that serotonergic neurons are central carbon dioxide sensors in maintaining pH homeostasis (Richerson 2004), and the primary serotonergic response to hypercapnia acidosis consists of an activation of the respiratory function aimed at restoring pH value to normal. Studies showing that hypercapnia acidosis causes an augmentation of PRL secretion in humans at rest (subjects inhaled 6 L of a gas mixture comprising 7% by volume carbon dioxide and 93% by volume of oxygen in 4 min from a respiration bag through a face mask) support the hypothesis that a chemosensitivity-related 5-HT system activation disturbs the hypothalamo-pituitary PIF-PRF balance, causing acute PRL secretion (Rojas Vega et al. 2003). In support of an acidosis etiology, buffering of metabolic acidosis during intensive cycling to exhaustion, resulting in a reduced drop of pH, has also been reported to reduce the increase of plasma PRL levels in humans (Rojas Vega et al. 2006b).

It is known that environmental stimuli such as thermal stress or oxygen availability can affect the PIF-PRF hypothalamic regulatory mechanisms modifying PRL secretion (Freeman et al. 2000; Strüder et al. 1996). Such modifications must be taken into account for interpretations of data obtained from exercise trials. For example, during exercise PRL levels were reported to increase during oxygen breathing (Strüder et al. 1996). In addition, an inhibition of exercise-induced increase of PRL levels was observed in males during GXT, who had been acutely exposed to hypoxia (Bouissou et al. 1987).

It is not yet clear how these increases of PRL affect the brain, but it is conceivable that they are linked to neurogenic processes. Augmented PRL levels during exercise might be important for boosting neurogenesis. This hypothesis is also based on the finding that the missing action of the hormone in PRL-receptor-deficient mice leads to a reduction of neurogenesis (Shingo et al. 2003). Combined with the findings that neurogenesis is augmented during conditions that increase PRL concentration, like pregnancy or after peripheral or central infusion of the hormone (Shingo et al. 2003), it may be argued that PRL plays a functional role in brain neuroplasticity, giving further support to the assumption that exercise may be beneficial for the brain.

8.4 Amino Acids and Neurotransmitters

5-HT and dopamine (DA) are neurotransmitters which have an important functional role during exercise in humans. An augmentation of the DA activity by administration of the DA agonist pergolid-mesylat was shown to reduce systolic blood pressure, pulse rate, and lactate level during GXT (De Meirleir et al. 1987). The maximal performance capacity was increased while the typical exercise-induced augmentations of PRL and ACTH were suppressed. During cycle ergometer exercise, 5-HT antagonism by the application of ketanserin induced a reduction of systolic blood pressure. The maximal performance capacity remained unchanged, while the lactate curve shifted to the right, which is an expression of either reduced lactate production in the working muscle cells or increased lactate elimination. Ketanserin also reduced the concentration of exercise-induced rise of ACTH, while the growth hormone (GH) concentration was not altered (De Meirleir et al. 1985b). Administration of the 5-HT reuptake inhibitor paroxetin reduced performance capacity to fatigue during continuous exercise, however, did not affect the exercise-induced PRL release (Strüder et al. 1998a) (Fig. 8.3).

Interestingly, a co-release between the BDNF and 5-HT has been demonstrated (Mattson et al. 2004). 5-HT regulates the most extensive modulatory behavioral system in the human brain. 5-HT projections are influenced by extrinsic and intrinsic impulses from different cortical brain areas, which reach Raphe nuclei over feedback loops and contain external and internal body information about planning, evaluation, motivation, or excitation (Graeff 1997). Although central serotonergic neurotransmission during exercise is predominantly regulated by neuronal complex

cooperation in the brain, precursor supply and plasma concentrations, fixation of TRP to albumin, hepatic and non-hepatic TRP pyrrolase, as well as competitive TRP uptake at the BBB are peripheral mechanisms that also influence central 5-HT neurotransmission. Motor neuron functions are primarily enhanced by the function of the serotonergic neurons in the brain, but also by the influence of central 5-HT and to a certain extent the neurons in the spinal cord.

The TRP stimulation of TRP hydroxylase is important for the central 5-HT impact, since this key enzyme is unsaturated. TRP uptake can also be aided by adrenoceptor-dependent dilatation of the microvessels or metabolically by an increased efflux of glutamine from the brain after central ammonia (NH_3) increases—e.g., during strenuous physical work (Mans et al. 1983). Exercise-dependent activation not only includes motoric neuronal activity, but also the release and reuptake of 5-HT and DA at presynaptic neuronal axons and somato-dendritic secretion. During the exercise detachment of TRP from albumin, TRP uptake at the BBB and TRP hydroxylase activity is increased, together with a higher TRP enzyme saturation and larger 5-HT yield. During exercise this is supported by faster anterograde TRP hydroxylase transport from cell body to axon terminal by neuron excitation, in which the 5-HT biosynthesis has increased. CA^{2+}-dependent 5-HT release into the synaptic cleft augments and postsynaptic 5-HT receptor subtype stimulation is enhanced.

But there are situations in which this well-balanced equilibration is disturbed and a dysfunction of the 5-HT system occurs. This might be induced by a non-physiological increase of free TRP liberation by adrenergic FFA mobilization with a consequent rise in their blood values after exercise, fasting, or emotional adrenergic exertion due to lipolysis in adipose tissue (McMenamy 1965). This might be the case during long-lasting strenuous exercise without ergogenic aid. In combination with augmented BCAA metabolism, an increase of the free TRP/BCAA ratio will occur, which favors free TRP uptake at the BBB and the resulting enhancement of 5-HT biosynthesis. Peripheral TRP concentration can be reduced by activation of the hepatic TRP pyrrolase. In addition, an increase in extrahepatic pyrrolase activity caused by γ-interferon diminishes plasma TRP concentration while simultaneously reducing viral and bacterial susceptibility (Strüder and Weicker 2001).

The 5-HT system adjusts impulses for behavior and mood modulation, but also supports complex cognitive or neuromuscular functions (Baumgarten and Grozdnovic 1995). Raphe nuclei are pacemakers of 5-HT central propagation, which control 5-HT projections by collaterals and receptor activation of many brain areas. Raphe nuclei receive information of behavioral modulation from diverse cortical regions. These impulses are already integrated in the Raphe nuclei before ascending and descending impulses arise. This equilibrating key function of the 5-HT system is essential in order to adjust neuro- and behavior modulation by coordination of different neurotransmitters, which are prerequisites for efficient neuronal networks. It seems that the adjustment of central neuro-modulation by 5-HT compensates central stress-induced dysregulation. Dysfunctions of the 5-HT system, however, are more obvious than the well-adjusted physiological implication of the 5-HT system, and this might be the reason for the underestimated beneficial impact of 5-HT in exercise-related studies.

8.5 Concluding Remarks

A large number of studies with differing methods of approach to the influence of physical exercise on the brain and cognitive factors are currently available. It may be concluded that the knowledge of the biochemical and biophysical connections between the functioning of the brain, mind, and body during physical exercise is important in preventive and therapeutic approaches. Exercise improves overall CNS health by augmenting neurotrophic factors and hormones as well as by affecting the neurotransmitter systems. Thus, from a clinical point of view, exercise is an ideal strategic tool for inducing anxiolytic and antidepressant effects, for enhancing cognition and facilitating functional recovery after injury (i.e., stroke) and through its influence on neurogenesis. Future studies should strive to establish a more precise dose–response relationship between exercise, humoral factors, and neurogenesis in humans, thereby allowing exercise's possible contribution to health to be optimized via prevention and also rehabilitation programs.

References

Aberg MA, Aberg ND, Hedbacker H, Oskarsson J, Eriksson PS (2000) Peripheral infusion of IG-1 selectively induces neurogenesis in the adult rat hippocampus. J Neurosci 20:2896–2903

Baker LD, Frank LL, Fosrter-Schubert K, Green PS, Wilkinson CW, McTiernan A, Plymate SR, Fhishel MA, Watson GS, Cholerton BA, Duncan GE, Mehta PD, Craft S (2010) Effects of aerobic exercise on mild cognitive impairment: a controlled trial. Arch Neurol 67:71–79

Bang P, Brandt J, Degerblad M, Enberg G, Kaijser L, Thoren M (1990) Exercise-induced changes in insulin-like growth factors and their low molecular weight binding protein in healthy subjects and patients with growth hormone deficiency. Eur J Clin Invest 20:285–292

Baumgarten HG, Grozdnovic Z (1995) Die Rolle des Serotonins in der Verhaltensmodulation. Fortschr Neurol Psychiatr 63:3–8

Ben-Jonathan N, Hnasko R (2001) Dopamine as a prolactin (PRL) inhibitor. Endocr Rev 22:724–763

Bole-Feysot C, Goffin V, Edery M, Binart N, Kelly PA (1999) Prolactin (PRL) and its receptors: actions, signal transduction pathways and phenotypes observed in PRL receptor knockout mice. Endocr Rev 19:225–268

Bondy CA, Lee WH (1993) Patterns of insulin-like growth factor and IGF receptor gene expression in the brain. Functional implication. Ann NY Acad Sci 692:33–43

Borst SE, De Hoyos DV, Garzarella L, Vincent K, Pollock BH, Lowenthal DT, Pollock ML (2001) Effects of resistance training on insulin-like growth factor-1 and IGF-1 binding proteins. Med Sci Sports Exerc 33:648–653

Bosco C, Colli R, Bonomi R, von Duvillard SP, Viru A (2000) Monitoring strength training: neuromuscular and hormonal profile. Med Sci Sports Exerc 32:202–208

Bouissou P, Brisson GR, Peronnet F, Helie R, Ledoux M (1987) Inhibiton of exercise-induced blood prolactin response by acute hypoxia. Can J Sport Sci 12:49–50

Breen EC, Johnson EC, Wagner H, Tseng HM, Sung LA, Wagner PD (1996) Angiogenic growth factor mRNA in muscle to a single bout of exercise. J Appl Physiol 81:355–361

Brisson GR, Ledoux M, Péronnet F, Dulac S, DeCarufel D, Volle MA, Rainville J, Audet A (1981) Prolactinemia in exercising athletes. Horm Res 15:218–223

Cao L, Xiangyang J, Zusgam DS, LiuY FDM, Young D, During MJ (2004) VEGF links hippocampal activity with neurogenesis, learning and memory. Nat Genet 36:827–835

Cappon J, Brasel JA, Mohan S, Cooper DM (1994) Effect of brief exercise on circulating insulin-like growth factor I. J Appl Physiol 76:2490–2496
Carro E, Nuñez A, Busiguina S, Torres-Aleman I (2000) Circulating insulin-like growth factor I mediates effects of exercise on the brain. J Neurosci 20:2926–2933
Castellano V, White LJ (2008) Serum brain-derived neurotrophic factor response to aerobic exercise in multiple sclerosis. J Neurol Sci 269:85–91
Chan KL, Tong KY, Yip SP (2008) Relationship of serum brain-derived neurotrophic factor (BDNF) in health related lifestyle in healthy human subjects. Neurosci Lett 447:124–128
Charifi N, Kadi F, Feasson L, Costes F, Geyssant A, Denis C (2004) Enhancement of microvessel tortuosity in the vastus lateralis muscle of old men in response to endurance training. J Physiol 554:559–569
Chicharro JL, López-Calderon A, Hoyos J, Martín-Velasco AI, Villa G, Villanúa MA, Lucía A (2001) Effects of an endurance cycling competition on resting serum insulin-like growth factor-1 (IGF-1) and its binding proteins IGFBP-1 and IGFBP-3. Br J Sports Med 35:303–307
Cotman CW, Berchtold NC (2002) Exercise: a behavioral intervention to enhance brain health and plasticity. Trends Neurosci 25:295–301
Croley AN, Zwetsloot KA, Westerkamp LM, Ryan NA, Pendergast AM, Hickner RC, Pofahl WE, Gavin TP (2005) Lower capillarization, VEGF protein, VEGF mRNA response to acute exercise in the vastus lateralis muscle of aged vs. young women. J Appl Physiol 99:1857–1882
Currie J, Ramsbottom R, Ludlow H, Nevill A, Gilder M (2009) Cardio-respiratory fitness, habitual physical activity and serum brain derived neurotrophic factor (BDNF) in men and women. Neurosci Lett 451:152–155
Daly W, Seegers CA, Rubin DA, Dobridge JD, Hackney AC (2005) Relationship between stress hormones and testosterone with prolonged endurance training. Eur J Appl Physiol 93:375–380
De Meirleir KL, Baeyens L, L'Hermite-Balériaux M, L'Hermite M, Hollmann W (1985a) Exercise-induced prolactin release is related to anaerobiosis. J Clin Endocrinol Metabol 60:1250–1252
De Meirleir K, Gerlo F, Hollmann W, Van Haelst L (1987) Cardiovascular effects of pergolide mesylate during dynamic exercise. Brit J Clin Pharmacol 23:633
De Meirleir K, L'Hermite-Balériaux M, L'Hermite M et al (1985b) Evidence for serotoninergic control of exercise-induced prolactin secretion. Horm Metab Res 17:380–381
De Souza MJ, Maguire MS, Maresh CM, Kraemer WJ, Rubin KR, Loucks AB (1991) Adrenal activation and the prolactin response to exercise in eumenorrheic and amenorrheic runnesrs. J Appl Physiol 6:2378–2387
Ding Y, Li J, Luan X, Ding YH, Lai Q, Rafols JA, Phillis JW, Clark JC, Diaz FG (2004) Exercise pre-condition reduces brain damage in ischemic rats that may be associated with regional angiogenesis and cellular overexpression of neurotrophin. Neuroscience 124:583–591
Ding Q, Vaynman S, Akhavan M, Ying Z, Gomez-Pinilla F (2006) Insulin-like growth factor I interfaces with brain-derived neurotrophic factor-mediated synaptic plasticity to modulate aspects of exercise-induced cognitive function. Neuroscience 140:823–833
Duman RS, Malberg J, Nakagawam S, D'Sa C (2000) Neuronal plasticity and survival in mood disorders. Biol Psychiatry 48:732–739
Eliakim A, Brasel JA, Mohan S, Wong WLT, Cooper DM (1998) Increased physical activity and the growth hormone-IGF-I axis in adolescent males. Am J Physiol 275:R308–R314
Elloumi M, El Elj N, Zaouali M, Maso F, Filaire E, Tabka Z, Lac G (2005) IGFBP-3 a sensitive marker of physical training and overtraining. Br J Sports Med 39:604–610
Eriksson PS, Perfilieva E, Björk-Eriksson T, Alborn AM, Nordborg C, Peterson DA, Gage FH (1998) Neurogenesis in the adult human hippocampus. Nat Med 4:1313–1317
Exton MS, Tillmann HC, Krüger T, Koch M, Paulson E, Knapp W, Hartmann U, Schedlowski M (2001) Coitus-induced orgasm stimulates prolactin secretion in healthy subjects. Psychoneuroendocrinology 26:287–294
Fabel K, Fabel K, Tam B, Kaufer D, Baiker A, Simmons N, Kuo CJ, Palmer TD (2003) VEGF is necessary for exercise-induced adult hippocampal neurogenesis. Eur J Neurosci 18:2803–2812

Flöel A, Ruscheweyh R, Krüger K, Willemer C, Winter B, Völker K, Lohmann H, Zitzmann M, Mooren F, Breinstein C, Knecht S (2010) Physical activity and memory functions: are neurotrophins and cerebral grey matter volume the missing link. Neuroimage 49:2756–2763

Ferris LT, Williams JS, Shen CL (2007) The effect of acute exercise on serum brain-derived neurotrophic factor levels and cognitive function. Med Sci Sports Exerc 39:728–734

Freeman ME, Kanyicska B, Lerant A, Nagy G (2000) Prolactin: structure, function and regulation of secretion. Physiol Rev 80:1523–1631

Fujimoto VY, Clifton DK, Cohen NL, Soules MR (1990) Variability of serum prolactin and progesterone levels in normal women: the relevance of single hormone measurements in the clinical setting. Obstet Gynecol 76:71–18

Goekint M, De Pauw K, Roelands B, Njemini R, Bautmans I, Mets T, Meeusen R (2010) Strength training does not influence serum brain-derived neurotrophic factor. Eur J Appl Physiol 110:285–293

Gold SM, Schulz KH, Hartmann S, Mladek M, Lang UE, Hellweg R, Reer R, Braumann KM, Heesen C (2003) Basal serum levels and reactivity of nerve growth factor and brain-derived neurotrophic factor to standardized acute exercise in multiple sclerosis and controls. J Neuroimmunol 138:99–105

Graeff FG (1997) Serotonergic systems. Psychiatr Clin North Am 20:723–739

Gunga HC, Kirsch K, Röcker L, Behn C, Koralewski E, Davila EH, Estrada MI, Johannes B, Wittels P, Jelkmann W (1999) Vascular endothelial growth factor in exercising humans under different environmental conditions. Eur J Appl Physiol 79:484–490

Gustafsson T, Knutsson A, Puntschart A, Kaijser L, Nordqvist AC, Sundberg CJ, Jansson E (2002) Increased expression of vascular endothelial growth factor in human skeletal muscle in reponse to short-term one-legged exercise training. Pflugers Arch 244:752–759

Gustafsson G, Lira CM, Johansson J, Wisén A, Wohlfahrt B, Ekman R, Westrin A (2009) The acute response to plasma brain-derived neurotrophic factor as a result of exercise in major depression. Psychiatry Res 169:244–248

Hagberg JM, Seals DR, Yerg JE, Gavin J, Gingerich R, Premachandra B, Holloszy JO (1988) Metabolic responses to exercise in young and older athletes and sedentary men. J Appl Phyisiol 65:900–908

Häkkinen K, Pakarinen A, Alen M, Komi PV (1985) Serum hormones during prolonged training of neuromuscular performance. Eur J Appl Physiol 53:287–293

Hickson RC, Hikada K, Foster C, Falduto MT, Chatterton RT Jr (1994) Successive time course of strength development and steroid hormone responses to heavy-resistance exercise. J Appl Physiol 76:663–670

Hiscock N, Fischer CP, Pilegaard H, Pedersen BK (2003) Vascular endothelial growth factor mRNA expression and arteriovenous balance in response to prolonged submaximal exercise in humans. Am J Physiol Heart Circ Physiol 285:H1759–H1763

Hollmann W, Strüder HK (2009) Sportmedizin. Grundlagen für körperliche Aktivität, Training und Präventivmedizin. Schattauer, Stuttgart, New York

Hollmann W, Strüder HK (2000) Brain function, mind, mood, nutrition and physical exercise. Nutrition 16:516–519

Hollmann W, Strüder HK, Tagarakis CVM (2003) Körperliche Aktivität fördert Gehirngesundheit und–leistungsfähigkeit. Nervenheilkunde 22:467–474

Hsieh J, Eich AJ (2010) Epigenetics, hippocampal neurogenesis, and neuropsychiatric disorders: Unraveling the genome to understand the mind. Neurobiol Dis 39:73–84

Izquierdo M, Ibañez J, Gonzales Badillo JJ, Häkkinnen K, Ratammes NA, Kraemer WJ, French DN, Eslava J, Altadill A, Asiain X, Gorostiaga EM (2006) Differential effects of strength training leading to failure not to failure on hormonal responses, strength and muscle power gains. J Appl Physiol 100:1647–1656

Jakeman PM, Hawthorne JE, Maxwell SR, Kendall MJ, Holder G (1994) Evidence for downregulation of hypothalamic 5-hydroxytryptamine receptor function in endurance-trained athletes. Exp Physiol 79:461–464

Jozsi AC, Dupont-Versteegden EE, Taylor-Jones JM, Evans WJ, Trappe TA, Campbell WW, Peterson CA (2000) Aged human muscle demonstrates an altered gene expression profile consistent with an impaired response to exercise. Mech Ageing Dev 120:45–56

Karege F, Bondolfi G, Gervasoni N, Schwald M, Aubry JM, Bertschy G (2005) Low brain-derived neurotrophic factor (BDNF) levels in serum of depressed patients probably results from lowered platelet BDNF release unrelated to platelet reactivity. Biol Psychiatry 57:1068–1072

Karege F, Perret G, Bondolfi G, Schwald M, Bertschy G, Aubry JM (2002) Decreased serum derived neurotrophic factor in major depressed patients. Psychiatry Res 109:143–148

Katoh-Semba R, Wakako R, Komori T (2007) Age-related changes in BDNF protein levels in human serum: differences between autism cases and normal controls. Int J Dev Neurosci 25:367–372

Keizer HA, Kuipers H, de Haan J, Janssen GM, Beckers E, Habets L (1987) Multiple hormonal responses to physical exercise in eumenorrheic trained and untrained women. Int J Sports Med 8:139–150

Kempermann G, Krebs J, Fabel K (2008) The contribution of failing adult hippocampal neurogenesis to psychiatric disorders. Curr Opin Psychiatry 21:290–295

Koziris LP, Hickson RC, Chatterton RT Jr, Groseth RT, Christie JM, Goldflies DG, Unterman TG (1999) Serum levels of total and free IGF-I and IGFBP-3 are increased and maintained in long-term training. J Appl Physiol 86:1436–1442

Kraemer WJ, Ratamess NA (2005) Hormonal responses and adaptations to resistance exercise and training. Sports Med 35:339–361

Kraus RM, Stallings HW, Yeager RC, Gavin TP (2004) Circulating plasma VEGF response to exercise in sedentary and endurance-trained men. J Appl Physiol 96:1445–1450

Lang UE, Hellweg R, Gallinat J (2004) BDNF serum concentrations in healthy volunteers are associated with depression-related traits. Neuropsychopharmacology 29:795–798

Laske C, Banschbach S, Stransky E, Bosch S, Straten G, Machann J, Fritsche A, Hipp A, Nitess A, Eschweiler GW (2010) Exercise-induced normalization of decreased BDNF concentration in elderly women with remitted major depression. Int J Neuropsychopharmacol 13:595–602

Lehmann M, Gastman U, Petersen KG, Bachl N, Seidel A, Khalaf AN, Fischer S, Keul J (1992) Training-overtraining: performance, and hormone levels, after defined increase in training volume versus intensity in experienced middle- and long-distance runners. Br J Sports Med 26:233–242

Leung DW, Cachianes G, Kuang WJ, Goeddel DV, Ferrara N (1986) Vascular endothelial growth factor is a secreted angiogenic mitogen. Science 246:1306–1309

Leventhal PS, Russell JW, Feldman EL (1999) IGFs and the nervous system. In: Rosenfeld RG, Roberts ChT (eds) The IGF system: molecular biology, physiology and clinical applications. Humana, New Jersey

Levinger I, Goodman C, Mathews V, Hare DL, Jerums G, Garnham A, Selig S (2008) BDNF, metabolic risks factors and resistance training in middle-aged individuals. Med Sci Sports Exerc 40:535–541

Llorens-Martin M, Torres-Alemán I, Trejo JL (2009) Mechanisms mediating brain plasticity: IGF1 and adult hippocampal neurogenesis. Neuroscientist 15:134–148

Lommatzsch M, Ziegler D, Shuhbaek K, Schloetcke K, Zingler C, Shuff-Werner P, Virchow JC (2005) The impact of age weight and gender on BDNF levels in human platelets and plasma. Neurobiol Aging 26:115–123

Lopez-Lopez C, LeRoith D, Torres-Aleman I (2004) Insulin-like growth factor I is required for vessel remodeling in the adult brain. Proc Natl Acad Sci USA 101:9833–9838

Luger A, Watschinger B, Deutser P, Svoboda T, Clodi M, Chrousos GP (1992) Plasma growth hormone and prolactin responses to graded levels of acute exercise and to lactate infusion. Neuroendocrinology 56:112–117

Manetta J, Brun JF, Maimoun L, Fédou C, Préfaut C, Mercier J (2003) The effects of intensive training on insulin-like growth factor 1 (IGF-1) and IGF binding proteins 1 and 3 in competitive cyclists: relationships with glucose disposal. J Sports Sci 21:147–154

Mans AM, Biebuyck JF, Hawkins RA (1983) Ammonia selectively stimulates neutral amino acid transport across blood–brain barrier. Am J Physiol 245:C74–C77

Matthews VB, Astrom MB, Chan MH, Bruce CR, Krabbe KS, Prelovsek O, Akerstrom T, Yfanti C, Broholm C, Mortensen OH, Penkowa M, Hojman P, Zankari A, Watt MJ, Bruunsgaard H,

Pedersen BK, Febbraio MA (2009) Brain-derived neurotrophic factor is produced by skeletal muscle cells in response to contraction and enhances fat oxidation via activation of AMP-activated protein kinase. Diabetologia 52:1409–1418

Mattson MP, Maudsley S, Martin B (2004) BDNF and 5-HT: a dynamic duo in age-related neuronal plasticity and neurodegenerative disorders. Trends Neurosci 27:589–594

Marx JO, Ratamess NA, Nindl BC, Gotschalk LA, Volek JS, Dohi K, Bush JA, Gomez AL, Mazzetti SA, Fleck SJ, Häkkinen K, Newton RU, Kraemer WJ (2001) Low-volume circuit versus high-volume periodized resistance training in women. Med Sci Sports Exerc 33:635–643

Mayberg HS, Keightley M, Mahurin RK, Brannan SK (2002) Neuropsychiatric aspects of mood and afective disorders. In: Yudofsky SC, Hales RE (eds) Textbook of Neuropsychiatry and clinical neurosciences, 4th edn. Washington: American Psychiatric publishing Inc, pp 1021–1048

McCall GE, Byrnes WC, Fleck SJ, Dickinson A, Kraemer WJ (1999) Acute and chronic hormonal responses to resistance training designed to promote muscle hypertrophy. Can J Appl Physiol 24:96–107

McMenamy RH (1965) Binding of indole analogues to human serum albumin. Effects of fatty acids. J Biol Chem 240:4235–4243

Meeusen R, de Meierleir K (1995) Exercise and brain neurotransmission. Sports Med 3:160–188

Neeper SA, Gómez-Pinilla F, Choi J, Cotman C (1995) Exercise and brain neurotrophins. Nature 373:109

Nemet D, Connolly PH, Pontello-Pescatello AM, Rose-Gottron C, Larson JK, Galasseti P, Cooper DM (2004) Negative energy balance plays a major role in the IGF-I response to exercise training. J Appl Physiol 96:276–282

Noel GL, Suh NK, Stone JG, Frantz AG (1972) Human prolactin and growth hormone release during surgery and other conditions of stress. J Clin Endocrinol Metab 35:840–851

Nofuji Y, Suwa M, Moriyama Y, Nakano H, Ichimiya A, Nishichi R, Sasaki A, Radak Z, Zhuzo K (2008) Decreased serum brain-derived neurotrophic factor in trained men. Neurosci Lett 437:29–32

Nokin J, Vekemans M, L'Hermite M, Robyn C (1972) Circadian periodicity of serum prolactin concentration in man. Br J Med 3:561–562

Pan W, Banks WA, Fasold MB, Bluth J, Kastin AJ (1998) Transport of brain-derived neurotrophic factor across the blood-brain barrier. Neuropharmacology 37:1553–1561

Pereira AC, Huddleston DE, Brickman AM, Sosunov AS, Hen R, McKhann GM, Sloan R, Gage FH, Brown TR, Small SA (2007) An in vivo correlate of exercise induced neurogenesis in the adult dentate gyrus. Proc Natl Acad Sci USA 104:5638–5643

Prior BM, Yang HT, Terjung RL (2004) What makes vessels growth with exercise training? J Appl Physiol 97:1119–1128

Poehlman ET, Copeland KC (1990) Influence of physical activity on insulin-like growth factor-I in healthy younger and older men. J Clin Endocrinol Metab 71:1468–1473

Raastad T, Glomsheller T, Bjro T, Hallen T (2003) Recovery of skeletal muscle contractility and hormonal responses to strength exercises after two weeks of high volume strength training. Scand J Med Sci Sports 13:159–168

Rasmussen P, Brassard P, Adser H, Pedersen MV, Leick L, Hart E, Secher N, Niels H, Pedersen BK, Pilegaard H (2009) Evidence for a release of brain-derived neurotrophic factor from the brain during exercise. Exp Physiol 94:1062–1069

Reichlin S (1998) Hypothalamus and pituitary: neuroendocrinology. In: Wilson JD, Foster DW, Kronenberg HM, Larsen PR (eds) Williams textbook of endocrinology. Saunders, Philadelphia

Richardson RS, Wagner H, Mudaliar SR, Henry R, Noyszewski EA, Wagner PD (1999) Human VEGF gene expression in skeletal muscle: effect of acute normoxic and hypoxic exercise. Am J Physiol 277:H2247–H2252

Richerson GB (2004) Serotonergic neurons as carbon dioxide sensors that maintain pH homeostasis. Nat Rev 5:449–461

Rojas Vega S (2001) Effects of respiratory stress on plasma prolactin concentration. Doctoral Thesis. German Sport University, Cologne

Rojas Vega S, Strüder HK, Hollmann W (2003) Plasma prolactin concentration increases after hypercapnia acidosis. Horm Metab Res 35:1–4

Rojas Vega S, Strüder HK, Vera Wahrmann B, Schmidt A, Bloch W, Hollmann W (2006a) Acute brain-derived neurotrophic factor and cortisol response to ramp incremental exercise to exhaustion in humans. Brain Res 1121:59–65, Erratum 2007 in Brain Res 1156:174–175

Rojas Vega S, Strüder HK, Vera Wahrmann B, Bloch W, Hollmann W (2006b) Bicarbonate reduces serum prolactin increase induced by exercise to exhaustion. Med Sci Sports Exerc 38:675–680

Rojas Vega S, Abel Th, Bloch W, Hollmann W, Strüder HK (2008) Impact of exercise on neuroplasticity-related proteins in spinal cord injured humans. Neurosci 153:1064–1070

Rojas Vega S, Knicker A, Hollmann W, Bloch W, Strüder HK (2010) Effect of resistance exercise on serum levels of growth factors in humans. Horm Metab Res 42:982–986

Rojas Vega S, Kleinert J, Sulprizio M, Hollmann Bloch W, Strüder HK (2012) Impact of exercise on serum concentrations of neurotrophic factors in pregnant and postpartum women. PNEC 36:220–227

Rojas Vega S, Hollmann W, Wahrmann B, Strüder HK (2012) Bicarbonate infusion does not influence BDNF responses to high intensity exercise. Int J Sports Med 33:8–12

Seifert T, Brassard P, Wissenberg M, Rasmussen P, Nordby P, Stallknecht B, Adser H, Jakobsen A, Pilegaard H, Nielsen H, Secher N (2010) Endurance training enhances BDNF release from the human brain. Am J Physiol Regul Integr Comp Physiol 298:R372–377

Schneider DJ, Tracy PB, Mann KG, Sobel BE (1997) Differential effects of anticoagulants on the activation of platelets ex vivo. Circulation 96:2877–2883

Schiffer T, Schulte H, Hollmann W, Bloch W, Strüder HK (2009) Effects of strength and endurance training on brain-derived neurotrophic factor and insulin-like growth factor 1 in humans. Horm Metab Res 41:250–254

Schiffer T, Schulte H, Sperlich B, Achtzehn S, Friecke H, Strüder HK (2011) Lactate infusion at rest increases BDNF blood concentration in humans. Neurosci Lett 488:234–237

Schulz K, Gold SM, Witte J, Bartsch K, Lang UE, Hellweg R, Reer R, Braumann KM, Heesen C (2004) Impact of aerobic training on immune-endocrine parameters, neurotrophic factors, quality of life and coordinative function in multiple sclerosis. J Neurol Sci 225:11–18

Schwarz AJ, Brasel J, Hintz RL, Mohan S, Cooper DM (1996) Acute effect of brief low-and high-intensity exercise on circulating insulin growth factor (IGF) I, IGF-binding protein-3 and its proteolysis in young healthy men. J Clin Endocrinol Metab 81:3492–3497

Shingo T, Gregg C, Enwere E, Fujikawa H, Hassam R, Geary C, Cross JC, Weiss S (2003) Pregnancy-stimulated neurogenesis in the adult female forebrain mediated by prolactin. Science 299:117–120

Shimizu E, Hashimoto K, Okamura N, Koike K, Komatsu N, Kumakiri C, Nakazato W, Watanabe H, Shinoda N, Okada S, Iyo M (2003) Alterations of serum levels of brain-derived neurotrophic factors (BDNF) in depressed patients with or without antidepressants. Biol Psychiatry 54:70–75

Smallridge RC, Whorton NE, Burman KD, Fergusson EW (1985) Effects of exercise and physical fitness on the pituitary-thyroid axis and on prolactin secretion in male runners. Metabolism 34:949–954

Smith AT, Clemmons DR, Underwood LE, Ben-Ezra V, McMurray R (1987) The effect of exercise on plasma somatomedin C/insulin like growth factor I concentrations. Metabolism 36:533–537

Ströhle A, Stoy M, Graetz B, Scheel M, Wittmann A, Gallinat J, Lang UE, Dimeo F, Hellweg R (2010) Acute exercise ameliorates reduced brain-derived neurotrophic factor in patients with panic disorder. Psychoneuroendocrinology 35:364–368

Strüder HK, Hollmann W, Donike M, Platen P, Weber K (1996) Effect of O_2 availability on neuroendocrine variables at rest and during exercise: O_2 breathing increases plasma prolactin. Eur J Appl Physiol 74:443–449

Strüder HK, Hollmann W, Platen P, Wöstmann R, Ferrauti A, Weber K (1997) Effect of exercise intensity on free tryptophan to branched-chain amino acids ratio and plasma prolactin during exercise. Can J Appl Physiol 22:280–291

Strüder HK, Hollmann W, Platen P, Donike M, Gotzmann A, Weber K (1998a) Influence of paroxetine, branched-chain amino acids and tyrosine on neuroendocrine system responses and fatigue in humans. Horm Metab Res 30:188–194

Strüder HK, Hollmann W, Platen P, Rost R, Weicker H, Weber K (1998b) Hypothalamic-pituitary-adrenal and -gonadal axis function after exercise in sedentary and endurance trained elderly males. Eur J Appl Physiol 77:285–288

Strüder HK, Weicker H (2001) Physiology and pathophysiology of the serotonergic system and its implications on mental and physical performance. Part I and II. Int J Sports Med 22:467–497

Tanaka H, Cleroux J, de Champlain J, Ducharme JR, Collu R (1986) Persisten effects of a marathon run on the pituitary-testicular axis. J Endocrinol Invest 9:97–101

Tang SW, Chu E, Hui T, Helmeste D, Law C (2008) Influence of exercise on serum brain-derived neurotrophic factor concentrations in healthy human subjects. Neurosci Lett 431:62–65

Trajkovska V, Maarcussen AB, Vinberg M, Hartvig P, Aznar S, Knudsen GM (2007) Measurements of brain-derived neurotrophic factor: methodological aspects and demographical data. Brain Res Bull 73:143–149

Trejo JL, Carro E, Torres Aleman I (2001) Circulating insulin-like growth factor I mediates exercise induced increases in the number of new neurons in the adult hippocampus. J Neurosci 21:1628–1634

Tuomisto J, Manisto P (1985) Neurotransmitter regulation of anterior pituitary hormones. Pharmacol Rev 37:249–332

Van de Kar LD, Rittenhhous PA, Qian L, Levy AD (1996) Serotonergic regulation of renin and prolactin secretion. Behav Brain Res 13:237–246

Vaynman S, Gomez-Pinilla F (2005) License to run: exercise impacts functional plasticity in the intact and injured central nervous system by using neurotrophins. Neurorehabil Neural Repair 4:283–295

Walker KS, Kambadur R, Sharma M, Smith HK (2004) Resistance training alters plasma myostatin but not IGF-1 in healthy men. Med Sci Sports Exerc 36:787–793

Winter B, Breitenstein C, Mooren FC, Voelker K, Fobker M, Lechtermann A, Krueger K, Fromme A, Korsukewitz C, Flöel A, Knecht S (2007) High impact running improves learning. Neurobiol Learn Mem 87:597–609

Yarrow JF, White LJ, McCoy SC, Borst SE (2010) Training augments resistance exercise induced elevation of circulating brain derived neurotrophic factor (BDNF). Neurosci Lett 479:161–165

Young DS, Bermes EW (1986) Specimen collection and processing: source of biological variation. In: Tiezt NW (ed) Textbook of clinical chemistry. Saunders, Philadelphia, pp 478–518

Zafra F, Lindholm D, Castrén E, Hartikka J, Thoenen H (1992) Regulation of brain-derived neurotrophic factor and nerve growth factor mRNA in primary cultures of hippocampal neurons and astrocytes. J Neurosci 12:4793–4799

Zoladz JA, Pilc A, Majerczak J, Grandys M, Zapart-Bukowska J, Duda K (2008) Endurance training increases plasma brain-derived neurotrophic factor concentration in young healthy men. J Physiol Pharmacol 59:119–132

Chapter 9
EEG: Theoretical Background and Practical Aspects

Stefan Schneider and Heiko K. Strüder

Abstract In the last two decades, the use of electroencephalography/electrotomography has gained increased attention in exercise settings. Today, up-to-date hardware and software solutions allow to record electrocortical activity even during exercise and appropriate software solutions (e.g., source localization) allow identifying specific brain regions that are affected by exercise. This chapter aims to give an overview of the genesis of EEG signals and describe techniques as well as current hardware and software solutions to record, process, and localize brain cortical activity during and after exercise.

9.1 Introduction

Methods such as positron emission tomography (PET), functional magnetic resonance imaging (fMRI), and near-infrared spectroscopy (NIRS) enable the exploration of regional brain function, yet their use in exercise studies is still in its beginning (Boecker et al. 2008; Caglar et al. 2005; Thomas and Stephane 2008), probably due to the associated financial, technical, and logistical limitations. fMRI studies have been limited to studies of aerobic or local muscular exercise such as handgrip exercise (Benwell et al. 2007; Wong et al. 2007), and obtaining measurements immediately after exercise can be problematic because of the time required to prepare subjects for scanning (fMRI, PET) (Caglar et al. 2005). Whereas NIRS would allow measuring regional changes in activation, the technique has a limited spatial resolution and can cover only parts of the brain. Moreover, to date, it remains unclear whether a systemic increase in blood flow during exercise superimposes any neural effect.

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In contrast to these techniques, electroencephalography (EEG) in combination with electrotomography offers a simple, manageable, economical, and reliable method to assess changes in brain cortical function in exercise settings.

For some time now, EEG has been used to examine exercise-induced changes in brain activation (Crabbe and Dishman 2004; Thompson et al. 2008). The human brain consists of several billions of neurons, which communicate via electrical and chemical signals ("electrochemical coupling"). Once a neuron receives a signal, evoked by some internal or external stimulus, an electrical signal (action potential) travels along the axon to the presynaptic membrane where, due to a Ca^{2+} influx through voltage-gated Ca^{2+} channels, specific neurotransmitters (glutamate as prototypic excitatory and Gamma-aminobutyric acid (GABA) as prototypic inhibitory neurotransmitter) are released in the synaptic cleft. Following the "key-lock principle," these neurotransmitters dock at specific receptors at the postsynaptic membrane. This results either in an influx of Ca^{2+} and Na^{+} ions through the postsynaptic membrane, producing an excitatory postsynaptic potential (EPSP), or an influx of Cl^{-} accompanied by a K^{+} efflux, causing the negative inhibitory postsynaptic potential (IPSP). A single EPSP is far too small to be recorded at the scalp; thus scalp-recorded cranial EEG activity reflects the summation of the synchronous activity of a cluster of pyramidal cells within the cortex whose dendrites are aligned orthogonal to the cortical surface (Kirschstein and Kohling 2009; Martin 1991). Further illustration regarding the underlying neural mechanism of this rhythmic activity and the formation of scalp-recorded potentials can be obtained from Kirschstein and Kohling (2009), Wang (2010), and Miller (2007).

The electrical activity of these postsynaptic potentials (PSPs) can be recorded in μV ranges (Fig. 9.1). A typical adult human EEG signal is about 10–100 μV in amplitude when measured from the scalp. However, the EEG is a highly individual signal, and especially the alpha rhythm might oscillate at higher amplitudes.

Scalp-recorded EEG activity oscillates at a variety of synchronous rhythms reflecting temporal coordination of neural activity in the cerebral cortex. For example, alpha activity (8–13 Hz) measured on the scalp is a result of rapid bursts of pyramidal cells of laminae III–V, consisting out of cortico-cortical interneurons (lamina III), thalamo-cortical connections (lamina IV), and pyramidal cells connecting to deeper brain areas as basal ganglia (lamina V), firing at frequencies above 100 Hz. In contrast to higher frequency activity, these bursts occur in a synchronized state due to, for example, missing sensory input (Fig. 9.2a). Obviously, the summation of synchronized bursts (simultaneous postsynaptic potentials) will result in more distinct slower frequencies than desynchronized bursts (Fig. 9.2b), which are reflected on the scalp by predominately low amplitude, high Hz EEG waveforms (beta-activity, 13–35 Hz) and are assumed to reflect complex patterns of impulse traffic in neural assemblies (Miller 2007).

It is important to stress that an EPSP will result in a negative polarity at the scalp, which normally is displayed with an upward deflection in the EEG.

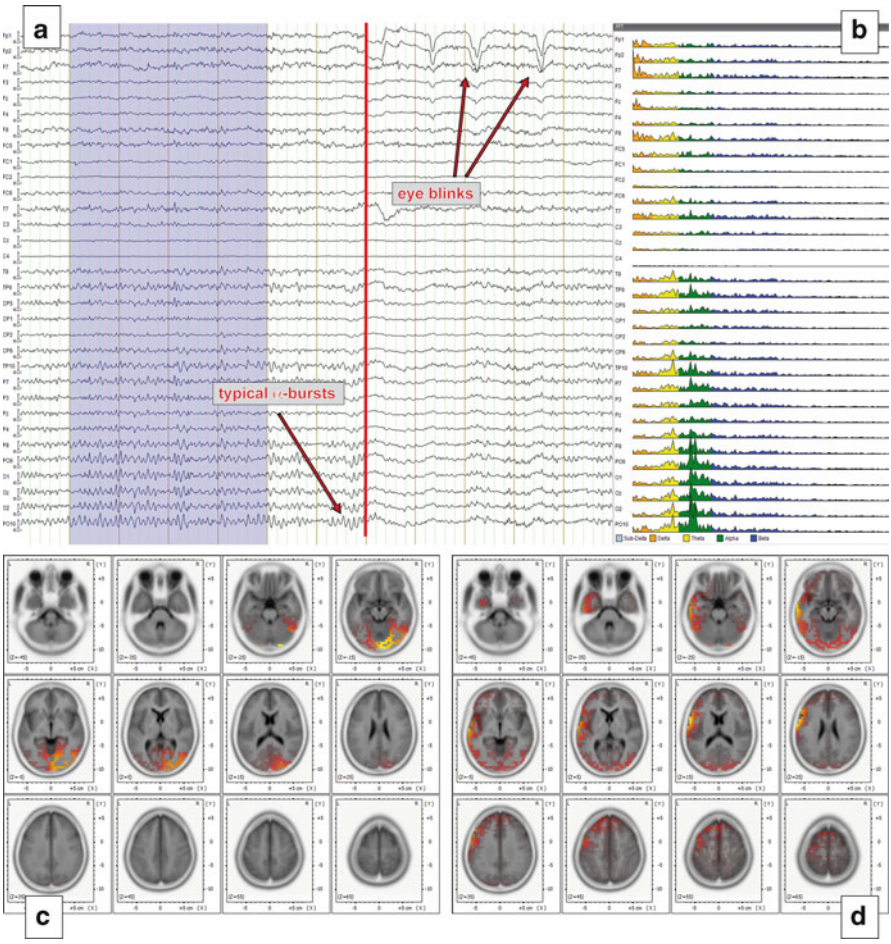

Fig. 9.1 (**a**) An EEG recording showing the classical alpha rhythm, which mainly occurs in bursts over occipital regions when eyes are closed (*left* to *red line*) and vanishes when eyes are opened (*right* to *red line*). (**b**) Fast Fourier transformation of the *shaded area* in (**a**). It clearly shows the dominant alpha frequency (*green*) in occipital areas. Channel C4 can be easily identified as artifact due to low activity. (**c**) Localization of alpha activity (*shaded area*) using sLORETA in different cortical slices. *Red* and *yellow colors* indicate increased activity. (**d**) Localization of beta activity using sLORETA in different cortical slices. *Red* and *yellow colors* indicate increased activity

9.2 EEG Analysis

9.2.1 Frequency Analysis

Dividing the EEG signal in predefined frequency ranges allows determining a neurocognitive state (Table 9.1). Within each frequency range, the spectral power (μV^2) defines the amount of activity. A classical model of cortical arousal assumes slower

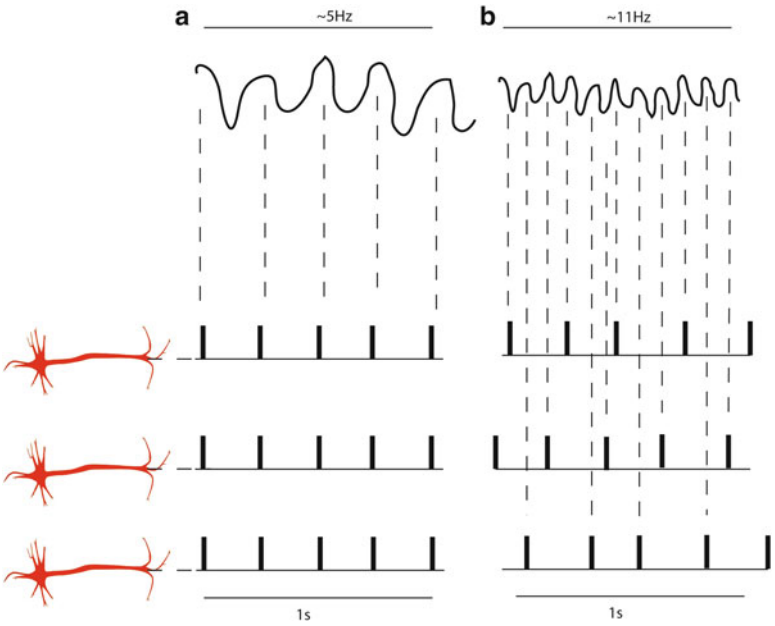

Fig. 9.2 Activity of three cortical neurons, each firing at a constant rate. If all neurons fire in a synchronized state (**a**), this will result in a sum of slow but high-amplitude signals, whereas a desynchronized mode (**b**) will result in fast, low-amplitude waveforms

Table 9.1 Allocation of the EEGs frequency ranges and corresponding cognitive states. Different authors might define slightly different frequency ranges. Also, some authors use their own specific boundaries depending on the frequency range they choose to focus on. Additionally, some researchers define subbands, for example, low beta (13–18), high beta (18–35) bands

Area	Frequency (Hz)	Cognitive state
Delta (δ)	0.5–3.5	Reduction in vigilance, especially sleep. Regarded as pathological in the normal waking EEG
Theta (ϑ)	3.5–7.5	Transition between sleep and vigilance (e.g., meditation); recently been described to be involved in memory formation (Axmacher et al. 2006; Duzel et al. 2010)
Alpha (α)	7.5–12.5	Synchronized state of the brain. Might play a role in inhibitory processes (Klimesch et al. 2007); strongest brain rhythm when eyes closed in occipital regions (visual cortex)
Beta (β)	12.5–35	Any kind of information processing. Increase in beta activity is found with arousal, attention, stress, etc.
Gamma (γ)	35–100	Similar to theta activity, gamma activity has recently been associated with memory consolidation (Axmacher et al. 2006; Duzel et al. 2010)

frequency activity (alpha activity) to be dominant in a relaxed, unstressed condition, whereas the generalized effect of attention, arousal, and alertness is a shift toward the faster frequencies and a decrease in alpha activity (Bonnet and Arand 2001; Lindsley 1960; Zuckermann 1991). Also, higher beta and gamma activity is well known to be associated with the processing of sensory information (Gray and Singer 1989) and memory formation (Axmacher et al. 2006; Duzel et al. 2010).

Currently, there is an intense debate about the functional relevance of different frequency ranges. Once it became clear that synaptic inhibition plays a fundamental role in the generation of frequency spectra (for a recent review, see Wang 2010), the traditional assignment of specific frequencies to specific neurocognitive states was questioned, especially as experimental evidence revealed partly inconsistent results. For example, alpha activity, traditionally connected to a relaxed cortical state, has recently been argued to be present also in the activated cortex caused by long-distance interactions (Miller 2007).

Although recently there have been some attempts to record and analyze higher frequency ranges (gamma activity), some authors question that it is possible to record frequencies beyond the beta-band with scalp electrodes, as gamma activity seems to be too localized to be recorded on the scalp. Opinions also differ concerning the lower frequency spectrum (lower theta and delta activity). Especially, in exercise neuroscience, a number of studies (Crabbe and Dishman 2004; Mechau et al. 1998) reported these frequencies to be influenced by exercise. But as theta and especially delta activity mainly occur during sleep (non-REM, slow wave sleep) and are rare or nonexistent in the normal waking EEG (Miller 2007), there is good reason to speculate that exercise-induced changes in these frequency ranges are artifacts caused by intrinsic rhythms (see below).

9.2.2 Event-Related Potentials

Whereas an analysis of the EEGs frequency spectrum allows determining a psycho-cognitive state, event-related potentials (ERPs) are brain responses evoked by thought or perception, for example, time-locked stereotyped electrophysiological responses to an internal or external stimulus. For a description of typical ERP responses, see Hillman et al. (2012) (Fig. 9.1). ERPs are caused by "higher-order" cognitive processes that might involve memory, expectation, and attention. Especially, theta oscillations in frontal and limbic brain areas have been described with ERPs [theta activity being the most stable component of the P300 response (Basar 1998a)] and have shown to be highly correlated with mechanisms of learning and attention as well as retrieval of information (Basar 1998b). ERPs require the repetition of events in order to generate averages, which is used to increase the signal-to-noise ratio (for a recent review, see Pontifex and Hillman 2008).

9.2.3 Electrotomography/Source Localization

A fundamental limitation of traditional EEG recording procedures is the inverse solution, i.e., the challenge in determining activated brain regions by scalp-recorded EEG activity. Approaches such as EEG mapping views or wavelet analysis are restricted to display cortical events as they were recorded on the scalp but do not calculate their three-dimensional origin. Even with multiple electrodes, it has been impossible to obtain a clear localization of the three-dimensional distribution or the origin, power, and orientation of neuro-electrical activity obtained by EEG recordings. In the recent years, electrotomography has become an accepted tool for localizing brain cortical activity (Grech et al. 2008). Electrotomography is a source localization method relying on mathematical models of the bioelectrical generators and the volume conductors within which they are located. The technique is based on standardized EEG recordings, which are subsequently fitted to a probabilistic head model. Active cortical regions are identified by allocating the raw electrotomographical values of individual volume elements (voxels) of the head model to corresponding Brodmann areas (BA) or cerebral gyri. This is achieved, for example, using the coordinates of the digitized Talairach Atlas (Talairach and Tournoux 1988). By comparing different source-localization algorithms like standardized low-resolution brain electrotomography (sLORETA) (Pascual-Marqui 2002; Pascual-Marqui et al. 2002), brain electrical source analysis (BESA) (Hoechstetter et al. 2004), spatiotemporal regularization (ST-MAP) (Galka et al. 2004), multiple-signal classification algorithm (MUSIC) (Mosher and Leahy 1998), and other, it becomes clear that each of these programs has its own specific advantages, but sLORETA was shown to give the most satisfactory results (Grech et al. 2008).

The major advantage of source localization algorithms lies within the possibility to detect three-dimensional changes in neuro-cortical activity by analyzing standardized EEG signals. Electrotomography offers a reliable spatial and temporal detection of brain cortical activity, together with a simple, economical, and noninvasive applicability. Of course, this method is limited by the fact that it uses EEG recordings for localization and therefore is just able to display changes in the cortex, whereas deeper brain regions cannot be captured. Meanwhile, electrotomography is a well-established technique, which has proved reliability and has been validated against fMRI and PET (Bai et al. 2007; Gamma et al. 2004; Mulert et al. 2004).

Source localization algorithms either refer to the model of current density or the frequency model, which allows specifying which frequency dominates at which time point in which area of the brain (Fig. 9.1). Current density, on the other hand, is the measure of the density of flow of electrical charge and is calculated in $\mu A/mm^2$ or for brain activity, as brain regions are split in voxels in $\mu A^2/mm^4$. Therefore, current density defines the electrical activity of neurons in a given area and might be compared to the blood oxygen level dependence (BOLD) signal (Ogawa et al. 1990), which assumes that neuronal activity requires glucose and oxygen delivered through the bloodstream. Nevertheless, current density might be regarded as predominant to this hemodynamic response, especially regarding the temporal resolution.

9.3 EEG Activity and Exercise

9.3.1 Introduction

It is generally agreed that there is a temporary increase in the EEG alpha activity (7.5–12.5 Hz) after exercise: This increase was first reported in the 1950s (Beaussart et al. 1959) and is thought to reflect a state of postexercise relaxation. Although other EEG frequencies (theta [3.5–7.5 Hz], beta [12.5–35 Hz], gamma [>35 Hz]) are believed to play a major role in central processing, cognition, and mood, exercise-induced changes in those frequencies have initially received less attention. However, when analysis of brain cortical activity after exercise was extended to a wider range of frequencies, changes were of similar magnitude to those observed in the alpha range (Crabbe and Dishman 2004; Mechau et al. 1998). Moreover, many studies just took into consideration global field power (GFP) but did not differentiate between different subsystems of the brain, which seem essential when describing the effects of exercise on cognition and emotion. Only recently, attempts were made to attribute exercise-induced changes to specific brain regions, for example, the prefrontal cortex, which seems to play a major role in cognitive processing as well as the regulation of emotion (see also Chaps. 21 and 22). Besides the number of variables that seem to have an influence on brain cortical activity, such as the time span between exercise and measurement after exercise (Kubitz and Pothakos 1997; Schneider et al. 2009b), exercise intensity (Hall et al. 2010), room temperature (Nielsen et al. 2001), type of exercise (Oda et al. 1999), and duration of exercise (Woo et al. 2009), it seems of utter importance to address also the influence of individual differences in fitness level and its relationship to exercise intensity (Pontifex and Hillman 2008). However, not only individual fitness levels (physiological values) but also individual ratings of intensity, duration, and exercise modes are thought to have an influence on brain cortical activity, cognitive performance, and mood (Schneider et al. 2009a, b).

Therefore, instead of only standardizing general parameters of exercise (intensity, duration, environmental temperature), it is proposed to also standardize the perceived attitude toward exercise. It is obvious that a less preferred exercise will show different emotional ratings than ones' preferred kind of exercise. Therefore, psychophysiological approaches need to refrain from traditional exercise tests in a sterile lab. In addition, to display effects of exercise on mental processes, not only the number but also the time schedule of measurements after exercise needs to be standardized (see also Chap. 6).

9.3.2 Data Acquisition and Processing

9.3.2.1 Electrode Positioning

Electrocortical activity is traditionally recorded by highly conductive silver or silver chloride (Ag/AgCl) electrodes. Whereas these electrodes formerly have been stuck

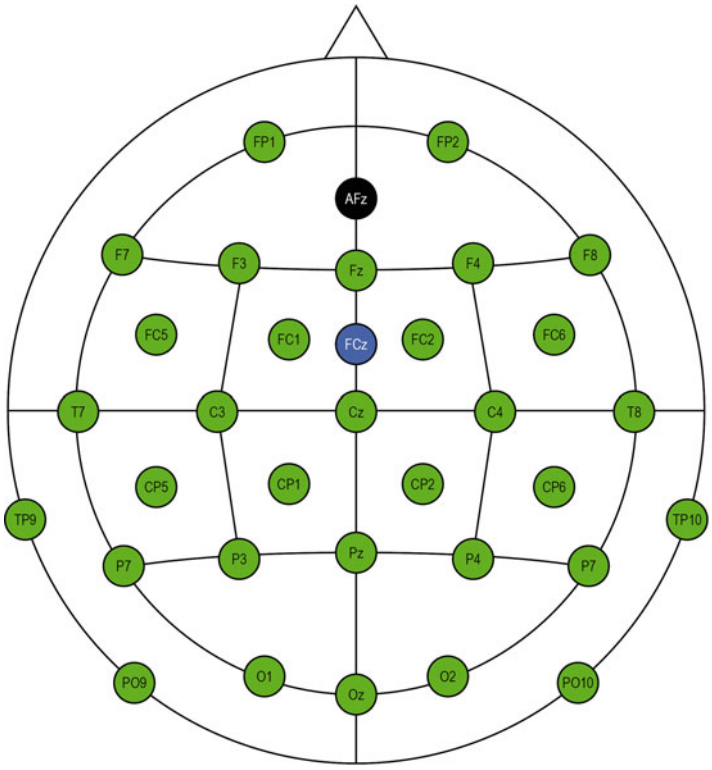

Fig. 9.3 EEG standard montage using 32 electrodes referring to the international 10–20 system. In this montage, FCz is defined as the reference electrode and AFz as the ground electrode

to the scalp using conductive paste, nowadays, electrode caps or electrode nets are used where electrodes are prearranged according to the international 10–20 system (Jasper 1958). Electrodes are placed at sites that correspond to 10% or 20% of a measured length from internationally refereed landmarks on the skull (Fig. 9.3). To reduce heat and sweat production, some experimenters prefer to use an electrode net, instead of a cap. On the other hand, cap fabrics absorb sweat and prevent cross talk between electrodes. Depending on the experimental question, different numbers of electrodes can be used. Simple approaches referring to the model of frontal asymmetry (see also Chap. 21) might therefore require only two electrodes linked to the left and right mastoids or ear lobes. Similarly, approaches interested in biofeedback mechanisms require only a limited number of electrodes. In contrast, software-based source localization methods require a minimum of 19 electrodes distributed across the entire scalp (Grech et al. 2008). In fact, the more electrodes are used, the better the resulting resolution: Whereas 19 electrodes only allow displaying functional differences within a lobe (frontal, temporal, parietal, occipital),

32 or 64 electrodes achieve a resolution at the Brodmann area (BA) level. As sweat might result in cross talk between electrodes, the number of electrodes is limited by exercise intensity. Today, most exercise studies use up to 32 electrodes (Schneider et al. 2010a; Brümmer et al. 2011), which is a good compromise for source localization without major sweat artifacts, as electrodes are arranged in sufficient distance. A higher number of electrodes of up to 256 could be used in the context of less sweat-producing exercise, for example, evaluation of force production on motor cortex activity. If the experimental focus is only a specific brain area, it is also possible to arrange a number of electrodes in vicinity to this region of interest (ROI).

A specific electrolyte gel bridges the electrical conductivity between the scalp and the electrode. This is done with a blunt cannula, which at the same time abrades the skin for better conductance. It is also possible, but more time-consuming, to use an abrasive paste. As electrodes absorb the gel over time, we found it helpful and time-saving to fill up the electrode cups before mounting the cap. However, caution is needed to avoid gel bridges between electrodes when mounting the cap. A good signal transduction requires low resistance of <10 kΩ; hence, impedance measurements for checking adequate resistance should be performed before each new measurement. Most systems allow recording the impedance values for off-line data analyses.

Although preparing a subject with a cap or a net using 32 electrodes does not take more than 5–10 min, when done by an experienced experimenter, in most studies, the electrodes will remain on the scalp during exercise. Therefore, the position of the electrodes should be carefully checked prior to each new recording. Especially, electrotomography requires a very careful positioning and control of the electrodes during the course of an experiment.

9.3.2.2 Reference

The EEG voltage signal represents the difference between the voltages at two electrodes. There are different ways to define to which electrode the recorded signal on a specific position (e.g., Fp1) is "referenced":

- Bipolar reference: Difference between two adjacent electrodes, for example, the channel "Fp1-F3" represents the difference in voltage between the Fp1 electrode and the F3 electrode.
- Single reference: Each channel represents the difference between a certain electrode and a designated reference electrode.
- Average reference: The outputs of all electrodes are summed and averaged, and this averaged signal is used as the common reference for each channel.

In addition, one distinguishes between active and passive references: Active references are located on the scalp, i.e., the recorded EEG signal is a difference between the activity under the reference electrode and any other electrode. Often, Cz or another point above the midline is used, as cortical activity is lowest here. Current cap or net systems often have an integrated reference located in the triangle of Fp1, Fp2, and Fz. In contrast, passive electrodes are located in regions that do not show

any activity, for example, located at the mastoids or earlobes on the contralateral side (e.g., Fp1 to right earlobe).

In the area of exercise science, there is no advantage or disadvantage concerning a specific reference model. As most caps have an integrated reference, this makes data recording and subject preparation easy and should be used. Although modern data recording systems allow to rereference the signal off-line, electrode montage as well as reference electrode should be kept constant during the course of one study.

9.3.2.3 Recording

Data recording is performed at a rate between 256 and 2,000 Hz. In most exercise EEG studies, one recording is performed ahead of an exercise intervention and several times after this intervention. We would propose to cover a wide range of time points starting <1 min after exercise, continue 15 min after exercise, and 30 min after exercise at a minimum. The recording should last at least 2, better 3 min, to have an adequate time span for analysis. If required, this time span might be subdivided into minutes, allowing a detailed analysis of the effects of exercise. Recordings are usually performed during eyes-closed states so that changing visual inputs do not affect the EEG. Otherwise, a carefully controlled eyes-open condition should lead to similar results, but both methods should not be mixed within one study. Traditionally, it is recommended to record EEGs recordings in a quiet, shielded room with the subject sitting still and the experimenter being located in a separated room in order to prevent noise artifacts. Although this is desirable, today, highly sophisticated portable EEG systems allow also for field recordings (e.g., BrainAmp family by Brain Products, battery powered and designed to be used in extreme environments, e.g., in Antarctica, the MARS500 study, during roller coaster or table tennis). While external stimuli may influence the data quality, there are ways to control for these effects.

Especially when analyzing effects of exercise, which per se is a nonlaboratory "life" event, on mood and cognitive performance (see also Chap. 22), the effects of a natural exercise setting compared to a sterile lab environment should not be underestimated. In addition, today's recording software is designed to add markers or comments during pertinent recordings, whereby special events that might have an impact on the EEG data and can be marked for subsequent analysis.

There is some debate whether subjects should be in a seated or supine position for the EEG recording, but as long as the recording is repeated in the same position and analysis compares two measurements performed at the same position, this can be neglected. After exhaustive exercise, experimenters need to take care that subjects do not pass out. Here, a supine position might be more comfortable than sitting on a bike ergometer.

9.3.2.4 Technological Developments

Recent technological developments offer further possibilities to record EEGs even during exercise. So far, movements of experimental participants were probably the

most prominent source for artifacts (see below). A new generation of EEG electrodes including a noise reduction amplifier at the electrode enable to record a nearly artifact free EEG signal until submaximal exercise levels (e.g., on a bike, Fig. 9.4; Brümmer et al. 2011). In addition, active shielding can be used, where a signal is passed down the outer shielding layer of the cable to block external electromagnetic interference. To allow for further mobility, a wireless system using active electrodes has recently been introduced by, for example, Brain Products (MOVE).

Although there are some initial promising results using dry electrodes, i.e., electrodes that do not require any gel for improved conductance, their actual size does not permit placement of a sufficient number on the scalp. Nevertheless, for specific experimental conditions like assessment of frontal asymmetry or biofeedback, these electrodes offer interesting opportunities.

9.3.2.5 Artifact Rejection

Before analysis, the data should be routinely inspected visually. Whereas AC/DC artifacts (50 Hz Europe/Asia/Africa/Australia; 60 Hz N/S America) can be easily avoided using a notch filter, sometimes electromagnetic artifacts (e.g., through interference with technical equipment) are not recognized before a frequency analysis is performed. Often, this type of artifact results in a clear peak over all electrodes.

In the waking rest EEG, most artifacts are visible upon inspection. Especially, eye blink artifacts as well as horizontal drifts, which are caused by activity of the eye muscles, can be identified easily as they result in a strong peak (blinks) or a delta wave (lateral eye movements) mainly in Fp1 and Fp2. Modern software based on independent component analysis (ICA) allows to identify and reject pertinent artifacts (Romo-Vazquez et al. 2007). Alternatively, eye movement artifacts can be identified with one or two additional channels that record the electrooculogram (EOG = activity of the eye muscles). The EOG should ideally consist of a horizontal channel (one electrode lateral to the left and right eye) and one vertical channel (one electrode above and under one eye). Another source of muscular artifacts can result from jaw movements, typically manifesting at positions T7/T8.

When subjects are studied during exercise, muscular artifacts increase considerably. Muscular activity mainly occurs above 20 Hz (Pontifex and Hillman 2008). Therefore, the most dominant frequency, alpha activity, is not contaminated with muscular artifacts. ICA is the method of choice to eliminate muscular artifacts that contaminate other frequency ranges (Crespo-Garcia et al. 2008). Again, one method besides visual inspection to eliminate muscular artifact is to use ICA (Crespo-Garcia et al. 2008). ICA, first described by Bell and Sejnowski (1995), is a higher-order statistical method which was developed to extract individual signals (components) from composition of signals, based on the assumption that different physical processes (sources) will generate unrelated signals (Delorme et al. 2007; Onton et al. 2006).

EEG measurements postexercise might be blurred with ECG or respiration artifacts. In nearly all of our studies, we have found very unspecific and global changes in the delta and lower theta frequency range. Some interesting correlations with intrinsic

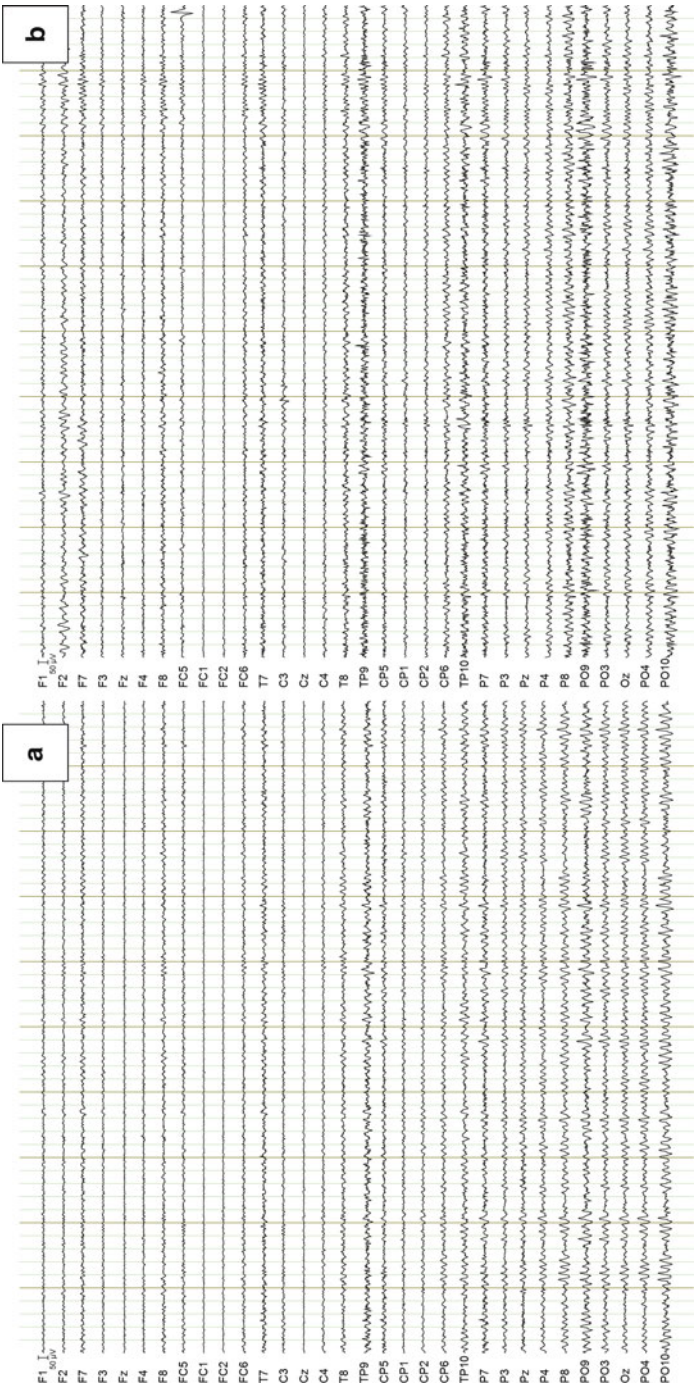

Fig. 9.4 Ten seconds of electrocortical activity recorded by an active EEG system (actiCAP®) at different sites after applying low-pass (6 Hz) and high-pass (50 Hz) filters at rest (**a**) and during the penultimate stage of a bike ergometry (**b**)

and extrinsic rhythms (Schneider et al. 2010b) let us speculate that this increase is due to artifacts either from the cardiovascular system or similar oscillatory effects (e.g., respiration) postexercise, especially running. There is a peak around 2 Hz in the gravity axis when analyzing oscillations of the center of gravity during locomotion (MacDougall and Moore 2005; Murray et al. 1964). It is assumed that this highly tuned locomotor frequency reflects the intrinsic temporal domain of the spinal central pattern generator (MacDougall and Moore 2005). These generators have been established as the basis for locomotor rhythmicity in invertebrates, fish, and cats (Grillner 1985; Grillner and Wallen 1985). Although their existence in humans can only be inferred from indirect evidence (Dietz 2003; Marder 2001), it can be assumed that this oscillation is maintained by oscillatory neurons after exercise. This notion is speculative and requires the inclusion of movement or acceleration data to better establish the relationship between delta activity and oscillatory activity of neurons in the central nerval system. In addition, sweat artifact is known to produce similar low-frequent and high-potential fluctuations. For a more in-depth discussion of artifacts and issues related to their removal, see Talsma and Woldorff (2005).

9.3.2.6 Data Acquisition and Processing

There are a number of software solutions to process EEG data, the most prominent being EEGLAB, which is an open-source Matlab-based toolbox for electrophysiological research. Alternatively, a number of commercial software tools exist that do not require Matlab (e.g., BrainVision Analyzer).

For frequency analyses, the EEG is low- and high-pass filtered (depending on the frequency band to be analyzed). Then, the data are segmented in ±4 s epochs (10% overlap accepted). A systematic artifact rejection protocol is followed (visual inspection, ICA, automated exclusion procedures), and the segments containing artifacts are excluded from further analyses. If the number of rejected segments is too high and only parts of the rejected segments are affected, a possibility is to increase the number of segments by defining shorter (e.g., 2 s) epochs. After the data have been baseline-corrected and frequency-analyzed, the data are averaged across all remaining segments. After visual inspection of the frequency bands, the data are exported within each frequency range for statistical analysis.

For ERP analyses, identical steps are followed, only that the data are segmented around a time-locked event and no frequency analysis is performed. Instead, the data are filtered, and artifact-corrected segments are averaged across all segments.

9.4 Summary

EEG can be regarded as the classical neurophysiological assessment. Although current brain imaging techniques like fMRI outmatch EEG regarding spatial resolution, the specific characteristics of exercise as well as improving software

(e.g., electrotomography) and hardware (e.g., active electrodes) technologies make EEG recordings the method of choice to determine *acute* cortical effects of exercise. EEG is the only tool that allows analyzing changes in brain cortical activity *during* exercise and offers a number of principal advantages compared to, for example, fMRI:

- EEG is comparably inexpensive.
- EEG sensors can be employed in a wider range of environments.
- EEG enables higher temporal resolution in the order of milliseconds.
- EEG in combination with electrotomography provides a means of noninvasively investigating the localization of changes in brain cortical activity in response to exercise.

In addition, EEG recordings can be combined with fMRI recordings, thus making use of the inherent advantages of both techniques. Especially for exercise studies, it seems advisable to combine EEG and NIRS studies (see also Chap. 10), as both are easy to apply in an exercise setting, and provide a means to investigate neurovascular coupling, describing the coherence between hemodynamic changes and neuronal activity, in the context of exercise challenges (Fumoto et al. 2010).

The disadvantage of EEG recordings arises from the fact that the EEG just covers the cortex and cannot capture deeper brain regions. Applying EEG data to an average head model using source localization algorithms might blur effects when pictured on an individual level. Here, it is recommended to apply these EEG data to an individual head model received from an MRI scan.

References

Axmacher N, Mormann F, Fernandez G, Elger CE, Fell J (2006) Memory formation by neuronal synchronization. Brain Res Rev 52:170–182

Bai X, Towle VL, He EJ, He B (2007) Evaluation of cortical current density imaging methods using intracranial electrocorticograms and functional MRI. Neuroimage 35:598–608

Basar E (1998a) Brain function and oscillations: Volume I: Brain oscillations. Principles and approaches. Springer, New York

Basar E (1998b) Brain function and oscillations: Volume II: Integrative brain function. Neurophysiology and cognitive processes. Springer, New York

Beaussart M, Niquet G, Gaudier E, Guislain F (1959) [The EEG of boxers examined immediately after combat. Comparative study with the EEG recorded before combat in 52 cases]. Rev Obstet Ginecol Venez 101:422–427

Bell AJ, Sejnowski TJ (1995) An information-maximization approach to blind separation and blind deconvolution. Neural Comput 7:1129–1159

Benwell NM, Mastaglia FL, Thickbroom GW (2007) Changes in the functional MR signal in motor and non-motor areas during intermittent fatiguing hand exercise. Exp Brain Res 182:93–97

Boecker H, Henriksen G, Sprenger T, Miederer I, Willoch F, Valet M, Berthele A, Tolle TR (2008) Positron emission tomography ligand activation studies in the sports sciences: measuring neurochemistry in vivo. Methods 45:307–318

Bonnet MH, Arand DL (2001) Impact of activity and arousal upon spectral EEG parameters. Physiol Behav 74:291–298

Brümmer V, Schneider S, Strüder HK, Askew CD (2011) Primary motor cortex activity is elevated with incremental exercise intensity. Neuroscience 181:150–162

Caglar E, Sabuncuoglu H, Keskin T, Isikli S, Keskil S, Korkusuz F (2005) In vivo human brain biochemistry after aerobic exercise: preliminary report on functional magnetic resonance spectroscopy. Surg Neurol 64(Suppl 2):S53–S56, discussion S56–S57

Crabbe JB, Dishman RK (2004) Brain electrocortical activity during and after exercise: a quantitative synthesis. Psychophysiology 41:563–574

Crespo-Garcia M, Atienza M, Cantero JL (2008) Muscle artifact removal from human sleep EEG by using independent component analysis. Ann Biomed Eng 36:467–475

Delorme A, Sejnowski T, Makeig S (2007) Enhanced detection of artifacts in EEG data using higher-order statistics and independent component analysis. Neuroimage 34:1443–1449

Dietz V (2003) Spinal cord pattern generators for locomotion. Clin Neurophysiol 114:1379–1389

Duzel E, Penny WD, Burgess N (2010) Brain oscillations and memory. Curr Opin Neurobiol 20:143–149

Fumoto M, Oshima T, Kamiya K, Kikuchi H, Seki Y, Nakatani Y, Yu X, Sekiyama T, Sato-Suzuki I, Arita H (2010) Ventral prefrontal cortex and serotonergic system activation during pedaling exercise induces negative mood improvement and increased alpha band in EEG. Behav Brain Res 213:1–9

Galka A, Yamashita O, Ozaki T, Biscay R, Valdes-Sosa P (2004) A solution to the dynamical inverse problem of EEG generation using spatiotemporal Kalman filtering. Neuroimage 23:435–453

Gamma A, Lehmann D, Frei E, Iwata K, Pascual-Marqui RD, Vollenweider FX (2004) Comparison of simultaneously recorded [H2(15)O]-PET and LORETA during cognitive and pharmacological activation. Hum Brain Mapp 22:83–96

Gray CM, Singer W (1989) Stimulus-specific neuronal oscillations in orientation columns of cat visual cortex. Proc Natl Acad Sci USA 86:1698–1702

Grech R, Cassar T, Muscat J, Camilleri KP, Fabri SG, Zervakis M, Xanthopoulos P, Sakkalis V, Vanrumste B (2008) Review on solving the inverse problem in EEG source analysis. J Neuroeng Rehabil 5:25

Grillner S (1985) Neurobiological bases of rhythmic motor acts in vertebrates. Science 228:143–149

Grillner S, Wallen P (1985) Central pattern generators for locomotion, with special reference to vertebrates. Annu Rev Neurosci 8:233–261

Hall EE, Ekkekakis P, Petruzzello SJ (2010) Predicting affective responses to exercise using resting EEG frontal asymmetry: does intensity matter? Biol Psychol 83:201–206

Hillman CH, Kamijo K, Pontifex MB (2012) The relation of ERP indices of exercise to brain health and cognition. In: Boecker H, Hillman CH, Scheef L, Strüder HK (eds) Functional neuroimaging in exercise and sport sciences. Springer, New York

Hoechstetter K, Bornfleth H, Weckesser D, Ille N, Berg P, Scherg M (2004) BESA source coherence: a new method to study cortical oscillatory coupling. Brain Topogr 16:233–238

Jasper HH (1958) The ten-twenty electrode system of the international Federation. Electroencephalogr Clin Neurophysiol Suppl 35:371–375

Kirschstein T, Kohling R (2009) What is the source of the EEG? Clin EEG Neurosci 40:146–149

Klimesch W, Sauseng P, Hanslmayr S (2007) EEG alpha oscillations: the inhibition-timing hypothesis. Brain Res Rev 53:63–88

Kubitz KA, Pothakos K (1997) Does aerobic exercise decrease brain activation? J Sport Exerc Psychol 19:291–301

Lindsley DB (1960) Attention, consciousness, sleep and wakefulness. In: Field J, Magoun HW, Hall VE (eds) Handbook of physiology. American Physiological Society, Washington, DC, pp 1553–1593

MacDougall HG, Moore ST (2005) Marching to the beat of the same drummer: the spontaneous tempo of human locomotion. J Appl Physiol 99:1164–1173

Marder E (2001) Moving rhythms. Nature 410:755

Martin JH (1991) The collective electrical behavior of cortical neurons: the electroencephalogram and the mechanisms of epilepsy. In: Kandel ER, Schwartz JH, Jessel TM (eds) Principles of neuroscience. Prentice-Hall, London, pp 777–791

Mechau D, Mucke S, Weiss M, Liesen H (1998) Effect of increasing running velocity on electroencephalogram in a field test. Eur J Appl Physiol Occup Physiol 78:340–345

Miller R (2007) Theory of the normal waking EEG: from single neurones to waveforms in the alpha, beta and gamma frequency ranges. Int J Psychophysiol 64:18–23
Mosher JC, Leahy RM (1998) Recursive MUSIC: a framework for EEG and MEG source localization. IEEE Trans Biomed Eng 45:1342–1354
Mulert C, Jager L, Schmitt R, Bussfeld P, Pogarell O, Moller HJ, Juckel G, Hegerl U (2004) Integration of fMRI and simultaneous EEG: towards a comprehensive understanding of localization and time-course of brain activity in target detection. Neuroimage 22:83–94
Murray MP, Drought AB, Kory RC (1964) Walking patterns of normal men. J Bone Joint Surg Am 46:335–360
Nielsen B, Hyldig T, Bidstrup F, Gonzalez-Alonso J, Christoffersen GR (2001) Brain activity and fatigue during prolonged exercise in the heat. Pflugers Arch 442:41–48
Oda S, Matsumoto T, Nakagawa K, Moriya K (1999) Relaxation effects in humans of underwater exercise of moderate intensity. Eur J Appl Physiol Occup Physiol 80:253–259
Ogawa S, Lee TM, Nayak AS, Glynn P (1990) Oxygenation-sensitive contrast in magnetic resonance image of rodent brain at high magnetic fields. Magn Reson Med 14:68–78
Onton J, Westerfield M, Townsend J, Makeig S (2006) Imaging human EEG dynamics using independent component analysis. Neurosci Biobehav Rev 30:808–822
Pascual-Marqui RD (2002) Standardized low-resolution brain electromagnetic tomography (sLORETA): technical details. Methods Find Exp Clin Pharmacol 24(Suppl D):5–12
Pascual-Marqui RD, Esslen M, Kochi K, Lehmann D (2002) Functional imaging with low-resolution brain electromagnetic tomography (LORETA): a review. Methods Find Exp Clin Pharmacol 24(Suppl C):91–95
Pontifex MB, Hillman CH (2008) Neuroelectric measurement of cognition during aerobic exercise. Methods 45:271–278
Romo-Vazquez R, Ranta R, Louis-Dorr V, Maquin D (2007) EEG ocular artefacts and noise removal. Conf Proc IEEE Eng Med Biol Soc 2007:5445–5448
Schneider S, Askew CD, Diehl J, Mierau A, Kleinert J, Abel T, Carnahan H, Strüder HK (2009a) EEG activity and mood in health orientated runners after different exercise intensities. Physiol Behav 96(4–5):709–716
Schneider S, Brümmer V, Abel T, Askew CD, Strüder HK (2009b) Changes in brain cortical activity measured by EEG are related to individual exercise preferences. Physiol Behav 98:447–452
Schneider S, Askew CD, Abel T, Mierau A, Strüder HK (2010a) Brain and exercise: a first approach using electro tomography. Med Sci Sports Exerc Mar 42:600–607
Schneider S, Askew CD, Abel T, Strüder HK (2010b) Exercise, music, and the brain: is there a central pattern generator? J Sports Sci 28(12):1337–1343
Talairach J, Tournoux P (1988) Co-planar stereotaxic atlas of the human brain. Thieme, Stuttgart
Talsma D, Woldorff MG (2005) Methods for the estimation and removal of artifacts and overlap in ERP waveforms. In: Handy TC (ed) Event-related potentials: a methods handbook. MIT, Cambridge, pp 116–148
Thomas R, Stephane P (2008) Prefrontal cortex oxygenation and neuromuscular responses to exhaustive exercise. Eur J Appl Physiol 102:153–163
Thompson T, Steffert T, Ros T, Leach J, Gruzelier J (2008) EEG applications for sport and performance. Methods 45:279–288
Wang XJ (2010) Neurophysiological and computational principles of cortical rhythms in cognition. Physiol Rev 90:1195–1268
Wong SW, Kimmerly DS, Masse N, Menon RS, Cechetto DF, Shoemaker JK (2007) Sex differences in forebrain and cardiovagal responses at the onset of isometric handgrip exercise: a retrospective fMRI study. J Appl Physiol 103:1402–1411
Woo M, Kim S, Kim J, Petruzzello SJ, Hatfield BD (2009) Examining the exercise-affect dose-response relationship: does duration influence frontal EEG asymmetry? Int J Psychophysiol 72(2):166–172
Zuckermann M (1991) Psychobiology of personality. Cambridge University Press, New York

Chapter 10
NIRS: Theoretical Background and Practical Aspects

Matthias Kohl-Bareis

Abstract In this chapter, an introduction to near-infrared spectroscopy (NIRS) as a tool for brain functional monitoring and imaging is presented. The basic physical principles are outlined for the measurement of physiological parameters like cortical haemoglobin oxygenation and blood flow. The advantages of spatially resolved as well as time- and frequency-domain techniques are discussed and compared with the modified Lambert–Beer approach which is used in most topographic imaging systems.

10.1 Introduction

Optical methods seem perfectly suited for the monitoring and imaging of brain functions in sports as the required instrumentation is potentially portable, lightweight, and easy to use. Therefore, it can cope with both lab and outdoor environment. Since the pioneering work by Jobsis (1977), near-infrared spectroscopy (NIRS) has been widely applied, with two of the main applications in the neurosciences and in the exercise and muscle physiology. The technical aspects are very similar for both applications, with the main objective to non-invasively retrieve information of haemoglobin oxygenation and blood perfusion.

Since it has been shown that NIRS can monitor functional activity in the brain of adults (Chance et al. 1993; Hoshi and Tamura 1993; Kato et al. 1993; Villringer et al. 1993), a vast number of work has been performed to show the usefulness of the method for the assessment of neurovascular coupling, with the emphasis on different functions and brain areas (e.g. visual, motor, auditory cortex, or cognitive tasks).

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The objective of this chapter is to outline the very basic of the optical methods for the monitoring and imaging of brain functions and discuss technical and methodological issues. It is not attempted to review all work that has been done over the last years but rather to summarize the concepts for a successful application of the instrumentation in the sports science environment. Reviews can be found in the literature (Villringer and Chance 1997; Madsen and Secher 1999; Obrig and Villringer 2003; Hoshi 2003; Hillman 2007; Wolf et al. 2007). The perspective taken here is from the methodological point of view and applications during exercise are discussed in a later chapter of this volume (see also Chap. 14).

10.2 Measurement Principle of NIRS

The starting point for any discussion of near-infrared spectroscopy of biological tissue is the wavelength dependence of the main tissue absorbers (chromophores). Surprisingly, the transport of light in tissue is governed by a very limited number of absorbers as well as the scattering properties. Generally, the absorption of a chromophore in a non-scattering medium is defined by the Lambert–Beer law, which relates the attenuation A to the absorption coefficient μ_a. A is calculated from the light intensity before (I_0) and after (I) the probed volume:

$$A = \log_e\left(\frac{I_0}{I}\right) = \mu_a \cdot L = \sum_i \varepsilon_i \cdot c_i \cdot L. \tag{10.1}$$

Here L is the optical path length in the probe which is the geometrical length without scattering. μ_a corresponds to the product of the extinction coefficient ε and the concentration c of the absorbers, with a sum over all chromophores (i). The physical unit of μ_a is an inverse length, and the inverse of μ_a can be interpreted as a penetration depth, i.e. the distance where the light intensity has dropped to $1/e \approx 0.37$.

The absorption spectrum of pure water (Fig. 10.1) explains a large number of facts in tissue optics as well as the light conditions during diving or the cooking by a microwave oven. Only the visible and near-infrared wavelength range shows a low μ_a with a minimum of about 10^{-5} mm^{-1} corresponding to a penetration depth of about 100 m. For the UV and the IR range, the penetration depth is as low as a few μm. Next to water, the strongest absorber for most tissues is the haemoglobin in both its oxygenated and deoxygenated component (oxyHb, deoxyHb; see Fig. 10.1) which has a high absorption in the UV and VIS range. For this reason, only NIR wavelengths in the narrow optical window from about 650 to 1,000 nm are suitable to probe deep tissues.

The scattering properties of the tissue determine the light transport and depend on differences in the refractive index (n) between cell compartments and extra- and intracellular fluids, the geometry of the scattering particles, and the relative

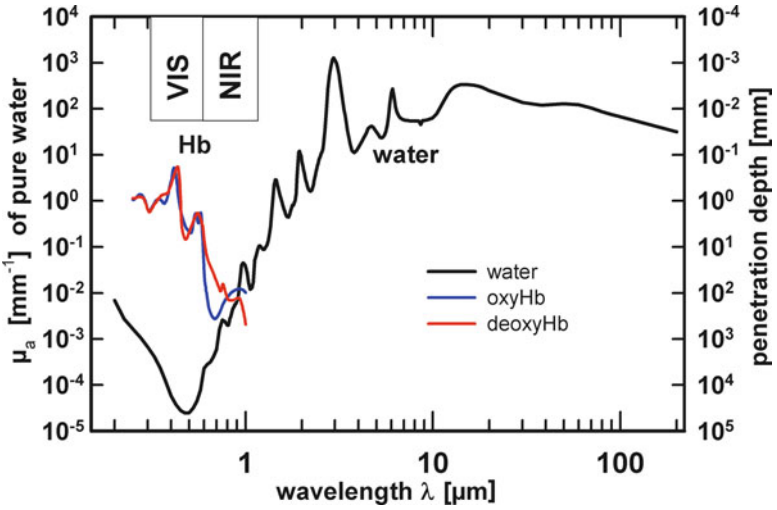

Fig. 10.1 Absorption spectrum (μ_a, *left-hand scale*) of pure water from the UV to IR wavelength range. The penetration depth ($1/\mu_a$) can be read by the *right-hand scale*. For the visible (VIS) and near-infrared (NIR) range, the haemoglobin absorption (Hb, for both the oxygenated and deoxygenated form, details see Fig. 10.3) is given as well

size between particle and wavelength. The number of scattering events per length is in the order of $0.5–5 \times 10^2$ mm^{-1} with a scattering strongly in the forward direction. After many scattering events, i.e. when the optical path length is large, the transport of light is well described by a diffusive process which is governed by the transport scattering coefficient μ'_s. The inverse of μ'_s has the physical interpretation as the length after which the scattering appears to be isotropic, i.e. independent of the scattering angle. In this multi-scattering regime, any polarization of light is lost and can be ignored. μ'_s is a monotonic decreasing function with wavelength.

Any instrumentation that attempts to gain information of tissues deeper than a few mm needs to detect light at a source-detector distance (r) from the injection point. The key questions are: How much light, i.e. how many photons, are reflected back? What is the dependence on the absorption and scattering properties and the wavelength dependence? How does light travel in the tissue and what is the depth sensitivity? Does the measurement of the photon transit time contain any useful information? Answers to these physical questions can then be linked to tissue physiology.

For an understanding of the NIRS methods, it is instructive to consider the measurement parameters as a function of the absorption and scattering coefficients. For a homogeneous, semi-infinite medium described by μ_a, μ'_s and the refractive index n, the diffuse reflectance $R(r)$, i.e. the number of photons emitted at a distance r from the source position per unit of the detector area, and the mean photon path

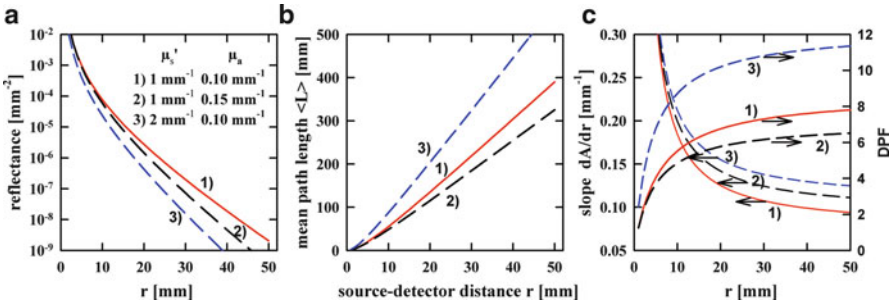

Fig. 10.2 (**a**) Example of light reflectance R as a function of source-detector distance r calculated for a homogeneous semi-infinite medium. Three different sets of transport scattering and absorption coefficients are considered. (**b**) For the same parameters, the mean optical path length $\langle L \rangle$ is shown. In (**c**) the slope $\partial A/\partial r$ for a detector area of 1 mm^2 and the differential path length factor $\mathrm{DPF} = \langle L \rangle / r$ is plotted

length $\langle L \rangle$, i.e. the mean-transit time $\langle t \rangle(r)$ multiplied by the velocity of light c, can be expressed as

$$R(r) = \frac{1}{\mu_s'} \cdot \left(\frac{1}{\rho} + \mu_{\mathrm{eff}} \right) \cdot \frac{\exp(-\mu_{\mathrm{eff}} \cdot \rho)}{2\pi \cdot \rho^2} \tag{10.2}$$

and

$$\langle L \rangle(r) = c \cdot \langle t \rangle = \frac{\rho^2}{2(D + \rho \cdot \sqrt{\mu_a \cdot D})}, \tag{10.3}$$

respectively (Patterson et al. 1989; Arridge et al. 1992). Here is $\rho = (r^2 + 1/\mu_s'^2)^{1/2}$ and the velocity of light in the medium $c = c_0/n$ (where the speed of light in vacuum is $c_0 = 3 \times 10^{11}$ mm/s). $\mu_{\mathrm{eff}} = (3 \cdot \mu_a(\mu_a + \mu_s'))^{1/2}$ is known as the effective attenuation coefficient and $D = (3 \cdot (\mu_a + \mu_s'))^{-1}$ is the diffusion coefficient. Though somewhat simplifying the situation by e.g. ignoring the boundary effects between tissue and air, these equations are a fair description of the general properties of detected light.

In Fig. 10.2a, the reflectance $R(r)$ is plotted for three combinations of μ_s' and μ_a, and the following conclusions can be derived: It is apparent that R drops rapidly with increasing source-detector distance r. In many lab situations, the experimentalist is tempted to increase the source-detector distance in order to increase the depth sensitivity (see below). But the figure shows that this comes at a price of lower signal amplitude. As a rough estimation for most tissues, an increase in the source-detector distance Δr of about 10 mm gives a drop in intensity by about one order of magnitude. The magnitude of R is low, typically in the range of 10^{-6}–10^{-7} of the incident light intensity for a detector area of 1 mm^2 at $r = 30$ mm. For an incident power of 1 mW, this corresponds to a reflected intensity in the sub-nW range.

This indicates one difficulty in all NIRS measurements of brain functions: the intensity and the signal-to-noise ratio are potentially very low. The effect of different $\mu'_s - \mu_a$-combinations is apparent in Fig. 10.2a. It is obvious that a stronger absorption results in a lower intensity emitted at r. A similar effect can be seen from the data for a stronger scattering and this might be counter-intuitive. However, it can be understood by the mean path length $\langle L \rangle$ of the light in tissue, which is shown in Fig. 10.2b. $\langle L \rangle$ increases with r, and this increase is approximately linear for large r. A higher absorption (line 2) suppresses all photons with a large path length more strongly, and consequently the mean path length is lower. In contrast, a higher scattering (line 3) increases the mean path length of the detected photons.

The mean path length is further analysed by plotting the ratio $\langle L \rangle / r$, which is called differential path length factor (DPF) in the modified Lambert–Beer approach (see below). For larger r, the DPF is approximately independent of r; however, it depends on the absorption and scattering properties. Here, it has values in the range of 5–10. This roughly corresponds to experimental data on muscle or head (e.g. Essenpreis et al. 1993). Furthermore, when converting the reflectance data of Fig. 10.2a into attenuation $A = \log(I_0/R)$, the derivative data $\partial A/\partial r$ of Fig. 10.2c are obtained. It is apparent that this derivative (slope) depends on the scattering and absorption coefficients, and this can be used in the spatially resolved approach (see below).

While the data of Fig. 10.2 give a rough picture of what is to be expected for light reflected from tissue, it has to be noted that the absorption and scattering coefficients are wavelength dependent. Therefore, the wavelength has an imprint on all these measurement parameters; spectroscopic measurements at different wavelengths therefore supply further information.

10.3 Measurement of Absorption Properties: Haemoglobin

Though NIRS allows a number of tissue parameters to be measured, the most widely exploited functional marker is haemoglobin which is accessible by the wavelength-dependent extinction spectra of the oxygenated and deoxygenated form (oxyHb, deoxyHb, respectively). From Fig. 10.3, it is apparent that the absorption in the NIR is much lower than in the VIS and that the spectra have fairly broad peaks. Different concepts have been developed to determine haemoglobin concentrations (c_{oxyHb}, and c_{deoxyHb}), either as a trend or as absolute values and these will be discussed below. Next to the concentrations, the tissue oxygen saturation

$$\mathrm{SO}_2 = \frac{c_{\mathrm{oxyHb}}}{c_{\mathrm{oxyHb}} + c_{\mathrm{deoxyHb}}} \tag{10.4}$$

is of interest. SO_2 is a relative number and therefore less prone to errors due to e.g. uncertainties in scattering or optical path length. In some instruments and work, the tissue oxygen saturation SO_2 is called tissue oxygenation index (TOI).

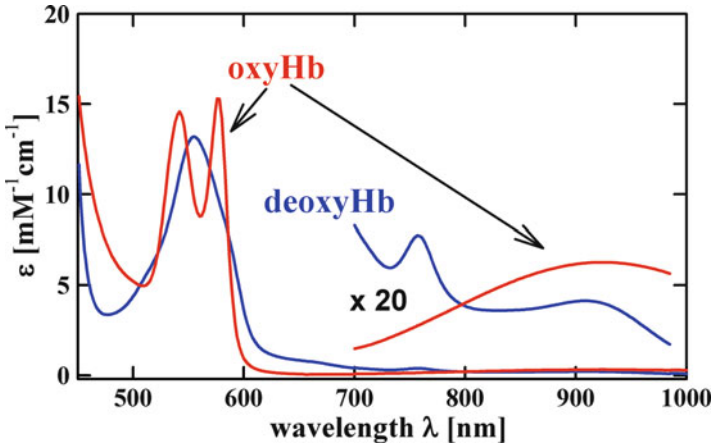

Fig. 10.3 Extinction spectra of oxygenated and deoxygenated haemoglobin (oxyHb, deoxyHb) in the VIS and NIR wavelength range. For better readability, the spectra have been scaled by factor of 20 for $\lambda > 700$ nm

In muscle the contribution of myoglobin to the absorption needs to be taken into account, which can be ignored for functional brain studies. NIRS is sensitive to haemoglobin in the smaller vessels of the microcirculation. In larger veins or arteries, the high concentration of haemoglobin has the effect of a "black hole" on the photons, i.e. all photons are absorbed and no information about these large vessels can be retrieved.

The concept of neurovascular coupling is based on relating an increased functional activity and oxygen consumption to changes in blood flow and oxygenation (see also Chaps. 11 and 12). The close relationship of NIRS haemoglobin data to the BOLD (blood oxygenation level dependent) contrast in fMRI, which predominantly monitors deoxyHb, is obvious. As in fMRI where stimulus related changes are usually monitored, a recording of trends is sufficient for NIRS in many cases. Surprisingly, there are still some differences in the published haemoglobin extinction spectra and its wavelength dependence (Prahl 2001; BORL 2005) which have minor effects on the calculated haemoglobin spectra. More important to note is that some of the published spectra are based on the haem group and others on the functional group (tetrahaem) of the haemoglobin molecule giving a difference of 4 in the magnitude of haemoglobin concentrations.

From the different NIRS approaches to measure haemoglobin, the following are most widely used:

10.3.1 Modified Lambert–Beer Law/Quantified Trend Measurements

The most widely used approach is based on relative measures of intensity of a single source, single detector combination (see Fig. 10.4a). It has been noted (Delpy et al.

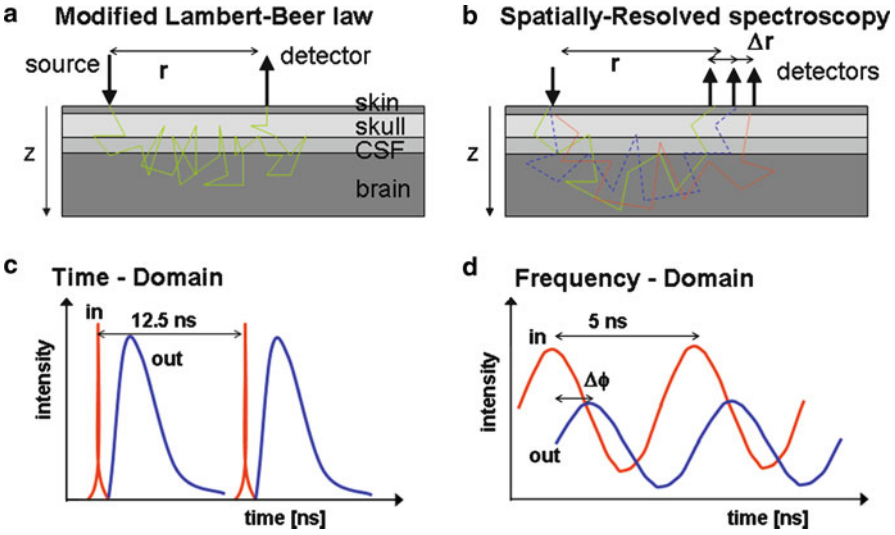

Fig. 10.4 (**a**) A single source and a single detector are sufficient for the modified Lambert–Beer approach. (**b**) Spatially resolved spectroscopy requires at least two distances. (**c**) Timing diagram for time-domain spectroscopy (TDS) with short laser pulses and delayed and temporally broadened reflectance. (**d**) In frequency-domain spectroscopy (FDS) the phase (delay) of a modulated intensity wave is measured

1988; Delpy and Cope 1997) that in a scattering medium (10.1) does not hold but needs to be adapted:

$$A(\lambda) = \log_e\left(\frac{I_0}{R}\right) = \mu_a \cdot r \cdot \mathrm{DPF} + G. \tag{10.5}$$

Again, R is the reflectance. G is constant depending both on the geometry and the tissue properties (μ_a, μ'_s). The differential path length factor (DPF) takes into account that the path length in tissue is longer than the source-detector distance r. Generally, both G and the DPF are unknown and therefore an absolute quantification of μ_a is not feasible. However, when only small changes are considered, it can be written

$$\Delta A(\lambda) = \log\left(\frac{R_{\mathrm{ref}}}{R}\right) = \Delta\mu_a \cdot r \cdot \mathrm{DPF}, \tag{10.6}$$

i.e. changes with respect to the reflectance R_{ref} at a reference time are calculated. The product r·DPF corresponds to the mean optical pathlength in tissue which has already been discussed above (compare with Fig. 10.2b) and can experimentally be obtained from frequency-domain or time-domain measurements (see below).

Once changes in attenuation have been measured at a number of wavelengths, concentration changes of chromophores can be calculated. In particular, when

assuming that only the concentration changes of oxyHb and deoxyHb give rise to attenuation changes, a linear set of equations can be written with one equation for each wavelength:

$$\Delta A(\lambda) = \Delta\mu_a(\lambda) \cdot r \cdot \mathrm{DPF}(\lambda) = (\varepsilon_{\mathrm{oxyHb}}(\lambda) \cdot \Delta c_{\mathrm{oxyHb}} + \varepsilon_{\mathrm{oxyHb}}(\lambda) \cdot \Delta c_{\mathrm{oxyHb}}) \cdot r \cdot \mathrm{DPF}(\lambda). \quad (10.7)$$

In vector notation, this reads as

$$\overrightarrow{\Delta A} = \overline{\overline{E}}_{\mathrm{DPF}} \cdot \overrightarrow{\Delta c}, \quad (10.8)$$

with the $1 \times n$ vector of attenuation changes for n wavelengths $\overrightarrow{\Delta A}$, and the $2 \times n$ matrix $\overline{\overline{E}}_{\mathrm{DPF}}$ containing the extinction coefficients of oxyHb and deoxyHb at the n wavelengths, each multiplied by the DPF at the corresponding wavelength. $\overrightarrow{\Delta c}$ is the 2×1 vector with the two unknown concentration changes. Equation (10.8) can be solved for $\overrightarrow{\Delta c}$.

This approach is still widely used, in both lab prototypes and commercial instruments. The main advantage is its simplicity and the low instrumental demand due to the continuous wave (cw) technique. The experimental set-up does not require more than one source and one detector position and a recording of intensity changes at a minimum of two wavelengths. It is important to recognize that these trend values of $\overrightarrow{\Delta c}$ assume that, first, the DPF(λ)-spectrum is known, and, second, the concentration changes are homogeneous throughout the tissue. For the monitoring of brain function, this does not hold and as the haemoglobin changes are likely to be restricted to cortical tissue, the calculated haemoglobin changes would appear smaller than they are in the limited activated volume. For a discussion of the expected depth sensitivity, see below. The disadvantage is that absolute values of tissue haemoglobin cannot be obtained and, therefore, the oxygen saturation not determined.

10.3.2 Spatially Resolved Spectroscopy

Next to the modified Lambert–Beer law, the spatially resolved approach is most widely used. Its principle is shown in Fig. 10.4b with three closely arranged detectors and one source. Above it has been pointed out that the slope $\partial A,\ \mathrm{r}$ of attenuation with respect to source-detector distance r depends on the tissue absorption coefficient. Assuming a homogeneous scattering tissue the absorption coefficient μ_a can be expressed in analytical form as

$$\mu_a(\lambda) = \frac{1}{\mu'_s(\lambda)} \cdot \frac{1}{3} \cdot \left(\ln(10) \frac{\partial A(\lambda)}{\partial r} - \frac{2}{r} \right)^2 \quad (10.9)$$

(Matcher et al. 1995; Suzuki et al. 1999). The slope $\partial A/\partial r$ can be approximated by the experimental data of $\Delta A/\Delta r$, and therefore the μ_a-spectrum is assessable by a cw intensity measurement. The haemoglobin concentrations can be obtained by inverting the linear set of equations given by

$$\overrightarrow{\mu_a} = \overline{\overline{E}} \cdot \vec{c}, \tag{10.10}$$

with $\overline{\overline{E}}$ being the matrix of the extinction coefficients of the chromophores at all wavelengths. Again, the underlying assumption is a homogeneous medium. Furthermore, the μ_a-spectrum contains components from other chromophores like lipid and water, which either are subtracted or need to be included in the matrix inversion.

There are a number of important differences to the modified Lambert–Beer approach: First, absolute haemoglobin values are obtained and therefore the tissue oxygen saturation SO_2 can be calculated. Second, SRS probes somewhat deeper tissues than MLB law (see below). Third, while in the MLB law DPF values are needed which are either taken from the literature or require a separate measurement, in the SRS approach the scattering coefficient is required. μ'_s values might differ by more than ±10% for the same site on different subjects. While this directly translates in uncertainties in the calculated concentrations, the oxygen saturation is unaffected as it is a relative measure. Therefore, SO_2 data are likely to be more robust to differences between measurement sites or subjects.

10.3.3 Time-Domain Spectroscopy

When illuminating the tissue with a short light pulse, the path length in the tissue is different for different photons and therefore the reflectance is temporally spread. The shortest time travelled between source and detector corresponds to $t_{min} = r/c = r/c_0 \cdot n$, i.e. for $r = 40$ mm, $c_0 = 3 \times 10^{11}$ mm/s, and $n = 1.4$, this gives $t_{min} = 40/(3 \times 10^{11}) \times 1.4$ s $= 1.87 \times 10^{-10}$ s $= 0.187$ ns. This estimate illustrates that the required temporal resolution is very high and non-standard instrumentation is needed. Figure 10.4c illustrates the experimental situation, with a train of short (laser) light pulses at a typical separation of 12.5 ns (corresponding to 80 MHz repetition rate) illuminating the tissue and the reflected light emerging with a delay and a broad temporal spread. As for (10.2) and (10.3), in the homogeneous medium there are analytical solutions for the full description of the temporal spread of the reflectance, which is

$$R(r,t) = (4 \cdot \pi \cdot D \cdot c)^{-3/2} \frac{1}{\mu'_s} \cdot t^{-5/2} \exp(-\mu_a \cdot c \cdot t) \cdot \exp\left(\frac{-(\rho^2 + 1/\mu'^2_s)}{4 \cdot D \cdot c \cdot t}\right) \tag{10.11}$$

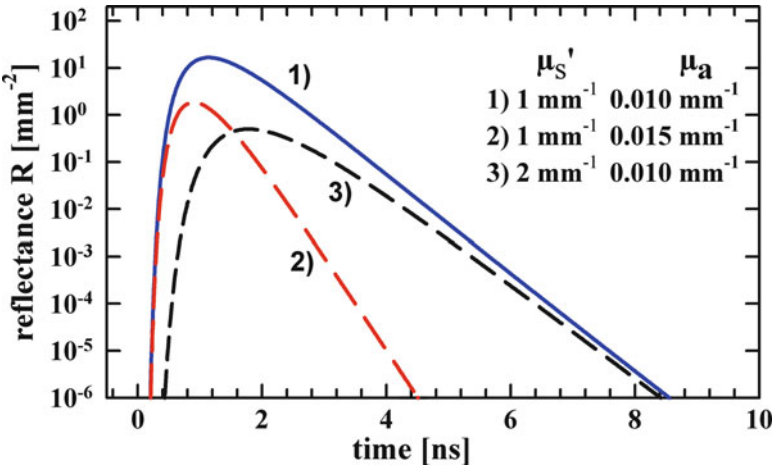

Fig. 10.5 Time-dependent reflectance R calculated for an infinite short light pulse injected at time $t=0$ ns at a distance $r=40$ mm for the same optical parameters of a homogeneous semi-infinite medium as used in Fig. 10.2. Note that the time axis is in units of nanoseconds (ns) and that the reflectance is in logarithmic scale

(Patterson et al. 1989). In Fig. 10.5 data calculated from (10.11) are plotted for the same optical parameters as in Fig. 10.2. It is apparent that the temporal spread is much larger than t_{min} and that it depends on both the scattering and absorption properties. A higher absorption "squeezes" the function as photons with a longer path length are further suppressed (absorbed). In contrast, a larger scattering pushes the function towards longer times. When the aim is to measure haemoglobin, i.e. the tissue absorption coefficient, it has been shown in the literature that this analytical function can directly be fitted to experimental reflectance data with μ_a and μ'_s as fitting parameters (e.g. Patterson et al. 1989; Delpy et al. 1988; Essenpreis et al. 1993; Matcher et al. 1997; Torricelli et al. 2001). Furthermore, it has been pointed out that for large times t the reflectance $R(t)$ is approximated by $\exp(-\mu_a.c.t)$. Therefore μ_a can be determined from the asymptotic slope of $\log(R)$ versus t (Chance et al. 1988; Patterson et al. 1989). This behaviour can be seen in Fig. 10.5. In practice, however, a limited dynamic range and noise of the detector restrict this approach.

In NIRS, time-domain spectroscopy (TDS) has been first applied to quantify the DPF (Delpy et al. 1988). TDS has further been exploited for the discrimination of absorption changes in different tissue layers (Steinbrink et al. 2001; Liebert et al. 2004) and topographical purposes (Schmidt et al. 2000).

10.3.4 Frequency-Domain Spectroscopy/Intensity-Modulated Spectroscopy

Next to TDS, the frequency-domain spectroscopy (FDS) has been developed to gain information both on photon path length and optical tissue properties. When modulating

the intensity of a light source with frequency ν_M (compare Fig. 10.4d), the modulated light reflected from the tissue has a phase shift $\Delta\Phi$ which is related to the mean time of flight and therefore the path length:

$$\Delta\Phi = 2\pi \cdot \nu_M \cdot \langle t \rangle = \frac{2\pi}{\lambda_M}\langle L \rangle = \frac{2\pi \cdot \nu_M}{c_0 / n}\langle L \rangle \tag{10.12}$$

Here use is made of the relationship $c = \lambda_M \cdot \nu_M$ between the modulation frequency ν_M and the modulation wavelength λ_M as well as $c = c_0 / n = \langle L \rangle / \langle t \rangle$. As the phase shift scales with ν_M, frequencies in the radio range are required to generate measurable shifts in optics where c is large. In most instruments developed ν_M is in the range 100–300 MHz, though some instruments work up to 1 GHz. In tissue ($n = 1.4$) an intensity wave modulated at 200 MHz (corresponding to $T = 1/\nu_M = 5$ ns) would have a wavelength λ_M of about 1 m. Therefore, for a typical mean path length of 0.2 m (compare with Fig. 10.2) the phase shift is about $2/5 \cdot \pi$ rad.

Next to the instrumentation, algorithms have been developed for the diffusive regime to calculate tissue scattering and absorption coefficients from frequency-domain spectroscopy (Patterson et al. 1991; Tromberg et al. 1993; Pogue and Patterson 1994; Fantini et al. 1994; Fishkin et al. 1995; Kohl et al. 1997; Chance et al. 1998). Equations (10.3) and (10.12) already point at a close association between the path length (or phase or $\langle t \rangle$) measurements and μ_a and μ'_s of the tissue. Mathematically, FDS and TDS are related via a Fourier transform, i.e. both approaches would generate the same information when $\Delta\Phi$ is measured at all frequencies ν_M.

The hardware of a FDS system is simpler than a TDS system especially after advances in the GHz-electronics took place with the rapid development of telecommunication. Since the advent of solid-state lasers with short pulse lengths, most experimental labs seem to prefer TDS. Nevertheless, the main advantages of FDS are that the instruments are potentially easier to use and more robust than TDS. FDS systems have been successfully applied in functional brain monitoring.

10.3.5 Derivative Spectroscopy

The key obstacle for an easy quantification of haemoglobin is the light scattering which has the effect to generate an unknown attenuation offset. However, this can be eliminated by analysing the derivates of attenuation A with respect to wavelengths, e.g. $\partial A/\partial\lambda$, $\partial^2 A/\partial\lambda_2$, or higher orders (Matcher et al. 1993). While this can supply absolute chromophore concentrations, this method is not well suited for functional studies of the brain as it is sensitive to tissue inhomogeneities and rather slow.

10.3.6 Optical Topography and Tomography

Clearly a limitation of the before mentioned approaches is a lack of spatial resolution which is crucial for a detection of small foci of functional activation. To this end,

systems comprising many light source positions and detectors can be employed, where the signal of each source-detector pair is analysed according to cw, TDS, or FDS method. The ideal instrument provides a 3D-imaging of haemoglobin which requires both demanding technology and reconstruction algorithms (e.g. Hebden et al. 2002; Schmitz et al. 2002; Arridge 1999). For most functional studies, this approach is too slow, demanding, and cumbersome to be applied. When mapping functional changes of haemoglobin, the simple and robust MLB approach (see above) is well suited and multi-source, multi-detector systems have been successful to detect and differentiate between different cortical areas like the motor, auditory, visual, or somatosensory centres (Yamashita et al. 1996; Koizumi et al. 2003; and references in Hillman 2007). With this topographic approach, functional activation has been mapped during exercise (Miyai et al. 2001; Suzuki et al. 2008; Atsumori et al. 2010). Furthermore, a multi-modal imaging combining NIRS with fMRI or EEG has been achieved in a number of studies. The spatial resolution is limited by the source-detector distances and in most cases >5–10 mm, though an interpolation for display purposes might pretend a higher resolution. A combination of imaging and multi-distance measurement allows a rough depth differentiation to be achieved (e.g. Boas et al. 2004) and models were developed for an better understanding of the limits of functional activation studies (e.g. Steinbrink et al. 2001; Kawaguchi et al. 2004).

10.4 Other Optical Measurement Parameters

Over the last years a number of other NIRS signals have been looked at as potential parameters for the status of the brain function and neurovascular coupling.

10.4.1 Cytochrome-Oxidase

Starting with the early work by Jobsis (1977), one of the main attractions of NIRS was the potential to monitor oxygen sufficiency of the brain by the intracellular chromophore cytochrome oxidase, which would give a direct, mitochondrial oxygenation status rather than the supply conditions given by haemoglobin. The concentration of cytochrome does not change during a function activation and therefore its oxygenation level is accessible by including a third extinction spectrum in the MLB law analysis. Much work focussed on the detection of these changes in the redox state of cytochrome oxidase in vivo by the MLB law (Wray et al. 1988; Cooper and Springett 1997; McGown et al. 2003) and functional changes of cytochrome oxidase have been reported (Obrig et al. 2000). However, it must be noted that there are many issues that might confound the interpretation of observed attenuation changes, notably that a localized absorption changes in a functional focus might cause crosstalk between the chromophores when the calculation assumes a homogeneous medium. Some of the first commercial instruments (e.g. NIRO-1000, 500, and 300 by Hamamatsu Photonics, Japan) included a calculation of cytochrome oxidase changes. The latest

monitors by Hamamatsu Photonics (NIRO-100, NIRO-200) and other companies do not incorporate cytochrome oxidase as a measurement parameter, and this must be taken as a statement of a lack of confidence in the robustness of this signal.

10.4.2 Blood Flow and Perfusion

Next to haemoglobin and oxygenation data, blood flow changes are correlated with functional activation and therefore a key parameter for a functional monitoring of cortical activation. It is desirable to measure perfusion as the combined knowledge of haemoglobin and perfusion is potentially able to supply data on the cerebral metabolic rate of oxygen ($CMRO_2$) (Dunn et al. 2005). Optical spectroscopy is in routine use for blood flow measurements in tissue, with laser-Doppler monitoring and imaging and—more recent—laser speckle contrast imaging as the methodological approaches (Bonner and Nossal 1981; Briers 2001). The low depth sensitivity of these methods, however, allows only perfusion data to be retrieved from the upper few mm, at most. To achieve a sufficient depth sensitivity for transcranial blood flow of brain tissue in humans, an extension of the laser-Doppler method has been developed called diffuse correlation spectroscopy (DCS) or diffusive wave spectroscopy that measures the autocorrelation function of laser light reflected from tissue. It has been shown to measure cortical blood flow changes in humans (Durduran et al. 2004; Li et al. 2005). The published data seem to limit hopes for a common and widespread application of coherent blood flow monitoring of cortical tissue during exercise challenges due to a poor signal-to-noise ratio. However, rapid technical innovations especially for photon detectors might deliver significant improvements in the near future.

As an alternative approach for blood perfusion monitoring of cortical tissue, the bolus tracking of a light absorbing dye has been established. Especially the dye indocyanine green (ICG) is well suited with its absorption spectrum close to 800 nm (Prahl 2001). It has FDA approval and is in routine use for liver and cardiac function tests. Following an intra-venous injecting of ICG, absorption changes are monitored with a delay relative to the dye bolus depending on the perfusion or blood flow. This method has been successfully tried e.g. for stroke monitoring (Kuebler et al. 1998; Gora et al. 2002; Liebert et al. 2005). As an alternative to the light absorption signal of the ICG bolus, its ICG fluorescence which peaks at a wavelength close to 800 nm can serve as a independent measure for blood perfusion (Liebert et al. 2006). However, transient blood flow changes following functional activation might be too fast to be assessable with the ICG bolus method.

10.4.3 Scattering Changes and Fast Optical Signals

Besides the vascular, haemodynamic response following a functional activation it has been claimed for some time that there is a fast signal directly correlating with the electrophysiological changes in brain. This has been found in studies on peripheral

nerves and the opened cortex (Cohen et al. 1968; Rector et al. 2005) and can be understood as linked to scattering changes due to shifts in electrolytes during neuronal activation. It is plausible that this translates to a NIRS signal that is characterized by a short latency with respect to the stimulus onset, and in a number of publications this signal has been found to correlate with the sensory input (e.g. Gratton et al. 2006, and other publications by the same group). Steinbrink et al. (2005) shed doubts on the existence of this signal by model estimates and experimental data of exceptional signal-to-noise ratio and analysis of movement artefacts. It seems highly unlikely that there will be a robust fast optical signal in NIRS for any application in exercise studies or in any other area of neuroscience.

10.5 Photon Propagation in Tissue, Depth Sensitivity, and Spatial Resolution

For a detection of brain functional activation, the propagation of photons in the brain has been investigated in experiments and described in physical and mathematical models. Analytical solutions for the measurement parameters only exist for simple geometries of the scattering volume like a semi-infinite halfspace, a cylinder, or layered structures (e.g. Arridge et al. 1992). For other geometries mainly Monte Carlo simulations are exploited which follow the statistical path of many photons through the medium. For layered media, some of these programs are available as open source (e.g. Wang et al. 1995; Alerstam et al. 2008). In Fig. 10.6 an example is shown for a head model where different absorption and scattering properties were attributed to geometries of skull, cerebrospinal fluid (CSF), and grey and white brain matter (Okada et al. 1997). Superimposed on this geometry is the calculated statistical propagation density for photons that were injected at the source and detected at a distance. The “banana shape” of this propagation density marks two key attributes of the NIRS method: First, the spatial, lateral resolution is fairly low. Second, the depth sensitivity is high enough to detect cortical signals, but is insufficient to probe deeper brain areas. It must be kept in mind that all these simulations are based on rough assumptions of geometry and especially the optical tissue properties, which are difficult to determine and might vary between subjects.

Figure 10.7 illustrates the depth sensitivity of a homogeneous layered medium for the modified Lambert–Beer (MLB) and the spatially resolved spectroscopy (SRS) methods calculated from Monte Carlo simulations. The relative sensitivity is plotted as a function of depth z for source-detector distances $r = 20$, 30, 40, and 50 mm. For SRS, the slope $\Delta A/\Delta r$ is the measurement parameter and mean detector separations of 30 and 40 mm were considered. For MLB it is apparent that the depth sensitivity has a strong bias towards the upper tissue layers with the function peaking at a depth $z = 6$–8 mm. The fast decaying sensitivity for larger depths indicates that functional changes from deeper brain layers will have low amplitude and that any small extracerebral hemodynamic changes might dominate. A larger source-detector distance does help to increase the depth profile. Surprisingly, the SRS approach probes deeper

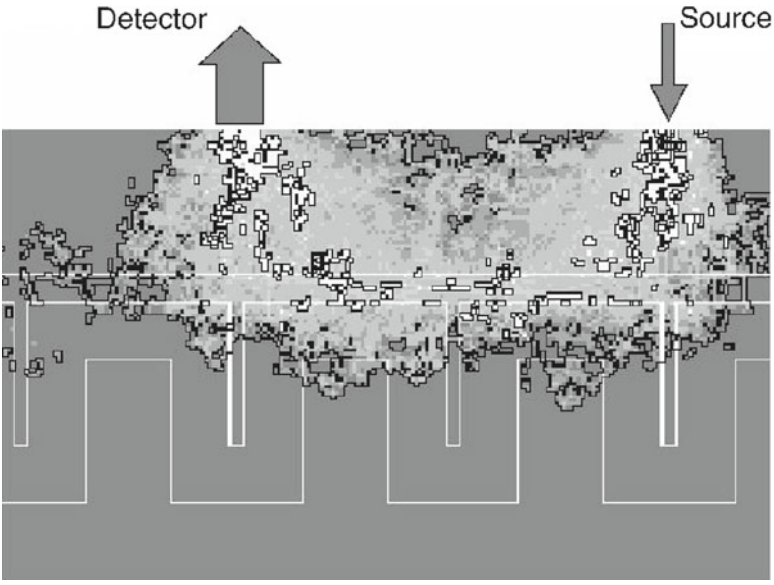

Fig. 10.6 Example of a model of the head with cortical and extracortical tissue, showing the propagation density ("banana shape") of photons travelling from source to detector (Okada et al. 1997)

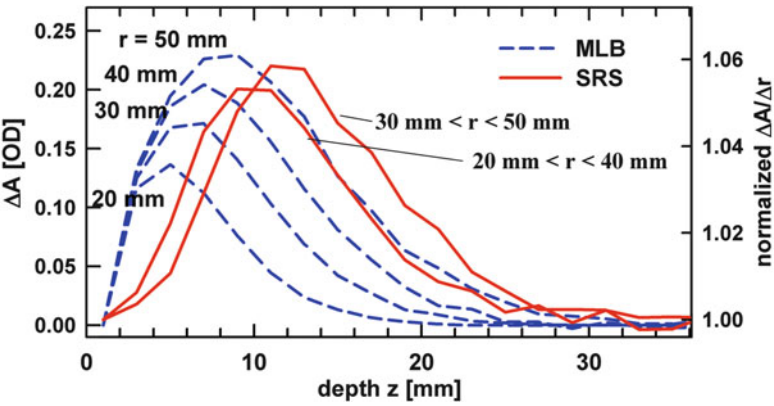

Fig. 10.7 Estimation of the depth sensitivity of NIRS monitoring for a homogeneous tissue model ($\mu_a = 0.01$ mm^{-1}, $\mu'_s = 1$ mm^{-1}). The relative sensitivity is shown for the modified Lambert–Beer (MLB; *dashed lines*) and the spatially resolved spectroscopy (SRS; *solid lines*) approach for different source-detector distances

tissues. The sensitivity is especially low for the upper few mm, indicating that hemodynamic changes in the skin are suppressed. From this perspective, SRS is advantageous compared to MLB for functional monitoring, and subjects with thinner skulls might give a stronger signal. Further calculations indicate that this difference is

further enhanced when a highly absorbing (melanin) skin is included. These estimates describe the overall picture of the depth sensitivity, though inhomogeneities of the tissues or localized functional activation might alter the sensitivity somewhat.

10.6 NIRS Instrumentation, Practical Aspects and Limitations

10.6.1 NIRS Instrumentation

In the growing literature of NIRS applied to brain functional monitoring, there is an abundance of instrumentation employed based on cw, TDS, or FDS. A list of commercial and non-commercial instruments for monitoring and imaging can be found in the literature (Wolf et al. 2007). There are a number of technical issues which are discussed for the NIR methods in the following section.

10.6.1.1 Light Source/Choice of Wavelengths

In the literature there is a plethora of different light sources in terms of wavelengths, number of wavelengths etc. and the obvious question is for the best choice. All the tissue spectra in the NIR are fairly broad, and therefore the narrow line width of a laser ($\Delta\lambda < 0.1$ nm) is of negligible advantage compared to a LED with line width of typically 5–10 nm. Therefore, some of the more recent instruments make use of the rapid advances in terms of output power and available wavelengths of LEDs. More severe is the rather poor beam quality of LEDs compared to lasers resulting in a low coupling efficiency into optical fibres. A recent trend is to directly attach LEDs to the skin.

It is tempting to assume that the quantification of haemoglobin is improved by a higher number of wavelengths. This, however, is not necessarily true. Any quantification of haemoglobin is based on the inversion of a linear set of equations (see (10.10)) which is over-determined (i.e. has more wavelengths than the number of unknowns oxyHb and deoxyHb) when using more than two wavelengths. This set of linear equations is likely to have the smallest crosstalk between oxyHb and deoxyHb for a specific pair of wavelengths. Any additional wavelength adds information for the quantification of other chromophores (like lipid, water, or cytochrome), for an analysis and quantification of errors (residuum), or for the use of different algorithms. This applies especially to broadband systems based on a white light source and a spectrograph which can record at 100 or more different wavelengths. When a standard algorithm of the data analysis like MLB is applied and no quality check of the data is intended or integrated in the software, the user might consider using a two wavelengths system. Some of the best matched wavelengths are around 850, 760 nm (where the absorption of deoxyHb peaks), and 690 nm. Both laser diodes and LEDs can be modulated and switched at frequencies in the 1–10 kHz range to enable e.g. lock-in detection for a higher signal-to-noise ratio.

While the early work on TDS made use of mode-locked laser systems for the generation of short laser pulses ($\Delta t < 5$ ps), in recent years pulsed diode laser with a

pulse width of about 100 ps is available for a number of wavelengths in the NIR. A high repetition rate of typically 80 MHz makes these lasers well suited for time-correlated single photon counting (TCSPC) as the technical approach for TDS, though the pulse length of diode lasers is typically 100–150 ps. Other pulsed sources (e.g. fibre lasers) are currently tested for the TCSPC and will certainly be used for tissue optics, especially after prices have come down and further technical improvements make them reliable for applications outside the optics lab. For FDS there is an abundance of laser diodes and even LEDs which can be intensity modulated at >100 MHz.

To comply with laser safety requirements, the irradiated power density of skin is usually kept below 2 mW/mm^2.

10.6.1.2 Detectors

As has already been pointed out when discussing Fig. 10.2, one of the main obstacles for the sensitive detection of cortical tissue is a low signal intensity, i.e. a low signal-to-noise ratio; therefore, sensitive detectors are needed. Silicon (Si) diodes are well suited due to their sensitivity peak at around $\lambda = 800$ nm (depending somewhat on type) and large detector areas. To achieve a higher sensitivity, avalanche photo diodes based on Si are often employed, as they give a higher output current per detected photon.

For the single photon counting detector needed in TDS, mainly photomultiplier tubes (PMT) are employed, which combine a high sensitivity, large detector area, and a sufficiently low noise with the required time resolution. The drawback of this detector type is in some cases an insufficient sensitivity in the NIR. Furthermore, they can more easily be damaged by mechanical impact or high light input, which makes them somewhat unsuited for a rough lab environment. Avalanche photo diodes can replace PMTs for TDS at a price of a lower detector area and a higher noise. In recent years, different new types of solid-state detectors combining the advantages of PMTs and Si-diodes were introduced to the market. For portable instrumentation mainly Si-detectors are in use as they are light weight and have low power consumption.

As the reflectance from the tissue is fairly low, ambient light might cause severe problems and therefore is often blocked by dark cloth around the detectors or suppressed by phase-sensitive detection techniques (lock-in) based on the light intensity modulated in the kHz range. An optical band-pass filter transmitting only in the NIR range in front of the detector can further reduce ambient light. Neurovascular coupling induced changes in haemoglobin vary typically on the timescale of a second; therefore, a time resolution of 1–2 Hz for the detection system is sufficient in most cases.

10.6.1.3 Optical Fibre Probes

In most cases optical fibres, often called “optodes”, are used for the transport of light. The transmission of these fibres (glass or quartz in most cases) is very high even at a length of a few metres and not restricting the signal quality. However, the bending radius of fibres is limited making them somewhat cumbersome to

position and fixate on the tissue. Often, fibre bundles of a few mm diameter consisting of single fibres (each ∅ = 30–50 μm) are used which have a relative active area of 50–60%. A severe practical limitation is the high weight when imaging at many source-detector positions. This will also result in increased movement artefacts. The rough estimate of intensity (see Fig. 10.2) gives a drop by about 25% per mm source-detector (i.e. fibre) displacement, which would translate into a big haemoglobin artefact. Therefore, the tight fixation of the fibres is crucial. As a consequence, the reliable placement of optical fibres over the same anatomical site might be challenging when not having a large number of positions. Crucial is the design of the fibre tip which connects with the tissue. A straight fibre tip is helpful for easy placement and to remove hair while a bended tip is better to guide the fibre bundle away from the head and facilitating fixation.

10.6.1.4 Compatibility with MRI & EEG

For a combined measurement with magnetic resonance imaging (MRI) the NIRS system has to be equipped with long and non-magnetic optical fibres. Otherwise, no further adaptation has to be done. Similarly, the integration with EEG recordings is straightforward and can be achieved by optical fibre bundles integrated in the EEG ring electrodes. In some respect, EEG and NIRS data suffer from comparable artefacts due to movements and problems of electrode and fibre positioning and fixation.

10.6.1.5 Portable Instrumentation

For application in e.g. exercise studies, NIRS systems can relative easily be miniaturized when limiting the specifications somewhat. Instrumentation based on continuous wave techniques like MLB, SRS, and multi-site measurements has been built with LEDs as sources, Si-detectors, and data acquisition and evaluation based on a microcontroller or digital signal processor (DSP). Battery-driven instrumentation can be built that either store data on-board or transmit them via wireless connection. Some of these portable systems have been described in the literature (e.g. Wolf et al. 2007; Atsumori et al. 2010).

10.6.2 Practical Limitations

10.6.2.1 Effect of Extracerebral Signals

One severe problem for the monitoring of brain activation is that extracerebral haemoglobin changes might occur and mimic brain function. A time correlation analysis of NIRS signals and stimuli, as well as topographic mapping, is therefore helpful

tool for discrimination of cortical and extracortical signals. However, heart rate, breathing, and vasomotion at much lower frequencies have been observed in NIRS signals of the head (Obrig et al. 2000). Even small variations in blood pressure might mimic activation, and a stimulus correlation has been found (Boden et al. 2007; Franceschini et al. 2003). During exercise, this might create a severe problem when large, systemic shifts in the cardiovascular system occur. The estimate of the depth sensitivity (compare Fig. 10.7) gives a rough indication that especially large changes in blood flow and oxygenation of skin might dominate smaller signals from deeper cortical layers. A monitoring of skin haemoglobin and oxygenation might help to rule out artefacts due to extracerebral variations and this seems even more advisable when being familiar with the often small and fragile cortical signals.

10.6.2.2 Usefulness of Different Haemoglobin Parameters

In contrast to fMRI-BOLD, NIRS provides data both on oxyHb and deoxyHb (and possibly of SO_2). Surprisingly, however, there seems to be limited additional information in the two haemoglobin signals. In some of the functional NIRS work mainly oxyHb is analysed and in other predominantly deoxyHb. Typically, the magnitude of the increase in oxyHb following functional activation is bigger than the deoxyHb decrease by a factor of 2–3. Therefore, the oxyHb signal should have the better signal-to-noise ratio. However, extracortical changes due to systemic changes e.g. in blood pressure or heart rate are more likely to influence oxyHb than deoxyHb. The observed haemoglobin dynamic is very different between individuals, which might be due to the variability in anatomy or skull thickness rather than due to differences in true Hb concentration changes.

10.6.2.3 Low Light Intensity

Besides skin melanin, light absorption by dark hair and follicles often limits the sensitivity of NIRS, and this might prevent the inclusion of some subjects. Therefore, some labs have a bias to use bold, fair skinned subjects to collect stronger NIRS signals.

10.7 Outlook

NIRS has shown to add valuable information about neurovascular coupling in humans. The main attraction is the relative simplicity of the method and its low demand in terms of equipment with the potential to supply data when other methods cannot be used. For example, NIRS can be applied at bed-site or in protocols that prevent the use of MRI. The potential of NIRS for exercise applications seems promising, as NIRS can be applied during exercise (see also Chap. 14). However,

artefacts induced during the exercise condition need to be carefully controlled for, especially due to blood flow and haemoglobin changes in the extracortical tissue.

References

Alerstam E, Svensson T, Andersson-Engels S (2008) Parallel computing with graphics processing units for high speed Monte Carlo simulation of photon migration. J Biomed Opt 13:060504

Arridge SR (1999) Optical tomography in medical imaging. Inverse Probl 5:41–93

Arridge S, Cope M, Delpy DT (1992) The theoretical basis for the determination of optical pathlengths in tissue: temporal and frequency analysis. Phys Med Biol 37:1531–1560

Atsumori H, Kiguchi M, Katura T, Funane T, Obata A, Sato H, Manaka T, Iwamoto M, Maki A, Koizumi H, Kubota K (2010) Noninvasive imaging of prefrontal activation during attention-demanding tasks performed while walking using a wearable optical topography system. J Biomed Opt 15:046002

Boas DA, Chen K, Grebert D, Franceschini MA (2004) Improving the diffuse optical imaging spatial resolution of the cerebral hemodynamic response to brain activation in humans. Opt Lett 29:506–1508

Boden S, Obrig H, Kohncke C, Benav H, Koch SP, Steinbrink J (2007) The oxygenation response to functional stimulation: is there a physiological meaning to the lag between parameters? Neuroimage 36:100–107

Bonner R, Nossal R (1981) Model for laser Doppler measurements of blood flow in tissue. Appl Opt 20:2097–2107

BORL (2005) http://www.ucl.ac.uk/medphys/research/borl/intro/spectra

Briers JD (2001) Laser Doppler, speckle and related techniques for blood perfusion mapping and imaging. Physiol Meas 22:R35–R66

Chance B, Nioka S, Kent J, McCully K, Fountain M, Greenfeld R, Holtom G (1988) Time resolved spectroscopy of hemoglobin and myoglobin in resting and ischemic muscle. Anal Biochem 174:698–707

Chance B, Zhuang Z, UnAh C, Alter C, Lipton L (1993) Cognition-activated low-frequency modulation of light absorption in human brain. Proc Natl Acad Sci USA 90:3770–3774

Chance B, Cope M, Gratton E, Ramanujam N, Tromberg B (1998) Phase measurement of light absorption and scatter in human tissues. Rev Sci Instrum 69:3457–3481

Cohen LB, Keynes RD, Hille B (1968) Light scattering and birefringence changes during nerve activity. Nature 218:438–441

Cooper CE, Springett R (1997) Measurement of cytochrome oxidase and mitochondrial energetics by nearinfrared spectroscopy. Philos Trans R Lond B Biol Sci 352(1354):669–676

Delpy DT, Cope M (1997) Quantification in tissue near-infrared spectroscopy. Philos Trans R Soc Lond B Biol Sci 352(1354):649–659

Delpy DT, Cope M, van der Zee P, Arridge SR, Wray S, Wyatt JS (1988) Estimation of optical pathlength through tissue from direct time of flight measurements. Phys Med Biol 33:1433–1442

Dunn AK, Devor A, Dale AM, Boas DA (2005) Spatial extent of oxygen metabolism and hemodynamic changes during functional activation of the rat somatosensory cortex. Neuroimage 27:279–290

Durduran T, Yu G, Burnett MG, Detre JA, Greenberg JH, Wang J, Zhou C, Yodh AG (2004) Diffuse optical measurement of blood flow, blood oxygenation, and metabolism in a human brain during sensorimotor cortex activation. Opt Lett 29:1766–1768

Essenpreis M, Elwell CE, Cope M, van der Zee P, Arridge SR, Delpy DT (1993) Spectral dependence of temporal point spread functions in human tissues. Appl Opt 32:418–425

Fantini S, Franceschini MA, Fishkin JB, Barbieri B, Gratton E (1994) Quantitative determination of the absorption spectra of chromophores in strongly scattering media: a light emitting diode based technique. Appl Opt 33:5204–5213

Fishkin JB, So PT, Cerussi AE, Fantini S, Franceschini MA, Gratton E (1995) Frequency-domain method for measuring spectral properties in multiple-scattering media: methemoglobin absorption spectrum in a tissue like phantom. Appl Opt 34:1143–1155

Franceschini MA, Fantini S, Thompson JH, Culver JP, Boas DA (2003) Hemodynamic evoked response of the sensorimotor cortex measured non-invasively with near-infrared optical imaging. Psychophysiology 40:548–560

Gora F, Shinde S, Elwell CE, Goldstone JC, Cope M, Delpy DT, Smith M (2002) Measurement of cerebral blood flow in adults using near infrared spectroscopy and indocyanine green. J Neurosurg Anesthesiol 14:218–222

Gratton G, Brumback CR, Gordon BA, Pearson MA, Low KA, Fabiani M (2006) Effects of measurement method, wavelength, and source-detector distance on the fast optical signal. Neuroimage 32:1576–1590

Hebden JC, Gibson A, Yusof R, Everdell N, Hillman E, Delpy DT, Arridge S, Austin T, Meek J, Wyatt J (2002) Three-dimensional optical tomography of the premature infant brain. Phys Med Biol 47:4155–4166

Hillman EM (2007) Optical brain imaging in vivo: techniques and applications from animal to man. J Biomed Opt 12:051402

Hoshi Y (2003) Functional near-infrared optical imaging: utility and limitations in human brain mapping. Psychophysiology 40:511–520

Hoshi Y, Tamura M (1993) Dynamic multichannel near-infrared optical imaging of human brain activity. J Appl Physiol 75:1842–1846

Jobsis F (1977) Noninvasive, infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. Science 198:1264–1267

Kato T, Kamei A, Takashima S, Ozaki T (1993) Human visual cortical function during photic stimulation monitoring by means of near-infrared spectroscopy. J Cereb Blood Flow Metab 13:516–520

Kawaguchi H, Hayashi T, Kato T, Okada E (2004) Theoretical evaluation of accuracy in position and size of brain activity obtained by near-infrared topography. Phys Med Biol 49:2753–2765

Kohl M, Watson R, Cope M (1997) Optical properties of highly scattering media from changes in attenuation and phase and modulation depths. Appl Opt 36:105–115

Koizumi H, Yamamoto T, Maki A, Yamashita Y, Sato H, Kawaguchi H, Ichikawa N (2003) Optical topography: practical problems and new applications. Appl Opt 42:3054–3062

Kuebler WM, Sckell A, Habler O, Kleen M, Kuhnle GEH, Welte M, Messmer K, Goetz AE (1998) Noninvasive measurement of regional cerebral blood flow by near-infrared spectroscopy and indocyanine green. J Cereb Blood Flow Metab 18:445–456

Li J, Dietsche G, Iftime D, Skipetrov SE, Maret G, Elbert T, Rockstroh B, Gisler T (2005) Noninvasive detection of functional brain activity with near-infrared diffusing-wave spectroscopy. J Biomed Opt 10:44002

Liebert A, Wabnitz H, Steinbrink J, Obrig H, Möller M, MacDonald R, Villringer A, Rinneberg H (2004) Time-resolved multidistance near-infrared spectroscopy of the adult head: intracerebral and extracerebral absorption changes from moments of distribution of times of flight of photons. Appl Opt 43:3037–3047

Liebert A, Wabnitz H, Steinbrink J, Moller M, Macdonald R, Rinneberg H, Villringer A, Obrig H (2005) Bed-side assessment of cerebral perfusion in stroke patients based on optical monitoring of a dye bolus by time-resolved diffuse reflectance. Neuroimage 24:426–435

Liebert A, Wabnitz H, Obrig H, Erdmann R, Möller M, Macdonald R, Rinneberg H, Villringer A, Steinbrink J (2006) Non-invasive detection of fluorescence from exogenous chromophores in the adult human brain. Neuroimage 31:600–608

Madsen PL, Secher NH (1999) Near-infrared oximetry of the brain. Prog Neurobiol 58:541–560

Matcher SJ, Cope M, Delpy DT (1993) Use of the water absorption spectrum to quantify tissue chromophore concentration changes in near-infrared spectroscopy. Phys Med Biol 38:177–196

Matcher SJ, Kirkpatrick P, Nahid K, Cope M, Delpy DT (1995) Absolute quantification methods in tissue near infrared spectroscopy. Proc SPIE 2389:486–495
Matcher SJ, Cope M, Delpy DT (1997) In vivo measurements of the wavelength dependence of tissue scattering coefficients between 760 and 900 nm measured with time resolved spectroscopy. Appl Opt 36:386–396
McGown AD, Makker H, Elwell C, Rawi PGA, Valipour A, Spiro SG (2003) Measurement of changes in cytochrome oxidase redox state during obstructive sleep apnea using near-infrared spectroscopy. Sleep 26:1–7
Miyai I, Tanabe HC, Sase I, Eda H, Oda I, Konishi I, Tsunazawa Y, Suzuki T, Yanagida T, Kubota K (2001) Cortical mapping of gait in humans: a near-infrared spectroscopic topography study. Neuroimage 14:1186–1192
Obrig H, Villringer A (2003) Beyond the visible – imaging the human brain with light. J Cereb Blood Flow Metab 23:1–18
Obrig H, Neufang M, Wenzel R, Kohl M, Steinbrink J, Einhaupl K, Villringer A (2000) Spontaneous low frequency oscillations of cerebral hemodynamics and metabolism in human adults. Neuroimage 12:623–639
Okada E, Firbank M, Schweiger M, Arridge SR, Cope M, Delpy DT (1997) Theoretical and experimental investigation of near-infrared light propagation in a model of the adult head. Appl Opt 36:21–31
Patterson MS, Chance B, Wilson BC (1989) Time resolved reflectance and transmittance for the non-invasive measurement of tissue optical properties. Appl Opt 28:2331–2336
Patterson MS, Moulton JD, Wilson BC, Berndt KW, Lakowicz JR (1991) Frequency-domain reflectance for the determination of the scattering and absorption properties of tissue. Appl Opt 30:4474–4476
Pogue BW, Patterson MS (1994) Frequency-domain optical absorption spectroscopy of finite tissue volumes using diffusion theory. Phys Med Biol 39:1157–1180
Prahl S (2001) Optical properties spectra. http://omlc.ogi.edu/spectra
Rector DM, Carter KM, Volegov PL, George JS (2005) Spatio-temporal mapping of rat whisker barrels with fast scattered light signals. Neuroimage 26:619–627
Schmidt FEW, Fry ME, Hillman EMC, Hebden JC, Delpy DT (2000) A 32-channel time-resolved instrument for medical optical tomography. Rev Sci Instrum 71:256–265
Schmitz Ch, Löcker M, Lasker J, Hielsher AH, Barbour RL (2002) Instrumentation for fast functional optical tomography. Rev Sci Instrum 73:429–439
Steinbrink J, Wabnitz H, Obrig H, Villringer A, Rinneberg H (2001) Determining changes in NIR absorption using a layered model of the human head. Phys Med Biol 46:879–896
Steinbrink J, Kempf FC, Villringer A, Obrig H (2005) The fast optical signal – robust or elusive when noninvasively measured in the human adult? Neuroimage 26:996–1008
Suzuki S, Takasaki S, Ozaki T, Kobayashi Y (1999) A tissue Oxygenation monitor using NIR spatially resolved spectroscopy. Proc SPIE 3597:582–592
Suzuki M, Miyai I, Ono T, Kubota K (2008) Activities in the frontal cortex and gait performance are modulated by preparation. An fNIRS study. Neuroimage 39:600–607
Torricelli A, Pifferi A, Taroni P, Giambattistelli E, Cubeddu R (2001) In vivo optical characterization of human tissues from 610 to 1010 nm by time-resolved reflectance Spectroscopy. Phys Med Biol 46:2227–2237
Tromberg BJ, Svaasand LO, Tsay T-T, Haskell RC (1993) Properties of photon density waves in multiple-scattering media. Appl Opt 32:607–616
Villringer A, Chance B (1997) Non-invasive optical spectroscopy and imaging of human brain function. Trends Neurosci 20:435–442
Villringer A, Planck J, Hock C, Schleinkofer L, Dirnagl U (1993) Near infrared spectroscopy (NIRS): a new tool to study hemodynamic changes during activation of brain function in human adults. Neurosci Lett 154:101–104
Wang L-H, Jacques SL, Zheng L-Q (1995) MCML – Monte Carlo modeling of photon transport in multi-layered tissues. Comput Methods Prog Biomed 47:131–146

Wolf M, Ferrari M, Quaresima V (2007) Progress of near-infrared spectroscopy and topography for brain and muscle clinical applications. J Biomed Opt 12(062104):1–14

Wray S, Cope M, Delpy DT, Wyatt JS, Reynolds EO (1988) Characterization of the near infrared absorption spectra of cytochrome aa3 and haemoglobin for the non-invasive monitoring of cerebral oxygenation. Biochim Biophys Acta 933:184–192

Yamashita Y, Maki A, Koizumi H (1996) Near-infra-red topographic measurement system: imaging of absorbers localized in a scattering medium. Rev Sci Instrum 67:730–732

Chapter 11
Theoretical Background of MR Imaging

Lukas Scheef and Frank Träber

Abstract As magnetic resonance imaging (MRI) has become the most widely applied imaging technique for studying structural and functional effects of exercise in the human brain, this chapter is aimed to provide the reader with the necessary background knowledge of MRI physics and tries to impart the key concepts of image acquisition. Even though functional MRI is primarily covered in the next chapter, the physical background and sequence issues are discussed here. Additionally, perfusion imaging and diffusion-based contrasts are discussed as well as MR spectroscopic techniques to explore cerebral metabolism.

11.1 Introduction

In the last 10–20 years, magnetic resonance imaging (MRI) has become one of the most important research techniques in neurosciences. It enables studying structure and functions of the central nervous system noninvasively and without radiation exposure. It has an excellent spatial resolution (up to the sub-mm range) and allows investigation of a broad range of scientific questions, starting from the analysis of localized brain function up to the analysis of the global network properties of the brain. Using MRI, a researcher is capable of access to local perfusion as well as the structural and functional connectivity between different brain regions or to infer on

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regional metabolite concentrations. Considering the broad spectrum of scientific questions that can be addressed using this instrument, it seems to be obvious that a profound knowledge in MRI physics, mathematics, and signal processing is needed to make full use of its power. It is not the scope of this chapter to train the reader to become a MRI physicist, but to introduce the reader to the basic concepts of MRI. Besides the basics of MRI (physics, image contrast, image construction, MRI sequences), we will cover the physics of functional imaging (BOLD-contrast), as well as perfusion and diffusion imaging and MR spectroscopy.

11.2 The Concept of MRI

Based on the discovery of the Dutch scientist Peter Zeeman that light emitted by a substance can be influenced by an external magnetic field (Zeeman 1897), the physicist Wolfgang Pauli proposed that atomic nuclei might have an intrinsic angular momentum $\vec{J}$, the so-called *spin*, which is accompanied by a parallel oriented magnetic momentum $\vec{\mu}$ (Pauli 1924). Both entities are linearly connected to each other:

$$\vec{\mu} = \frac{1}{2}\gamma\vec{j} \tag{11.1}$$

The constant γ is called gyromagnetic ratio. It depends on charge and mass and is therefore characteristic for a particle.

It should be mentioned here that due to quantum mechanical effects, the magnitude of $\vec{J}$ can only posses discrete values of $\hbar = h/2\pi$, where h denotes the Heisenberg constant. Twenty years later, the physicists Bloch (Bloch et al. 1946) and Purcell (Purcell et al. 1946) were the first to independently show that a proton (itself) absorbs energy at a certain frequency if the probe is brought into an external magnetic field. This phenomenon can be easily understood using Pauli's proposed concept of a nuclear spin $\vec{J}$: Without an external magnetic field the nuclei (and therefore the spin $\vec{J}$ and the associated magnetic momentum $\vec{\mu}$) do not have any preferred orientation. However, when an external magnetic field $\vec{B}_0$ is applied, a preferred direction is imposed onto the system, aligning the nuclear spins either parallel or antiparallel to $\vec{B}_0$. The energy of a magnetic moment $\vec{\mu}$ in an external field $\vec{B}_0$ is described by a rather simple formula:

$$E = -\vec{\mu}\vec{B}_0 \tag{11.2}$$

The energy difference ΔE between both energy states can be directly calculated, using the relation between magnetic momentum and spin:

$$\vec{\mu} = \frac{1}{2}\gamma\vec{j} \tag{11.3}$$

$$E_{-} = -\frac{1}{2}\gamma\hbar B_0, \tag{11.4}$$

$$E_{\downarrow} = +\frac{1}{2}\gamma\hbar B_0, \tag{11.5}$$

$$\Delta E = E_{\downarrow} - E_{-} = \gamma\hbar B_0. \tag{11.6}$$

Having said this, one would expect that if a probe were brought into an external magnetic field, all spins within the probe would seek to align parallel to B_0, as we would expect from a set of compass needles in the same situation. However, in a physiological temperature range ($T = 310°\ \mathrm{K} = 37°\mathrm{C} = 98°\mathrm{F}$) the difference between the number of spins oriented parallel n_{-} vs. antiparallel $n_{\downarrow}$ to the external field is rather small. This is caused by the fact that both energy states are in a thermal equilibrium, which is defined by the equation:

$$\frac{n_{-}}{n_{\downarrow}} = \exp\left(\frac{\Delta E}{k_B T}\right), \tag{11.7}$$

where $k_B T$ is the thermal energy of the system at the temperature T and k_B is the Boltzmann constant (1.3806×10^{-23} J/K). This equation means that the difference in occupation numbers is determined by the ratio between the thermal energy and the energy difference between both states. If the temperature ranges around room or physiological temperature, $\frac{\Delta E}{k_B T} \ll 1$ and (11.7) can be replaced by the approximation

$$\frac{n_{-}}{n_{\downarrow}} \approx 1 + \frac{\Delta E}{k_B T}. \tag{11.8}$$

It becomes immediately obvious that the aligning effect of the external field is almost vanished. Replacing the variables by real numbers reveals that of 10^6 protons brought into an external field of 3 Tesla (which is about 100,000 times stronger than the magnetic field of the earth), the difference $n_{-} - n_{\downarrow}$ is only about 9. In other words, there is almost no net effect observable. The thermal energy acts like a vibrating table for the compass needle example, neutralizing the influence of the external field.

This (thermal) equilibrium can be disturbed by applying a radiofrequency pulse (*RF*) of the frequency ν, which meets the resonance condition: $\Delta E = h\nu$. This frequency is called Larmor frequency and the pulse is called *excitation pulse*. The Larmor frequency ν can be directly related to external magnetic field using (11.6):

$$\upsilon = \frac{\gamma}{2\pi} B_0. \tag{11.9}$$

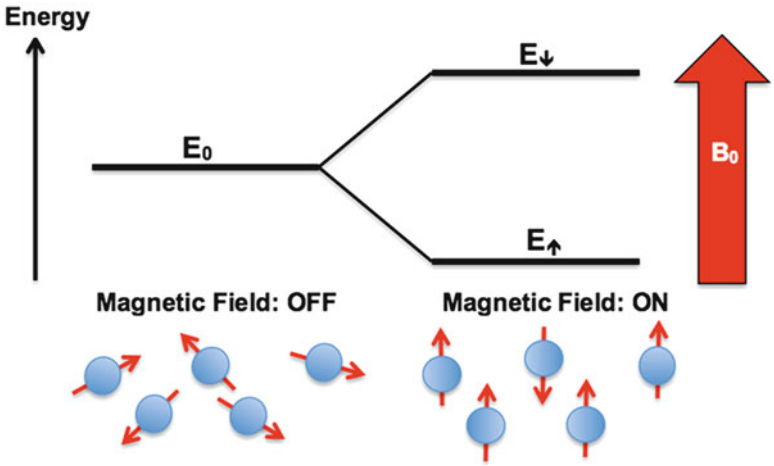

Fig. 11.1 In the absence of an external magnetic field no preferential orientation of the spins is defined, and every proton possesses the same energy level $\mathbf{E}_0$. This changes if an external magnetic field ($\mathbf{B}_0$) is applied. The energy level $\mathbf{E}_0$ splits into two different energy levels and the magnetic moments of the protons have to orient themselves either parallel or antiparallel to the external field. The orientation parallel to the magnetic field is associated with a lower energy ($\mathbf{E}_\uparrow$) content as compared to the anti-parallel orientation ($\mathbf{E}_\downarrow$). The ratio between both states depends on the temperature of the probe *blue circle*: proton; *small arrow*: magnetic momentum; *large arrow*: external magnetic field

This equation shows clearly that the Larmor frequency, and therefore any (nuclear) magnetic resonance experiment, depends on the applied magnetic field and is specific for a probe in a given field. If a proper RF-pulse is applied, the spin system is able to absorb the energy and a transition between the two energy states can be observed, leading to a system where "more" spins are oriented antiparallel to the external field (Fig. 11.1). When the RF-pulse is switched off, the system returns back toward its equilibrium state. It is this so-called *relaxation process*, which leads to the tissue contrast on MR images.

11.3 MR-Signal Formation and Relaxation Times

Even though the spin can only be described properly using quantum physics, the behavior of a macroscopic object can be approximated quite well if such an object is imagined as being made up of a collection of (very) small magnets, which are sufficiently spaced apart from each other to allow only a weak interaction in between. The magnetic momentum $\vec{\mu}$ of each single magnet is added up to a gross magnetization $\vec{M}$, which is almost oriented parallel to the external field. It is not exactly parallel

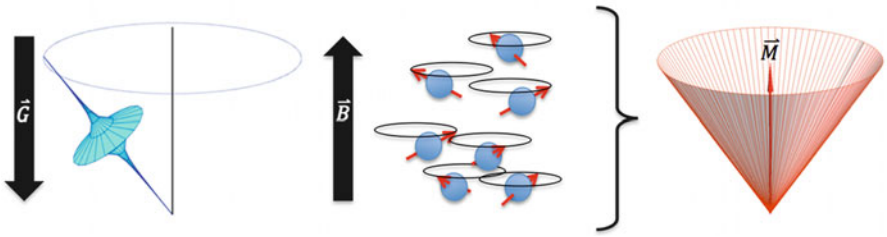

Fig. 11.2 A spinning gyroscope precesses around the axis parallel to the gravity force vector when gravity tries to flip the gyroscope. A comparable situation exists for the protons. When the magnetic field tries to orient them according to the field vector the angular momentum of the protons leads to a precessing motion around an axis parallel to the field vector. As a consequence, the magnetic moments are tilted a bit and cannot orient parallel to the external field. Interestingly, the precessing frequency equals the Larmor frequency. The magnetic moments of the spins add up to a macroscopic magnetization $\overline{M}$. Macroscopically, the precessing motion is not observed and only a (macroscopic) component in field direction exists. This is caused by the fact that the phases (between the protons) are not coupled and therefore every possible phase is represented in a large sample of protons. Since opposed phases cancel each other, no component perpendicular to the field exists. This is indicated by the translucent cone *blue circle*: proton; *red arrow*: magnetic momentum $\vec{\mu}$; macroscopic magnetization $\overline{M}$; *black arrow*: gravity $\vec{G}$; magnetic field $\vec{B}$

to the external field, because the magnetic moment is associated with an angular momentum, which causes all $\vec{\mu}$'s to be tilted a bit and to precess around $\vec{B}_0$ with the Larmor frequency. This behavior parallels the motion of a spinning gyroscope, which also starts to precess around its main rotation axis if an external force is applied (Fig. 11.2).

Felix Bloch described as early as 1946 how $\overline{M}$ interacts with an RF-pulse at the Larmor frequency and outlined how to measure the macroscopic magnetization $\overline{M}$ (Bloch et al. 1946). Every electromagnetic radiation consists of two components, an electric and a magnetic component, as indicated by the terminology. Bloch and colleagues showed that the magnetic component of an RF-pulse at the Larmor frequency causes $\overline{M}$ to tilt toward a plane perpendicular to $\vec{B}_0$ if the magnetic component of the pulse is perpendicular to $\vec{B}_0$. The *flip angle* α depends on the duration the radiation is applied. Similar to the magnetic momentum $\vec{\mu}$, the macroscopic magnetization $\overline{M}$ precesses with the Larmor frequency υ around $\vec{B}_0$ during the entire process (Fig. 11.3). In his seminal paper, Bloch suggested that $\overline{M}$ can be easily measured after flipping $\overline{M}$ by 90° with the help of a coil, exploiting the fact that a changing magnetic field induces a current in a coil. When $\overline{M}$ is precessing with the Larmor frequency, it induces an oscillating voltage in a coil, which then can be amplified and measured (Fig. 11.4). Even more than 50 years later, we still use this method to detect MRI signals. However, flipping the magnetization $\overline{M}$ by 90° and measuring the induced signal, when $\overline{M}$ is rotating (in the transversal plane), would not allow for gaining a lot of valuable information, if this process would be "stable". However, when switching off the RF-pulse after flipping the magnetization

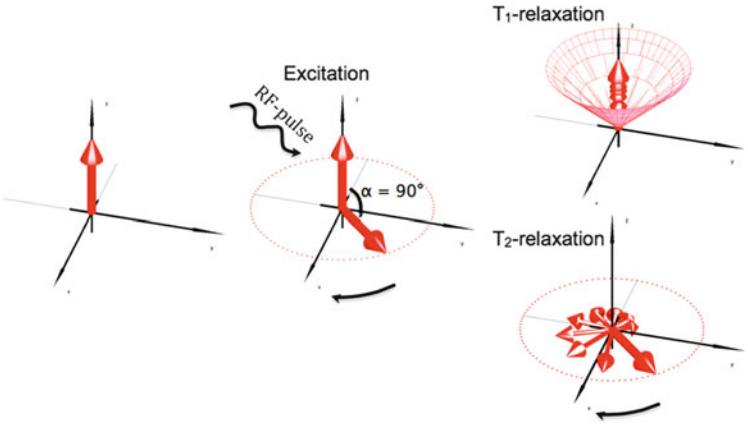

Fig. 11.3 The application of an RF-pulse (with the Larmor frequency) has two effects: (1) The phase of all spins couple to the phase of the RF-Pulse, and (2) the magnetization is flipped by the angle α. When the RF is switched off, the magnetization slowly returns to the initial state. This (relaxation) process is characterized by two independent relaxation processes. The transversal magnetization vanishes, due to the loss of phase coherence between the spins ($T2$-relaxation), and the longitudinal magnetization slowly rebuilds ($T1$-relaxation). The cones at the illustration of the $T1$-relaxation symbolize the lack of phase coupling when the longitudinal magnetization slowly rebuilds ($T1 >> T2$)

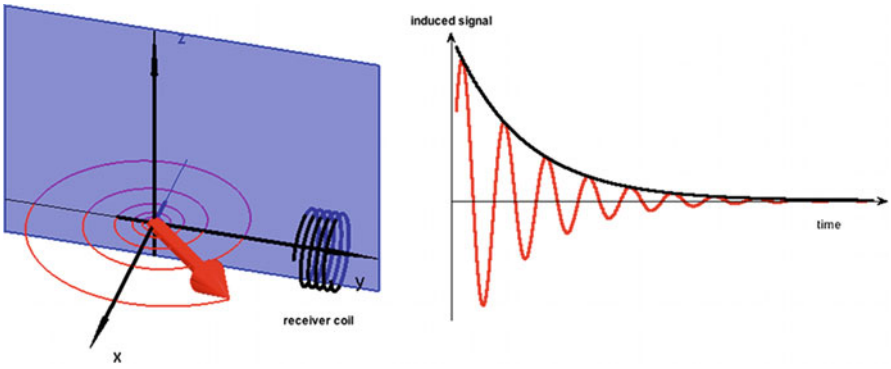

Fig. 11.4 Free induction decay (FID): The MRI signal is measured using a receiver coil. Its surface is aligned parallel to the Z-axis. Changes in the magnetic flux through this plane induce a current. Therefore, only the transversal component of M contributes to the (MR) signal, projecting on the "blue plane". When the magnetization decays it induces an alternating current with exponentially decaying amplitude, the FID signal. The spatial relation between receiver coil, magnetization and scanner coordinate system is given on the left, the FID signal is lined out on the right

Table 11.1 *T*1- and *T*2-relaxation times for different brain structures at different field strengths

	1.5 T		3.0 T		4.0 T[(5)]		7.0 T	
	*T*1[(1)]	*T*2	*T*1	*T*2	*T*1	*T*2	*T*1[(1)]	*T*2
cGM	1,188	80[(2)]	1,763[(3)]	70[a]	1,724	63.4	2,132	60[b]
WM	656	80[(2)]	847[(3)]	66[a]	1,043	49.8	1,220	40[b]
CSF	4,070	500[a]	3,500[a]	500[a]	4,550	70.4	4,425	60[(6)]
Caudate	1,083		1,483[(3)]	88[(4)]	1,458	45.7	1,745	
Putamen	981		1,337[(3)]	62[a]	1,372	47.3	1,700	

Please note. (1) *T*1 is always larger than *T*2 (*T*1 >> *T*2), and (2) *T*1 increases with increasing field strength whereas *T*2 decreases

[(1)]Rooney et al. (2007), [(2)]MacFall et al. (1987), [(3)]Slichter (1990), [(4)]Sumpf et al. (2011), [(5)]Jezzard et al. (1996), [(6)]Marjanska et al. (2011)

[a]Own measurements

[b]Estimates

by 90°, the system slowly returns back into the thermodynamic stable state which it possessed before application of the RF-pulse. Bloch proposed that this is an exponential process determined by two different time constants, *T*1 and *T*2. *T*1 describes the behavior of the "longitudinal" component of $\overline{M}$, which runs parallel to the external field $\overline{B}$. The component perpendicular to the external field is called transversal magnetization. The relaxation of transversal magnetization is described by *T*2. It is common to orient the frame of reference in MRI the way that the *z*-axis is parallel to the magnetic field $\overline{B}$. Using this convention, the Bloch equations for the relaxation after a 90° pulse can be written as follows:

$$\frac{\mathrm{d}M_z(t)}{\mathrm{d}t} = -\frac{M_z(t) - M_0}{T1}, \text{or} \quad M_z(t) = M_0 - M_0 \exp\left(\frac{-t}{T1}\right) \tag{11.10}$$

and

$$\frac{\mathrm{d}M_T(t)}{\mathrm{d}t} = -\frac{M_T(t)}{T2}, \text{or} \quad M_T(t) = M_0 \exp\left(\frac{-t}{T2}\right). \tag{11.11}$$

The term $M_z(t) - M_0$ reflects the fact that the magnetization in the *z*-direction (= external field direction) is slowly recovered, whereas the transversal magnetization vanishes. Table 11.1 gives an overview on *T*1 and *T*2 times for different brain structures and field strengths.

11.3.1 T1-Relaxation

The behavior of the longitudinal magnetization appears immediately plausible. When the "small magnets" move toward the thermal equilibrium, they flip back and

align parallel (or antiparallel) to $\bar{B}$ until the absorbed RF-energy is entirely dispensed. The transitions between energy states depend here on the motion of nearby molecules and their associated nuclear fields. If this random motion leads to a local changing field at the Larmor frequency, transitions can be induced and the system moves—transition by transition—toward an energetically stable state. Since the tumbling of the molecules depends on their environment, the relaxation time is tissue dependent and because the Larmor frequency is a function of the external magnetic field strength, T_1 is also field dependent. It usually increases with increasing field strengths (Table 11.1, Fig. 11.3).

11.3.2 T2- and T2-Relaxation*

Whereas the behavior of the longitudinal magnetization seems to be easily understood, it is not immediately obvious that different processes drive the transversal relaxation. As already mentioned above, the magnetic moment is associated with an angular momentum, which causes all $\bar{\mu}$'s to be tilted a bit and to precess around $\bar{B}_0$. The precession frequency always corresponds to the Larmor frequency, but the phase (= angle at a certain time) is random (Fig. 11.2). When the RF-pulse is applied, the magnetic moments are forced to couple and to precess with the same frequency and phase. Imagine a couple of swings on a playground, where parents push their kids. One would not expect that all swings be synchronized. Applying RF on the spin system is like playing music on this playground. The Larmor frequency corresponds to a song everybody likes and can sing and RF-energy absorption means in this case that everyone starts to sing. It is not difficult to image that if everybody starts to sing along, the pushing will slowly synchronize with the music and so will the swings, or in others words, the music synchronizes the phase of the swings. If the music is switched off, this coupling vanishes. The same happens when the RF-pulse is switched off: The phase coupling vanishes and leads to a reduction of the transversal magnetization, characterized by $T2$ (Fig. 11.3). The mechanism for the $T2$ decay is similar to the mechanism described by $T1$: its source is the field of the tumbling molecules in the close neighborhood. The associated varying local fields lead to locally and temporally varying Larmor frequencies. This causes a loss of the phase coupling, because the magnetic momentums start to precess with slight frequency differences, depending on their close neighbors. Because this effect only depends on the molecular motion and does not have to fulfill an additional boundary condition (like $T1$), it is not as field dependent as observed for $T1$, but it is also tissue dependent. $T2$ must be always shorter than $T1$ since the transversal component has to be zero when the thermal equilibrium is reached and the longitudinal component is fully restored (Table 11.1).

An additional effect has to be mentioned here, which accelerates the decay of the transversal magnetization. It is called "$T2$-star effect" (write $T2$*) and it is the basis for functional brain imaging. Spatial variations of the magnetic field lead to

Table 11.2 T2*-relaxation times for different brain structures at different field strengths (Peters et al. 2007)

	1.5 T [ms]	3.0 T [ms]	7.0 T [ms]
cGM	84.0	66.0	33.2
WM	66.2	53.2	26.8
Caudate	58.8	41.3	19.9
Putamen	55.5	31.5	16.1

spatially varying Larmor frequencies, causing dephasing as described above. As a consequence, the observed transversal relaxation is faster compared to the $T2$-relaxation. The time constant is called: $T2^*$. In an ideal spatially homogeneous magnetic field both relaxation times would be equal. Table 11.2 gives an overview on $T2^*$ times at different field strengths.

11.3.3 Measurement of MR Signals

MR signals are measured using coils, which are able to pick up the transversal magnetization. The precessing transversal magnetization induces a current in the coil when the associated field component perpendicular to the coil surface changes. Without relaxation this would induce a sinusoidal signal, oscillating with the Larmor frequency. The amplitude depends on the number of spins in the sample and, therefore, is a measure for the proton density. However, the transversal magnetization fades out due to $T1$- and $T2$-relaxation and the signal amplitude decays exponentially with time. This damped oscillation is called *free induction decay* (FID, Fig. 11.4). In order to gain information about relaxation times and, therefore, about properties of the probe (or tissue), it is not sufficient to observe the FID, but additional action has to be taken. The first step is to repeat the excitation pulse a couple of times. The time between consecutive pulses is called *repetition time* (TR). If TR is sufficiently short, not allowing for full $T1$-relaxation in between, the transversal magnetization depends on both relaxation times:

$$M_T(t) = M_0 M_z(t) = M_0 \left(1 - \exp\left(\frac{-TR}{T1}\right)\right) \exp\left(\frac{-t}{T2}\right), \tag{11.12}$$

and so does the FID signal. The equation shows that by choosing the TR properly, the extent of which the signal is influenced by T1 can be regulated (Fig. 11.5). However, this equation is not quite correct. As already discussed, the magnetic field is not entirely homogeneous. Therefore, $T2$ should be replaced by $T2^*$. However, there is a trick to minimize the influence of the field inhomogeneities. The local variations in B_0 cause an additional, but locally constant dephasing

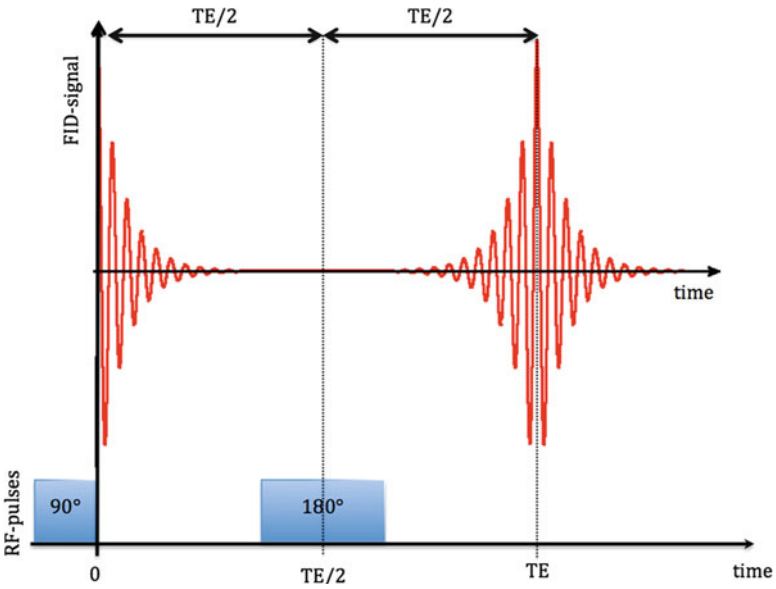

Fig. 11.5 The principle of a spin-echo experiment: The 90° RF-pulse flips the magnetization by 90° into the transversal plane. The relaxation processes start immediately after the RF-pulse is switched off. Local field variation leads to a fast dephasing of the transversal magnetization, because the spins all precess at different (local field dependent) Larmor frequencies. The 180° pulse flips the magnetization by 180°. The precessing direction is reversed and the signal rebuilds again

angle/time. When the dephasing direction is inverted at a certain time point *t,* all spins will be back in phase after the time *2t*. This can be achieved by applying an additional RF-pulse, tilting the transversal magnetization by 180°. The 180° pulse is of the same frequency as the 90° excitation pulse, but lasts twice as long or has twice the amplitude. This inverts the dephasing and the signal builds up again, minimizing any inhomogeneity effects. Therefore, it is called *inversion pulse* (Fig. 11.5). Just image a number of athletes, who start running at the same time in any direction, each at its own speed. They would be soon spread out across the track. However, if they were all to reverse their running direction at the time point *t*, keeping the exact track and speed they had taken before, they would all be back at the starting point at time *2t.* The time *2t* is called *echo time* (TE), due to the fact that at this time, the signal rebuilds after dephasing like an echo (Fig. 11.5). More generally one can say, the echo time (TE) determines the time delay after the excitation pulse when the signal is actually measured, whereas the TR determines the time between consecutive excitation pulses. By balancing TR and TE one can control whether the signal will be dominated by either proton density, *T*1 or *T*2 of the tissue (Fig. 11.6). TR and TE are the core parameters of every MR sequence. By properly adapting the TR and TE times to the expected (or measured) relaxation times, the image contrast can be influenced. It is important to understand

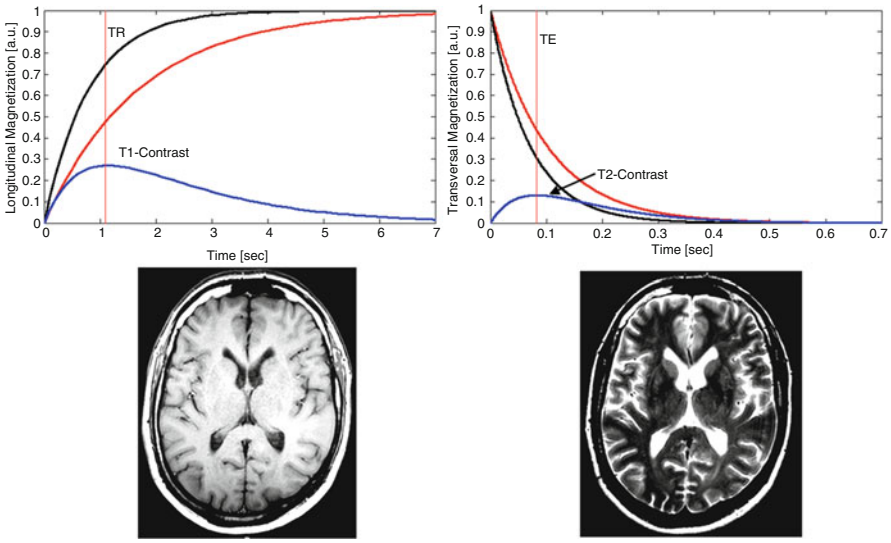

Fig. 11.6 By properly choosing repetition time (TR) and echo time (TE) one can influence whether the image contrast is either dominated by the *T*1- or the *T*2-effect. Consider two tissue types with different relaxation times (i.e., *black* = white matter; *red* = gray matter). The image contrast (black–red) will be dominated by the *T*1-effect if a very short TE is used (TE << *T*2), and the white matter appears brighter as compared to the gray matter. When a long TR is chosen and TE is within the range of the tissue *T*2 values or somewhat longer, the contrast will be *T*2-weighted and the contrast is almost reversed. The white matter is now darker compared to the gray matter. Please note that on the left-hand side the echo time (TE) was modified to optimize the contrast, whereas on the right-hand side it was the repetition time (TR)

that these parameters are field strength dependent, because the relaxation times are field dependent. As a consequence, image parameters cannot be easily transferred from one field strength to another and should be optimized for each system individually.

11.4 Spatial Gradients

Above, it was explained how MR signals are generated, measured, and which properties can be used to gain information about probes or tissue in general. However, without further actions taken, only statements regarding the averaged properties of a probe can be made. To gain spatial information, one takes advantage of the fact that the resonance effect is highly field dependent and that the transversal magnetization precesses with the Larmor frequency (and therefore is also field dependent). This field strength dependency can be used to gain spatial information by applying additional magnetic field gradients, i.e., to superpose B_0 with an additional magnetic field linearly increasing along (or perpendicular to) its axis. The amplitude of these

gradients is much smaller compared to the main magnetic field. Since they are applied only for a short time and repeated with a high frequency, an operating MR machine generates a lot of noise; hence switching magnetic fields provokes induction forces in the producing coil, leading to vibrations (partially) in the audible range.

11.4.1 Spatial Encoding

The resonance condition is frequency dependent and field dependent. Only when both match each other, the energy is absorbed and the magnetization is tilted by 90°, which is the precondition for measuring a MR signal. Therefore, superimposing a magnetic field gradient, ranging from $-\Delta B$ to $+\Delta B$, onto the main field, causes only that area in the probe to be in resonance when a RF-pulse of the Larmor frequency of B_0 is applied, where the superimposed field is zero. In this way, a slice can be selected and every signal acquired afterward has its origin from this region. By convention, the describing coordinate system is oriented in a way that its *z*-axis points in the direction of the main magnetic field; therefore, this gradient is called *z*-gradient (G_z). The *x*- and *y*- direction can be encoded by applying additional gradients, but at different time points. When measuring MRI signals, the decay of the precessing transversal magnetization is usually observed. The precessing frequency depends on the absolute field strength present at any moment. That means, if the local field strength changes, the precessing frequency changes as well. This behavior allows for encoding the additional directions. The y-direction is encoded by applying an additional gradient (G_y) in *y*-direction. The time during which this gradient is applied is very short and its intended purpose is to impose a phase difference along the *y*-direction (= phase encoding direction). Before it is applied, all magnetization vectors are in phase everywhere in the selected slice. When G_y is switched on, the precessing frequency changes for a short time along the *y*-direction until it is switched off. Because the precessing speed is different along the y-direction, a phase difference is imposed along the phase encoding direction after G_y is switched off. A third gradient is applied along the *x*-axis (G_x). It changes the precessing frequency along this axis, when observing the FID signal. Therefore, the FID signal is made up of a mixture of frequencies, not only of one, as it would be the case without this gradient. Obviously, knowing the gradient makes it possible to trace back a certain frequency to a certain point on the *x*-axis. Because the *x*-direction is encoded by modulating the frequency, it is called frequency direction.

11.4.2 Spatial Decoding and k-Space

Even though the principles of spatial encoding are easy to follow, it is harder to understand the decoding of the resulting FID signal. The resulting signal is a mixture of frequencies and phases. Mathematically, this can be decoded back into an

image by a transformation, which is known as Fourier transformation (FT, Jean Baptiste Joseph Fourier, 1768–1830). In general, FT is used to decompose a signal into its frequency components. Its application is not restricted to the time domain, but can be almost universally applied to any kind of signal. A nice aspect of FTs is that one can decode and encode via the same algorithm. In reverse, this means if one can use FT to decode (or deconvolve) the spatial distribution of the MR signals, the FID signal could also be interpreted as the FT of the spatial image. And indeed, one can prove mathematically (using the Bloch equations) that after applying the gradients, the resulting MRI signal is the FT of the selected slice. The gradients transform signals from the "image-space" into the so-called *k*-space. Ljuimagenggren (Ljunggren 1983) and Twieg (Twieg 1983) independently introduced the *k*-space concept in 1983. This concept is easily understood if one considers the fundamental idea behind the FT. Historically, FT was aimed to construct any one-dimensional periodic function by superimposing a finite number of sinus functions with different frequencies and phases. High frequencies decode small features of the composed function, whereas the low frequencies contain information about the overall shape (including information like the amplitude). This principle can be extended into two (or more) dimensions. If the frequency profile of the FID signal is plotted in a two-dimensional space, where the *x*-axis decodes the frequency and the *y*-axis the phase, one receives the two-dimensional representation of the acquired slice in Fourier space. Because the *x*-axis is scaled by the factor $k_x \sim \gamma G_x$ and $k_y \sim \gamma G_y$, this representation is called *"k-space"* representation (Fig. 11.7). The dependency of the scaling factors k_x and k_y from the phase- and frequency-decoding gradients reflects that every point in *k*-space can be addressed directly by applying a proper combination of G_x and G_y. This shows that the *k*-space representation has a practical meaning and it is not only an abstract mathematical description of the FID signal. Universal properties of *k*-space (based on the Fourier theory) have immediate practical consequences for MRI imaging:

1. The center of *k*-space contains the gross spatial information (including main signal intensity), whereas the outer lines contain the fine image details (Fig. 11.7). If one wants to increase the spatial resolution, the range the *k*-space line covered has to be increased, and therefore more gradient steps have to be applied. Since the latter is time-consuming, an increase of spatial resolution is always accompanied with an increased acquisition time.
2. The *k*-space is symmetric (Fig. 11.7). Image information is redundantly coded in *k*-space. k_x and $-k_x$ contain the same information. The same holds true for k_y and $-k_y$. In principle, it is sufficient to acquire only one half of *k*-space to reconstruct the full image information. This saves time, because less *k*-space lines have to be covered. It is sufficient to cover only about 50% of the *k*-space to reconstruct the full image without loss of spatial information. This shortens the image acquisition time by the same factor. However, one has to keep in mind that it also reduces the signal-to-noise ratio by approximately 30%. This technique is called either half or partial Fourier technique or partial echo technique depending on if the *k*-space sampling is reduced in frequency- or phase-encoding direction.

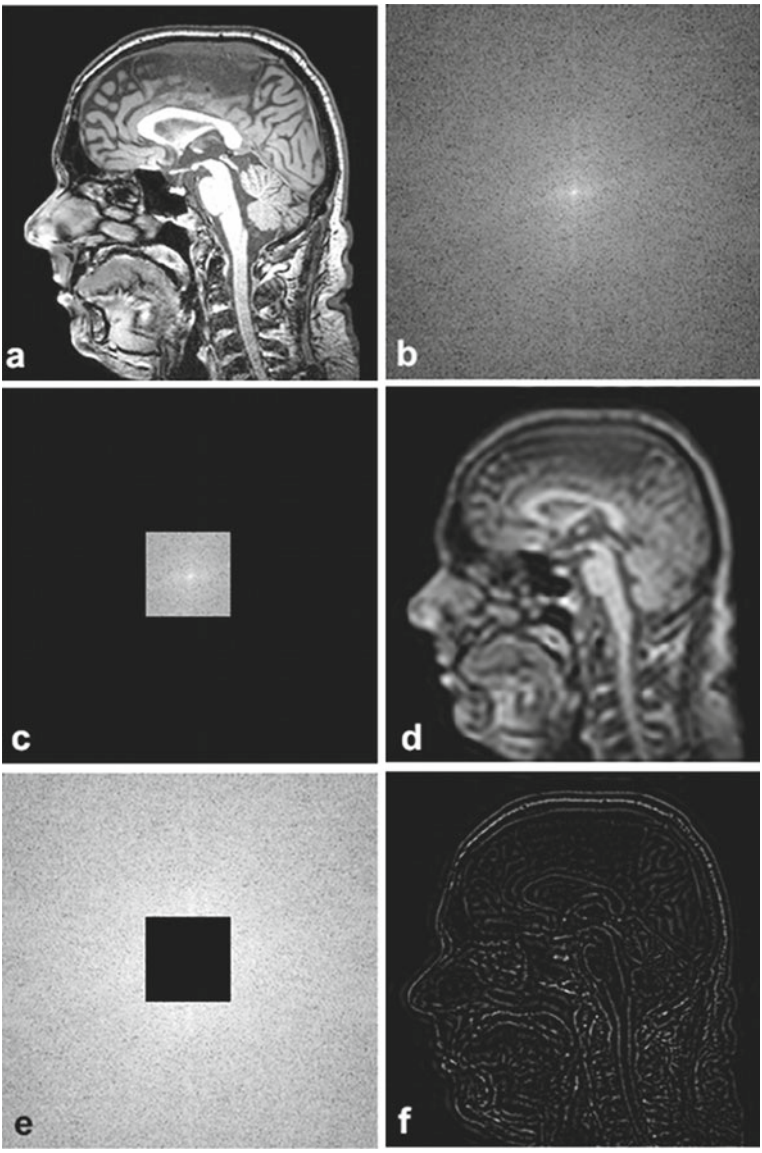

Fig. 11.7 Middle slice of a 3D-*T*1-weighted MRI volume of the author (**a**) and the corresponding *k*-space image (**b**). Most information about image intensity and object shape is stored in the center of *k*-space. If only the central part (i.e., 5%) of the *k*-space is used (**c**) almost all information can be gained (**d**). Only the fine details are missing. They are coded in outer parts (**e**, **f**). The *k*-space images are logarithmically intensity transformed in order to display the structure of the *k*-space in a black and white image with its 256 shades of *gray*. Without the log-transformation, the image would only show a couple of white spots in the center on a black background, because the intensity of the center is three to four orders larger compared with the periphery

3. A lot of image artifacts have an unambiguous counterpart in *k*-space and can only be understood, if the *k*-space concept is known, i.e., ghost, RF, ring, or folding artifacts.

It is off the scope of this book to go into details here. More information on this topic can be found in the literature (i.e., Filippi 2009). A nice online tutorial can be found at: http://www.revisemri.com/tools/kspace/ or examples in the article by Moratal et al. (2008).

11.5 Special MR-Contrasts

It was already mentioned above that the image contrast could be controlled by choosing the core sequence parameters (TE and TR) properly (Fig. 11.6). In the following, it will be explained how special contrasts are obtained that are currently used in neuroscience applications.

11.5.1 BOLD-Contrast

BOLD-Contrast is the abbreviation for Blood Oxygenation Level-Dependent Contrast. This contrast builds the foundation of functional MR imaging in its current form. As the terminology adumbrates, the key factor for this contrast is the blood oxygenation. Pauling and Coryell discovered in 1936 that the magnetic properties of blood (or more precisely of hemoglobin) change if its oxygenation state changes (Pauling and Coryell 1936). Oxygenated hemoglobin is diamagnetic, while deoxygenated hemoglobin is paramagnetic. If a diamagnetic probe is exposed to an external magnetic field, it tries to repel the field. Within the probe the field is reduced. The opposite behavior is observed for paramagnetic substance, the field is attracted to the material and, subsequently, the field in the probe increases. Therefore, changing blood oxygenation should change magnetic field properties and should be detectable by MRI with all sequences, which are sensitive to local field variations. These are *T*2- and *T*2*-weighted sequences. Oxygenation-dependent *T*2-changes were first shown by Thulborn et al. (1982) and *T*2*-changes by Ogawa and his group (1990). The latter researcher made the first BOLD experiment by showing that the signal around blood vessels decreases under hypoxia conditions and that this effect can be reversed when the oxygenation is restored. It was Ogawa's keen insight to propose that this effect might be used to image relative blood oxygenation changes that accompany focal brain activation. He also introduced the abbreviation BOLD, which has almost become synonymous with functional magnetic resonance imaging (fMRI).

Even though BOLD changes can also be measured utilizing *T*2-effects, in general BOLD-fMRI refers to *T*2*, because it yields the larger effect when measured at the common field strengths (1.5–3 T) (Bandettini et al. 1994). In the following, the terms BOLD-fMRI and fMRI will refer to *T*2*-based functional imaging.

The changing oxygenation state influences the local magnetic properties of the tissue around blood vessels. *T*2*-effects lead to rapid dephasing of the transversal magnetization for which reason very short echo times are needed to capture these effects. Usually a so-called gradient echo sequence (GE) is used in fMRI. The outline of this sequence type was already sketched above. After applying the slice encoding gradient simultaneously with the 90° excitation pulse, a phase encoding gradient is applied and the FID signal is recorded while the frequency encoding gradient is applied. The combination of a single phase encoding gradient and the frequency gradient only catches one line in *k*-space. To cover the complete *k*-space of one slice, this scheme has to be repeated multiple times (e.g., 64 times to cover 64 *k*-space lines). To acquire a complete slice would therefore take a long time and it is not very efficient. A better strategy is to acquire the whole image within one shot by alternating phase encoding and frequency encoding gradients multiple times after one excitation pulse. Imaging using this kind of "readout scheme" is called echo planar imaging (EPI). Together with recording the FID without applying refocusing pulses, this sequence is named GE-EPI, and because only one RF-pulse/slice is used, the full name is "single-shot GE-EPI". With standard clinical MRI systems a full slice through the brain can be acquired as fast as 100 ms with a spatial resolution of about $3 \times 3 \times 3$ mm^3. A whole brain volume can be acquired below 3 s. It is currently the standard sequence technique for fMRI. This sequence is almost completely independent of *T*1-effects and the TR is solely dependent on the number of slices that should be acquired. It can be shown that the optimum echo time TE for fMRI is the *T*2* for gray matter (50–80 ms for 1.5T; 30–60 ms at 3.0 T; see also Table 11.2). The sensitivity to detect *T*2*-related effects allows for detecting neuronal activity-related oxygenation changes; however, this causes problems in regions that intrinsically show large local field variations. These are the medial temporal lobe regions and the orbito-frontal regions. The neighborhood to the sinusoidal cavities and the mastoid process, respectively, leads to extremely short *T*2* times and field distortions. Signal losses and huge image distortions in these regions are the consequences. These artifacts can be only (partially) compensated if additional actions are taken (for details, see Deichmann et al. 2003; Deichmann et al. 2002; Gorno-Tempini et al. 2002; Hutton et al. 2002; Reichenbach et al. 1997; Schwarzbauer et al. 2010; Vargas et al. 2009; Weiskopf et al. 2006; Weiskopf et al. 2007).

11.5.2 Perfusion-Based Contrast (Arterial Spin Labeling)

Perfusion can be measured either invasively by applying contrast agents or noninvasively by tagging blood magnetically. Currently, invasive methods are mainly used for clinical purposes whereas noninvasive techniques are used clinically and for scientific applications.

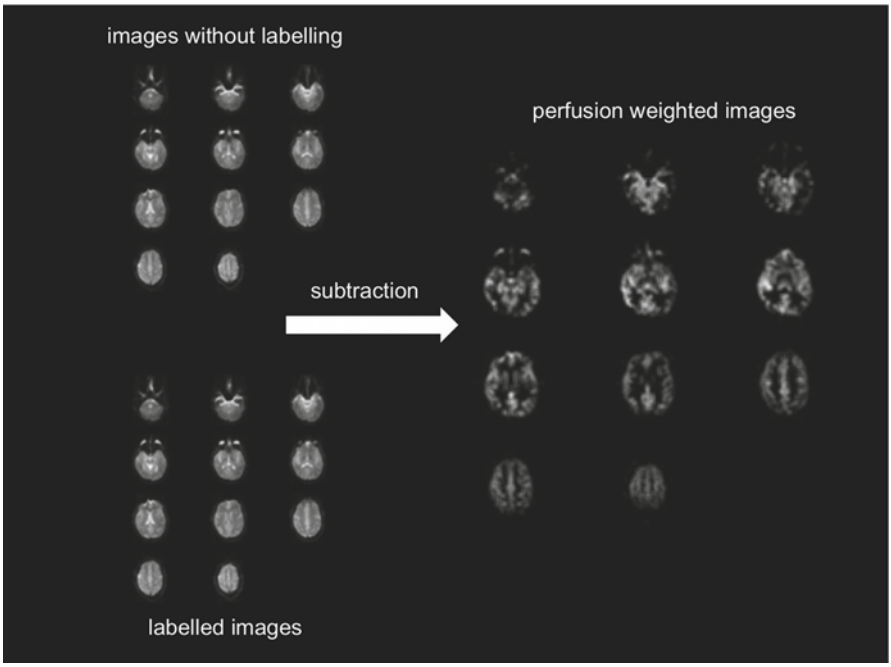

Fig. 11.8 CASL: The local cerebral blood flow (rCBF) can be calculated comparing the difference between a labeled and unlabeled image pair on a voxel-by-voxel basis: $rCBF_{i,j,k} \sim (UL_{i,j,k} - L_{i,j,k})/UL_{i,j,k}$. Please note that the image intensities appear to be almost equal for both image sets. Indeed, the difference between UL and L is very small and a high scanner stability is needed. The image parameters were as follows: CASL @ 3.0 T TR/TE 4,200/38 ms, 11slices, slice thickness: 8 mm, matrix: 64×64, "labeling delay": 700 ms, 40 dynamics, scan-time: 336 s. *UL* unlabeled, *L* labeled

The basic idea behind the noninvasive perfusion method is based on the following two MR properties: (1) RF-pulses can tilt the magnetization and (2) the transversal magnetization is measured. When applying two successive 90° pulses the magnetization would be tilted by 180° and would therefore be invisible, because no transversal component would exist. This can be utilized to label blood magnetically. By inverting the magnetization of blood before it reaches an area of interest in the brain, the blood becomes invisible. When comparing a slice acquired before and after tagging, one can relate the observed signal difference to blood perfusion (Fig. 11.8) The inversion is called "tagging" or "labeling", and the technique "arterial spin labeling" (ASL). The blood labeling can take place either on the level of the carotid arteries, followed by the acquisition of the whole brain or slice-by-slice, prior to the acquisition of single slices. The first method is called continuous arterial spin labeling (CASL), the other one is called pulsed arterial spin labeling (PASL). Both methods exist in various flavors with a plethora of names. The core sequences are CASL (Williams et al. 1992), FAIR (Kwong et al. 1995), EPISTAR (Edelman and Chen 1998; Edelman et al. 1994), PICORE (Wong et al. 1997), or QUIPSS (Wong et al. 1998). CASL-type sequences demand a highly stable MR system and

the ability to deliver a relatively long and stable RF-labeling pulse. Especially the latter is quite a challenge for modern MR amplifiers, which are usually optimized to deliver extremely short RF-pulses in the ms range. The duration of a labeling pulse, however, is about 1–2 s. Therefore, CASL sequences are difficult to implement and so far not widely used. The disadvantage of PASL is the limitation of spatial coverage, which is limited to a few slices. However, the newest development seems to overcome these obstacles by combining both approaches, i.e., by replacing the long pulse by a large number of very short pulses. This technique is called pseudo-continuous spin labeling (pCASL) (Dai et al. 2008; Wu et al. 2007). A comprehensive review on this topic is given by Detre et al. (2009).

11.5.3 Diffusion-Weighted Contrast

In liquid phase, water molecules are continuously in motion. They diffuse randomly without a preferred direction. The diffusion can be observed using MRI by applying two strong gradients between excitation and image acquisition. Both gradients equal each other in strength, orientation, and duration, but differ in their sign. If a molecule were static, the gradients would cause dephasing and rephasing to the same amount and there would not be a difference in the image acquired with and without diffusion gradients. However, the molecules move, and therefore the amount of dephasing also depends on the path they take when the gradients are applied. As a consequence, the phase cannot be fully recovered and the signal intensity decreases. This effect is strongest along the gradient direction and scales with the gradient strength, the time difference between the two gradients, as well as the mean diffusion speed. By acquiring several successive images with multiple diffusion gradients switched in different directions and strengths, the diffusion can be quantified (LeBihan 1995). This method does not only allow quantifying the average diffusibility, but also detecting whether the motion is restricted in a certain direction. The latter is called diffusion tensor imaging (DTI) and can be used to visualize white matter fiber bundles in the brain. The analysis of this data will be discussed later in the book (see also Chap. 12). At this point, we would only like to refer to some review articles, which cover the theoretical background efficiently and give a practical overview (Hasan et al. 2011; Le Bihan et al. 2001).

11.6 MR Spectroscopy

11.6.1 Theoretical Background

As mentioned before (11.9), the Larmor frequency of a nuclear spin system is directly proportional to the gyromagnetic ratio of the respective nuclei and the effective strength of the external magnetic field at the nuclear site. However, as the

nuclear spin system is usually not isolated but located in an atomic or molecular environment, this effective field strength B_{eff} will deviate from the applied external field B_0 as this is shielded by the additional electromagnetic fields of the electron shells surrounding the atomic nuclei. This weakening of the external field at the nuclear site by the ambient electron cloud of a molecule is called "diamagnetic shielding" and may be expressed as follows: $B_{eff} = (1 - \sigma)\, B_0$. Of course, the value of the diamagnetic shielding factor $1 - \sigma$ depends on the spatial structure of the electron cloud and thus on the chemical bond of the molecule. Thus, the Larmor frequency of the nuclear spins is not only determined by the gyromagnetic ratio of the selected isotope, but also by the choice of the chemical compound defining its molecular environment. Although this "chemical shift" δ is only of the order of a few parts per million (ppm) of the Larmor frequency for almost all molecular compounds and nuclear isotopes naturally occurring in biological samples, it can be measured with great precision even in the living human body. In this way, each chemical substance shows a characteristic "fingerprint" of one or more discrete lines or peaks along the frequency axis if the measured MR signal of a probe is decomposed by the Fourier transformation into its frequency components and their intensity plotted against the Larmor frequency—even without any additionally applied spatial field gradient. In analogy to the dispersion of light by a prism or optical grid this diagram is called an MR spectrum, and the initial signal strength of a specific spin ensemble in the free induction decay, which corresponds to their abundance within the probe, is represented by the area under the peak(s) of the respective component(s) in the frequency domain after FT. The linewidth $\Delta\nu$ (usually given in Hz) of the spectral peaks is inversely proportional to $T2^*$, and in an ideally homogeneous external magnetic field it approaches the "natural linewidth" defined by $1/(\pi T2)$. Therefore, the spectral resolution, i.e., the separability of the frequency components from different substances, can be greatly improved by preparation procedures ("shimming") to further reduce B_0 inhomogeneities, thus achieving smaller linewidths and less spectral overlap.

Of all nuclei carrying a net nuclear spin, only ^{31}P and, of course, ^{1}H are sufficiently abundant in the human body to allow the application of in vivo MR spectroscopy not only in highly specialized centers, but also in a clinical environment. While ^{31}P-MRS gained much interest especially for the investigation of muscular disorders and in sports medicine already in the two end decades of the last century due to the importance of phosphorus compounds in energy metabolism, the clinical introduction of ^{1}H-MRS was hampered in these early days by the lack of effective techniques for volume localization and for suppressing the intense signal of tissue water. Opposed to MRI, where all the image information is taken from the water protons, ^{1}H-MRS investigates the nuclear spin signal of ^{1}H metabolites like *N*-acetyl aspartate (NAA), which is exclusively synthesized in neurons and can be regarded as a marker for neuronal integrity, or creatine/phosphocreatine (tCr), involved in energy metabolism. Other important metabolites "visible" by ^{1}H-MRS are choline compounds (Cho), which mainly occur in the cell membranes and indicate cell proliferation when increased, thus acting as a tumor marker, and lactate signaling anaerobic condition in hypoxic tissue by its appearance in an MR spectrum (see Table 11.3 for

Table 11.3 A selection of ^{1}H metabolites commonly investigated by proton MR spectroscopy

Metabolite	Acronym	Cerebral occurence/function
Choline compounds	Cho	Cell membrane turnover
Total creatine	tCr	Energy metabolism
N-acetyl-aspartate	NAA	Marker of neuronal integrity
Lactate	Lac	Hypoxia, necrosis
Myo-inositol	MI	Cell membrane, osmolytes
Glutamate	Glu	Excitatory neurotransmitter
Glutamine	Gln	Glutamatergic neurotransmission
γ-amino butyric acid	GABA	Inhibitory neurotransmitter
Glucose	Glc	Energy metabolism

Please note. The overlapping multiple peaks of Glu, Gln, and GABA having very similar Larmor frequencies are often marked as "Glx" in MR spectrum annotations. "Total creatine" means the sum of creatine and phosphocreatine

a list of major ^{1}H metabolites). As all these metabolites occur in the human brain only in millimolar concentrations, the about 10,000-fold stronger signal from tissue water has to be suppressed by special RF-prepulses to detect the small spectral peaks from the low-abundant ^{1}H metabolites.

Similar to MRI, spatial encoding of a certain volume of interest in the body from which the metabolite signal will be collected is achieved by switching of magnetic field gradients. The two localization techniques most widely used in ^{1}H-MRS are named PRESS (Bottomley 1987) and STEAM (Frahm et al. 1989) and select a brick-shaped volume by successive application of three orthogonal field gradients during a 90°–180°–180° (PRESS) or a 90°–90°–90° (STEAM) spin excitation scheme. Example ^{1}H-MR spectra obtained at echo times of TE 30 ms and 140 ms from the left hippocampus are displayed in Fig. 11.9. Apart from these "single-voxel" techniques, metabolic information from a multitude of MR spectra sampled within one or several slices through the body may be obtained by "MR spectroscopic imaging" (MRSI) using 2D or 3D phase encoding in *k*-space (Pykett and Rosen 1983). Opposed to MRI, frequency encoding of one spatial dimension cannot be used in MRSI as the frequency axis is already occupied by the spectral pattern of the metabolite peaks, and the necessary double or triple phase encoding makes in vivo MRSI quite time-consuming. Figure 11.10 shows a sample of 15 selected spectra from a 2D-MRSI acquisition in a patient with a highly malignant brain tumor, together with color-coded maps of the local Cho and NAA concentrations overlaid on MRI.

11.6.2 Processing of MR Spectroscopy Data

While the spectral lines from the various biomolecules containing ^{31}P atoms, e.g., phosphocreatine (PCr) and adenosine-triphosphate (ATP), are spread over a chemical shift range of about 25 ppm and can be resolved from each other already at intermediate magnetic field strengths, the Larmor frequencies of the ^{1}H metabolites occurring in the human brain cover an interval of only about 5 ppm. Therefore, the

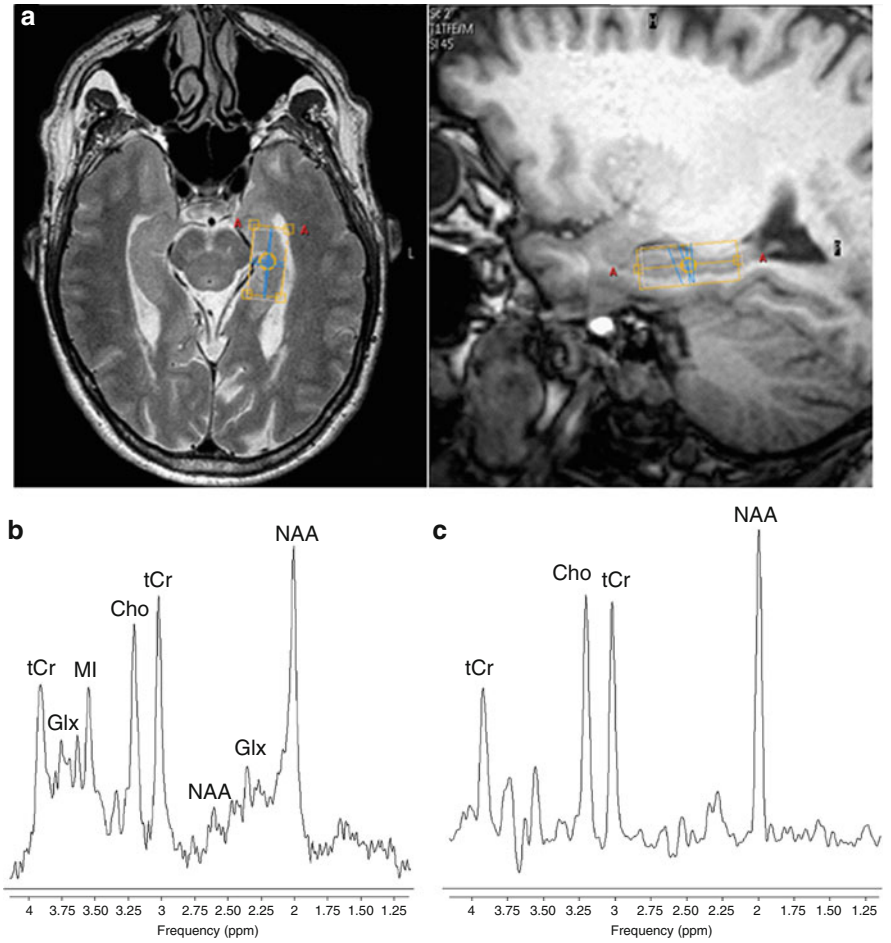

Fig. 11.9 Water-suppressed single-voxel ^{1}H-MR spectra at 3 T from a 5.4 ccm-volume (**a**) centered on the left hippocampus of a healthy volunteer, acquired with TR/TE 1,800/30 ms (**b**) and with TR/TE 2,000/140 ms (**c**). *Cho* choline compounds, *tCr* total creatine, *NAA N*-acetyl aspartate, *Glx* glutamate + glutamine, *MI* myo-inositol

lines from different molecules or even from different moieties within the same molecule often overlap each other, and accurate quantification of all the individual spectral components can be a demanding task and requires pre- and post-processing with advanced spectral filtering and analysis tools. Although in principle the line resolution can be improved simply by using higher magnetic field strengths (which by no means is as simple as it sounds) as the absolute frequency separation [Hz] is directly proportional to B_0 (while the *relative* shift δ in ppm remains the same), the linewidths also scale with the field strength (albeit to a smaller extent) due to increasing magnetic susceptibility.

Spectral preprocessing and quantification can either be performed directly on the detected spin signal measured over time ("time domain") or on its frequency

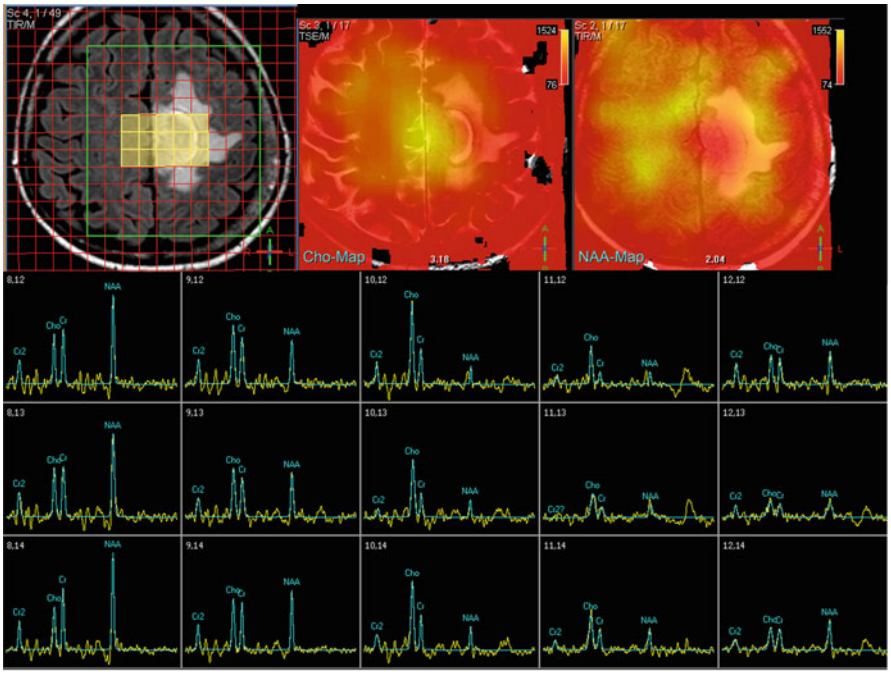

Fig. 11.10 MRSI at 3 T with 2D phase encoding (24 × 19 steps, red voxel grid) in a case of glioblastoma multiforme, a malignant primary CNS tumor. The displayed array of 15 selected spectra (TR/TE 2,000/140 ms) corresponds to the yellow voxels in the upper left image, covering the range from normal cerebral tissue of the right hemisphere over active tumor on the left side near the hemispheric fissure to necrotic tumor tissue and perifocal edema in the left hemisphere. The high choline peak in the central column of selected spectra (*yellow region* in the color-coded Cho map) is a marker for active tumor growth, while NAA signal is strongly reduced (central red spot in NAA map) in tumorous as well as in necrotic tissue. The green frame represents the PRESS localization volume

components after Fourier transformation ("frequency domain"). While time domain quantification is mathematically more complex and has therefore only recently been included in some online MR scanner software architectures, it has the advantage that no phase and baseline offsets have to be corrected as in the frequency spectrum. Distortions and broad humps in the spectrum baseline are often observed due to line broadening by fast relaxation, when macromolecules or the protons in hydrogen bonds (e.g., of hydroxyl groups −OH) contribute to the MRS signal from tissue.

11.6.3 Analysis of Spectroscopic Data

The two most widespread analytic tools for time domain MRS post-processing are the AMARES (Vanhamme et al. 1997) and QUEST (Ratiney et al. 2005) algorithms of the MRUI software package (Naressi et al. 2001) and the LC-Model

program (Provencher 1993). The common feature of both approaches is nonlinear least-squares fitting of the measured MRS signal decay to the superposition of a specified number of damped sinusoidal oscillations representing the spectral components from various metabolites. For mathematical convergence, these iterative procedures require suitable starting values and boundary conditions for the fitted spectral parameters (peak integral, line width, Larmor frequency of each component) as "prior knowledge" information, which is provided by user specification (AMARES) or taken from a metabolite basis set either created by quantum mechanical calculations (QUEST) or derived from MRS measurements of individual model solutions of these metabolites (QUEST, LCModel). The resulting peak integrals are proportional to the tissue concentration of the respective metabolite and are determined for each individual spectral component (AMARES) or as a composite measure for all lines of a certain molecule (QUEST, LCModel). In this way, relative metabolic concentrations can directly be established by taking the respective peak ratios, e.g., NAA/tCr. The latter is often used as reference metabolite as it has been found from in vitro comparisons that the concentration of total creatine (tCr = creatine + phosphocreatine, which cannot be separated in ^{1}H-MRS at field strengths used in vivo) remains quite stable even in many advanced diseases, except for malignant tumors. However, this statement is more and more questioned nowadays, and techniques to also determine absolute metabolite concentrations from the measured peak integrals are increasingly applied meanwhile.

Again, two methods for absolute quantification are competing with each other: First, the MRS signal intensity of a metabolite component may be compared to that from a subsequent measurement of an external reference probe with known concentrations either placed as near to the tissue voxel as possible or in situ after the patient examination with identical settings of all sequence and RF adjustment parameters. However, accounting for variations in RF coil loading and spatial characteristics between patient and probe acquisitions remains a challenge and limits the accuracy of this method (for detailed description and testing of external referencing, see e.g., (Reinert et al. 2010). Secondly, the metabolite signal may be related to that of the internal tissue water in the same MRS voxel obtained within a single non-water-suppressed MRS measurement or from an unsuppressed reference dataset acquired with identical transmitter/receiver settings after the water-suppressed "metabolite acquisition". This technique is less sensitive to homogeneity and temporal stability issues of the RF field in the MR coil influencing the comparability between patient and external probe acquisitions, but implies estimates or additional measurements of the relaxation times of water and the metabolites, and of the water contents in cerebral gray and white matter (Jansen et al. 2006; Keevil et al. 1998).

Finally, the absolute metabolite concentrations measured in the MRS voxel of interest can be corrected for the included fraction of CSF (which contains ^{1}H metabolites only in negligible quantities) and extrapolated to concentrations for "pure" gray or white matter. To achieve this, the MRS volume may be co-registrated on a high-resolution MRI sequence suited for tissue segmentation (see also Chap. 12) to determine the relative GM, WM, and CSF fractions. Alternatively, due to the largely

different water *T*2 values in brain tissue and CSF, the CSF fraction may also be derived from an unsuppressed MRS acquisition with varied echo times and bi-exponential fitting of the "short-*T*2" (GM/WM) and the "long-*T*2" (CSF) water component (Ernst et al. 1993). To obtain the "pure" GM and WM metabolite contents, however, MRS quantification in a second tissue volume with sufficiently altered GM/WM composition is essential.

11.7 MR Technology

A MR system is basically built by the following nested components: the main magnet with superconducting coils (creating the B_0-field), and gradient coils inset, and the RF-coil(s) for sending and/or receiving the electromagnetic signals. The system is built into a RF-shielded cabin protecting the scanner from any external RF-transmission and vice versa. The volunteer is placed inside the magnet bore, usually lying on its back. The scanner is operated from the control room, which is in front of the RF-cabin ("Faraday cage"). Figure 11.11 outlines the general setup of an MR facility.

11.7.1 The Main Magnetic Field

The magnetic field is commonly created by an electromagnet, in which superconductive coils generate a magnetic field via electric currents. For superconductivity, this coil has to be embedded into liquid helium, reducing the temperature below 4 K = −269°C. The coils are designed as solenoids. They look similar to the spring in a classical ballpoint pen. The diameter is small compared with its length, leading to a fairly homogenous field inside the solenoid. For human applications, this design pattern (the use of superconducting solenoids) is dominating, and field strengths between 0.5 and 11.0 T are currently available. For field strengths below 1 T permanent magnets are also used. It should be pointed out that the main magnetic field strength is a fixed property of a system and cannot be changed during operation. It should also be noted that the magnetic field is always present, even if the scanner is not operating. Any magnetic field "works against" its change due to magnetic induction. It takes a long time and a lot of energy to generate the main MR field or to break down the field in a controlled action.[1] On the other hand, no further energy is needed to maintain the magnetic field, because superconductive coils have no measurable electrical resistance. As a consequence, the field stays stable regardless of the operation status of the scanner.

[1] To break down the field, the contained energy has to be carefully (and slowly) removed from the system, which is achieved by large resistors.

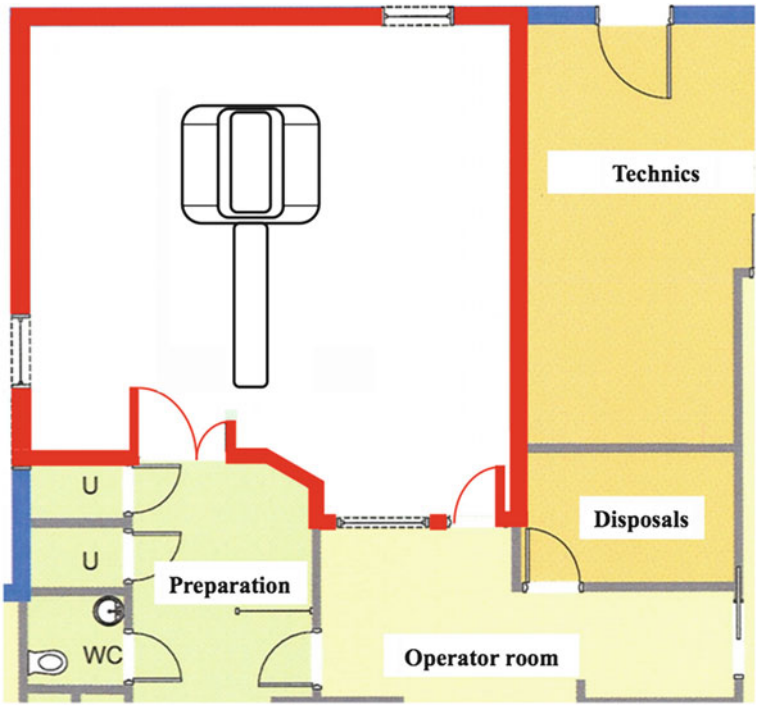

Fig. 11.11 Example of an MR facility: The RF-cage is indicated by *red* color. All doors and windows are RF-safe. The MR is operated from the operator room outside the RF-cage. Computer racks, gradient amplifiers, and amplifiers for receive and transmit coil(s) are located in the technic room. It usually contains also air conditioner for the RF-cage and additional cooling systems for the MR

The magnetic field gradients are not very strong and can be generated using conventional (non-superconductive) coils along the scanner bore, yet the requirement for ultrafast switching of high electrical currents turned out to be quite a technical challenge in the development of dedicated (high-performance) power supplies for these gradient coils.

11.7.2 Transmit and Receive Coils

In order to transmit the excitation RF-pulse additional coils are used. They are usually located along the bore, just as the gradient coils. For special applications, like spectroscopy, it is of advantage to integrate the transmit coil into the receive coil, which is usually placed as close as possible at the region of interest (i.e., the brain). By this approach less RF-power is needed and the RF-pulse can be delivered more evenly. Another technical advance is the multi-transmit concept. By using multiple

transmit coils the RF-dissipation can be optimized (and the energy deposition minimized), which is especially of advantage when imaging larger-diameter regions of the body like spine, abdomen, or pelvis.

In most applications, an additional coil is used for receiving the MR signal from the body. As mentioned before, this receiver coil should be placed as close as possible to the body. For brain imaging, this is usually realized with so-called volume coils. They look like a birdcage and the head is placed into it. The diameter is close to the diameter of the head, therefore minimizing the distance between the sending source (brain) and the receiving coil elements. This leads to an improved signal-to-noise ratio (SNR). Currently, the most used receive coil systems are so-called multichannel coils, where a receiver coil is built from independent uncoupled coils, each of them sending an individual signal to its own amplifier. The multichannel approach yields an increased SNR, depending on the number of channels. As rule of thumb, one might state that the SNR scales with number of channels; however, this is partly paid for with an inhomogeneous sensitivity profile across the image volume. However, the spatial sensitivity profile of a single independent coil element contains spatial information that can be used to gain spatial information. Those "parallel scanning techniques", like SENSE (Pruessmann et al. 1999), PILS (Griswold et al. 2000), or GRAPPA (Griswold et al. 2002), can increase imaging speed, because less *k*-space lines have to be acquired. The maximal usable acceleration factor increases with the number of channels and the magnetic field strength (Wiesinger et al. 2004).

As the newest technical development, vendors start to integrate the RF amplifiers directly into the coil and transmit the already amplified signal digitally via light guides. Because the optical signal transmission via light guides is not disturbed by magnetic field gradients or RF-transmission, the noise can be significantly reduced leading to a SNR increase up to 20–40%.

11.7.3 RF-Shielding

The MR device is located in an RF-shielded room, and is operated from a controller room outside of the RF-shield. This is necessary to avoid any interference between external RF-sources and the scanner. RF-sources can be any electrical equipment, especially those operating with alternating currents. If the receiver coils pick up the unwanted RF, this causes image artifacts, and might decrease the image quality drastically. On the other hand, the RF-emission of the scanner and the fast switching gradients can also cause problems for any sensitive electronic device. Because any wire can also serve as an antenna, the RF-pulses can be absorbed and might disturb normal function or even destroy the device. The fast switching gradients induce currents in wire loops, which can also destroy a device. Therefore, any device (for stimulation or monitoring), which is operating inside the RF-cabin, has to be designed appropriately to avoid these problems.

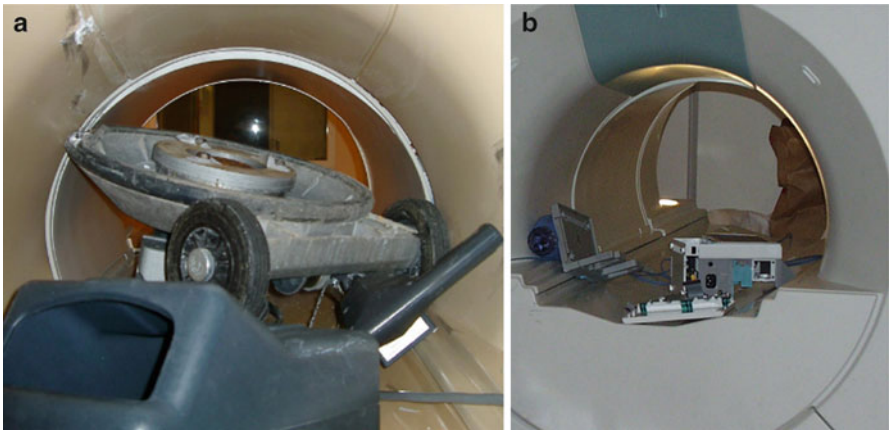

Fig. 11.12 Illustration of the power of a high magnetic field: Even heavy objects like a floor polisher can be lifted from the ground and dragged into the scanner bore if they are moved too close to the magnet (**a**). But also small devices (containing only a small amount of ferromagnetic material) are dragged into the bore (**b**). (**a**) Foor polisher dragged; field strength 3 T (**b**) control monitor; field strength 1.5 T. In both cases, the objects were completely destroyed, and the MR had to be repaired. Fortunately, nobody was harmed

11.7.4 Biohazards

MR is a safe technology as long as a couple of rules are followed. No magnetic objects should be brought close to the scanner and electronic devices should only be operated inside the RF-cabin if they have an appropriate MR safety certificate.

The main magnetic field is extremely strong and can reveal high forces on (ferro) magnetic materials. The forces scale linearly with the product of the field strength and its spatial gradient dB/dz and increase drastically in close distance to the scanner, where the local variation in the field strength is at maximum. They are strong enough to lift large and heavy objects from the ground and pull them into the scanner. Even a very strong person would not be able to hold such an object to prevent an accident (Fig. 11.12). Obviously, it would be life threatening to stand between the scanner and that object. But also small everyday devices, placed in a shirt or lab coat pocket like a ballpoint pen or (in a medical environment) a reflex hammer, are extremely dangerous. They can be accelerated to high speeds and are pulled into the center of the scanner making it very probable that the volunteer is hit in the face. As already mentioned above, the main field is always switched on even if the MR is not operating. Colleagues not frequently working in MR facilities often oversee this fact.

Medical implants like artificial hips or knee joints should be treated with care. If they were implanted within the last 10 years they should not be magnetic, but they might absorb RF-energy and heat up. Any wire inside the body or on the skin surface can absorb RF and might heat up and burn the tissue locally. The same holds

true for makeup (especially of the eyes), tattoos, or body piercings. Makeup and piercings should be removed beforehand. The safety of tattoos depends on their size, color, and location. Therefore, a general rule cannot be given. The scanning decision should be made on a case-by-case basis consulting the local MR physicist and/or radiologist.

As already pointed out in the section above, electronic devices (like medical pumps or pacemakers) can be disturbed or even destroyed by the magnetic field, the RF-pulses, or the magnetic gradients. A patient carrying such devices should only be examined if those have an appropriate MR safety certificate and a physician is supervising the patient during the complete MR examination. Please note that such a certificate should specify the field strength(s) the device can be operated at safely. One cannot assume that a device is safe at 3 T if the safety is only certified for 1.5 T.

11.8 Summary

In the preceding sections, we have tried to give a rough overview on the basic concepts of MRI. Proton spins tend to align along an external magnetic field either parallel or antiparallel to the field. This leads to a small net magnetization pointing parallel to the field. Applying a RF-pulse at the resonance frequency $\nu = \gamma/2\pi B_0$, the Larmor frequency, the equilibrium is disturbed and the net magnetization flips by an angle α in a precessing motion. The pulse is called excitation pulse. If the RF is switched off, the system slowly returns back into its equilibrium state. The relaxation process is defined by two time constants: the longitudinal relaxation time $T1$ and the transversal relaxation time $T2$. The longitudinal relaxation time describes the backward flipping spins, and the latter the loss of phase coherence between spins. Both relaxation times are field strength and tissue dependent.

The MR signal is measured via the voltage induced in a coil with wiring plane(s) parallel to the main field direction. This coil is then only sensitive to changes of the transversal magnetization. The signal fades out due to $T1$- and $T2$-relaxation and its signal amplitude decays exponentially with time. This damped oscillation picked up by the coil is called free induction decay. By properly choosing the repetition time and echo time, it can be determined if the resulting signal is either dominated by $T1$-effects and $T2$-effects or by the spin-density. In order to encode spatial information, the magnetic field dependency of the Larmor frequency, and therefore of the precessing frequency, is utilized. An MR image is constructed by applying a Fourier transform on the measured FID signal, which decodes the spatial information.

The above-described principles on MR imaging can be used to obtain a variety of physiological and anatomical data of the body. The spectrum reaches from analyzing brain structure up to investigating the dynamics of functional networks of the brain. The following chapter will introduce into analytic methods. The focus will be on the analysis of functional data but will also cover BOLD-physiology and the analysis of structural data.

References

Bandettini PA, Wong EC, Jesmanowicz A, Hinks RS, Hyde JS (1994) Spin-echo and gradient-echo EPI of human brain activation using BOLD contrast: a comparative study at 1.5 T. NMR Biomed 7:12–20

Bloch F, Hansen WW, Packard ME (1946) The nuclear induction experiment. Phys Rev 70:474–483

Bottomley PA (1987) Spatial localization in NMR spectroscopy in vivo. Ann N Y Acad Sci 508:333–348

Dai W, Garcia D, de Bazelaire C, Alsop DC (2008) Continuous flow-driven inversion for arterial spin labeling using pulsed radio frequency and gradient fields. Magn Reson Med 60:1488–1497

Deichmann R, Gottfried JA, Hutton C, Turner R (2003) Optimized EPI for fMRI studies of the orbitofrontal cortex. NeuroImage 19:430–441

Deichmann R, Josephs O, Hutton C, Corfield DR, Turner R (2002) Compensation of susceptibility-induced BOLD sensitivity losses in echo-planar fMRI imaging. NeuroImage 15:120–135

Detre JA, Wang J, Wang Z, Rao H (2009) Arterial spin-labeled perfusion MRI in basic and clinical neuroscience. Curr Opin Neurol 22:348–355

Edelman RR, Chen Q (1998) EPISTAR MRI: multislice mapping of cerebral blood flow. Magn Reson Med 40:800–805

Edelman RR, Siewert B, Darby DG, Thangaraj V, Nobre AC, Mesulam MM, Warach S (1994) Qualitative mapping of cerebral blood flow and functional localization with echo-planar MR imaging and signal targeting with alternating radio frequency. Radiology 192:513–520

Ernst T, Kreis R, Ross BD (1993) Absolute quantitation of water and metabolites in the human brain.1. compartments and water. J Magn Reson B 102:1–8

Filippi M (2009) FMRI techniques and protocols. Humana, New York

Frahm J, Bruhn H, Gyngell ML, Merboldt KD, Hanicke W, Sauter R (1989) Localized high-resolution proton NMR spectroscopy using stimulated echoes: initial applications to human brain in vivo. Magn Reson Med 9:79–93

Gorno-Tempini ML, Hutton C, Josephs O, Deichmann R, Price C, Turner R (2002) Echo time dependence of BOLD contrast and susceptibility artifacts. NeuroImage 15:136–142

Griswold MA, Jakob PM, Heidemann RM, Nittka M, Jellus V, Wang J, Kiefer B, Haase A (2002) Generalized autocalibrating partially parallel acquisitions (GRAPPA). Magn Reson Med 47:1202–1210

Griswold MA, Jakob PM, Nittka M, Goldfarb JW, Haase A (2000) Partially parallel imaging with localized sensitivities (PILS). Magn Reson Med 44:602–609

Hasan KM, Walimuni IS, Abid H, Hahn KR (2011) A review of diffusion tensor magnetic resonance imaging computational methods and software tools. Comput Biol Med 41:1062–1072

Hutton C, Bork A, Josephs O, Deichmann R, Ashburner J, Turner R (2002) Image distortion correction in fMRI: a quantitative evaluation. NeuroImage 16:217–240

Jansen JF, Backes WH, Nicolay K, Kooi ME (2006) 1H MR spectroscopy of the brain: absolute quantification of metabolites. Radiology 240:318–332

Jezzard P, Duewell S, Balaban RS (1996) MR relaxation times in human brain: measurement at 4 T. Radiology 199:773–779

Keevil SF, Barbiroli B, Brooks JC, Cady EB, Canese R, Carlier P, Collins DJ, Gilligan P, Gobbi G, Hennig J, Kugel H, Leach MO, Metzler D, Mlynarik V, Moser E, Newbold MC, Payne GS, Ring P, Roberts JN, Rowland IJ, Thiel T, Tkac I, Topp S, Wittsack HJ, Podo F et al (1998) Absolute metabolite quantification by in vivo NMR spectroscopy: II. A multicentre trial of protocols for in vivo localised proton studies of human brain. Magn Reson Imaging 16:1093–1106

Kwong KK, Chesler DA, Weisskoff RM, Donahue KM, Davis TL, Ostergaard L, Campbell TA, Rosen BR (1995) MR perfusion studies with T1-weighted echo planar imaging. Magn Reson Med 34:878–887

Le Bihan D, Mangin JF, Poupon C, Clark CA, Pappata S, Molko N, Chabriat H (2001) Diffusion tensor imaging: concepts and applications. J Magn Reson Imaging: JMRI 13:534–546
LeBihan B (1995) Diffusion and perfusion magnetic resonance imaging. Raven, NewYork
Ljunggren S (1983) A simple graphical representation of fourier-based imaging methods. J Magn Reson 54:338–343
MacFall JR, Wehrli FW, Breger RK, Johnson GA (1987) Methodology for the measurement and analysis of relaxation times in proton imaging. Magn Reson Imaging 5:209–220
Marjanska M, Auerbach EJ, Valabregue R, Van de Moortele PF, Adriany G, Garwood M (2011) Localized (1) H NMR spectroscopy in different regions of human brain in vivo at 7 T: T(2) relaxation times and concentrations of cerebral metabolites. NMR Biomed 25:332–339
Moratal D, VallÈs-Luch A, MartÌ-Bonmati L, Brummer ME (2008) k-Space tutorial: an MRI educational tool for a better understanding of k-space. Biomed Imaging Interv J 4:e15
Naressi A, Couturier C, Devos JM, Janssen M, Mangeat C, de Beer R, Graveron-Demilly D (2001) Java-based graphical user interface for the MRUI quantitation package. Magma 12:141–152
Pauli W (1924) Zur Frage der theoretischen Deutung der Satelliten einiger Spektrallinien und ihrer Beeinflussung durch magnetische Felder. Naturwissenschaften 12:741
Pauling L, Coryell C (1936) The magnetic properties and the structure of hemoglobin, oxyhemoglobin, and carbon monoxyhemoglobin. Proc Natl Acad Sci USA 22:210–216
Peters AM, Brookes MJ, Hoogenraad FG, Gowland PA, Francis ST, Morris PG, Bowtell R (2007) T2* measurements in human brain at 1.5, 3 and 7 T. Magn Reson Imaging 25:748–753
Provencher SW (1993) Estimation of metabolite concentrations from localized in vivo proton NMR spectra. Magn Reson Med 30:672–679
Pruessmann KP, Weiger M, Scheidegger MB, Boesiger P (1999) SENSE: sensitivity encoding for fast MRI. Magn Reson Med 42:952–962
Purcell EM, Torrey HC, Pound RV (1946) Resonant absorption by nuclear magnetic moments in a solid. Phys Rev 69:37–38
Pykett IL, Rosen BR (1983) Nuclear magnetic resonance: in vivo proton chemical shift imaging. Work in progress. Radiology 149:197–201
Ratiney H, Sdika M, Coenradie Y, Cavassila S, van Ormondt D, Graveron-Demilly D (2005) Time-domain semi-parametric estimation based on a metabolite basis set. NMR Biomed 18:1–13
Reichenbach JR, Venkatesan R, Yablonskiy DA, Thompson MR, Lai S, Haacke EM (1997) Theory and application of static field inhomogeneity effects in gradient-echo imaging. J Magn Reson Imaging: JMRI 7:266–279
Reinert M, Schneider P, Hofmann E, Semmler W (2010) Quantitative MR-Spectroscopy: implementation and quality assurance on a clinical MR-scanner. Zeitschrift fur medizinische Physik 20:176–187
Rooney WD, Johnson G, Li X, Cohen ER, Kim SG, Ugurbil K, Springer CS Jr (2007) Magnetic field and tissue dependencies of human brain longitudinal 1H2O relaxation in vivo. Magn Reson Med 57:308–318
Schwarzbauer C, Mildner T, Heinke W, Brett M, Deichmann R (2010) Dual echo EPI–the method of choice for fMRI in the presence of magnetic field inhomogeneities? NeuroImage 49:316–326
Slichter CP (1990) Principles of magnetic resonance. In: Cardona M, Fulde P, von Klitzing K, Queisser H-J (eds) Advanced concepts in pulsed magnetic resonance. Springer, Berlin, p 369
Sumpf TJ, Uecker M, Boretius S, Frahm J (2011) Model-based nonlinear inverse reconstruction for T2 mapping using highly undersampled spin-echo MRI. J Magn Reson Imaging: JMRI 34:420–428
Thulborn KR, Waterton JC, Matthews PM, Radda GK (1982) Oxygenation dependence of the transverse relaxation time of water protons in whole blood at high field. Biochimica et biophysica acta 714:265–270
Twieg D (1983) The k-trajectory formulation of the NMR imaging process with applications in analysis and synthesis of imaging methods. Med Phys 10:610–621
Vanhamme L, van den Boogaart A, van Huffel S (1997) Improved method for accurate and efficient quantification of MRS data with use of prior knowledge. J Magn Reson 129:35–43

Vargas MI, Delavelle J, Kohler R, Becker CD, Lovblad K (2009) Brain and spine MRI artifacts at 3Tesla. J Neuroradiol Journal de neuroradiologie 36:74–81

Weiskopf N, Hutton C, Josephs O, Deichmann R (2006) Optimal EPI parameters for reduction of susceptibility-induced BOLD sensitivity losses: a whole-brain analysis at 3 T and 1.5 T. NeuroImage 33:493–504

Weiskopf N, Hutton C, Josephs O, Turner R, Deichmann R (2007) Optimized EPI for fMRI studies of the orbitofrontal cortex: compensation of susceptibility-induced gradients in the readout direction. Magma 20:39–49

Wiesinger F, Van de Moortele PF, Adriany G, De Zanche N, Ugurbil K, Pruessmann KP (2004) Parallel imaging performance as a function of field strength–an experimental investigation using electrodynamic scaling. Magn Reson Med 52:953–964

Williams DS, Detre JA, Leigh JS, Koretsky AP (1992) Magnetic resonance imaging of perfusion using spin inversion of arterial water. Proc Natl Acad Sci USA 89:212–216

Wong EC, Buxton RB, Frank LR (1997) Implementation of quantitative perfusion imaging techniques for functional brain mapping using pulsed arterial spin labeling. NMR Biomed 10:237–249

Wong EC, Buxton RB, Frank LR (1998) Quantitative imaging of perfusion using a single subtraction (QUIPSS and QUIPSS II). Magnetic resonance in medicine 39:702–708

Wu WC, Fernández-Seara M, Detre JA, Wehrli FW, Wang J (2007) A theoretical and experimental investigation of the tagging efficiency of pseudocontinuous arterial spin labeling. Magn Reson Med 58:1020–1027

Zeeman P (1897) The effect of magnetism on the nature of light emitted by a substance. Nature 55:S347

Chapter 12
Functional and Structural MRI: Theoretical Background and Practical Aspects

Lukas Scheef and Henning Boecker

Abstract The following chapter will provide a treatise of MRI-based functional and structural imaging methods. It will start with a short summary of the physiological foundations of contemporary MRI-based functional imaging methods. We will continue with a general overview of pre- and post-processing steps that are relevant for the analysis of functional imaging time series. Data analysis issues will be presented as well as paradigm designs for assessing brain function. The subsequent discussion of structural image analysis methods will primarily focus on voxel-based morphometry (VBM), deformation-based morphometry (DBM), and diffusion tensor imaging (DTI).

12.1 Introduction

During the past 20 years, the field of functional magnetic resonance imaging (fMRI) has experienced a rapid development. At its beginning, the term fMRI was primarily referring to the acquisition and analysis of MRI time series that aimed to detect task-related changes in blood-oxygenation level dependent (BOLD) responses. Meanwhile, functional MRI-based applications have extended far beyond this initial narrow scope, now encompassing perfusion-based techniques (such as arterial spin labeling, ASL), as well as resting-state fMRI that observe spontaneous fluctuations of brain activity.

Moreover, the development of advanced scanner equipment and imaging sequences has afforded the time-efficient acquisition of structural imaging data: Today, almost every fMRI protocol contains a high-resolution T1-weighted sequence, and often, the scan protocol is also supplemented with a DTI sequence. Moreover, the development of (semi-) automated morphometric techniques for these structural imaging modalities

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(e.g., VBM, DBM) has enabled unprecedented venues for analyzing the functional correlates of brain morphological features.

The fMRI field has been growing exponentially over the last 20 years, and due to the truly interdisciplinary character of research, it is almost impossible to become an expert on every aspect of this field. A neuroscientist most likely won't become an expert on network sciences, advanced statistics, or a mathematician. And it is not necessary to become one, as one does not have to become an MRI physicist to run fMRI experiments, but it is necessary to get a general overview and a good working knowledge in order to decide which path has to be followed to answer a certain research question. This is not only necessary in order to choose the optimal experimental design and data acquisition methods, but also in order to estimate the human and technical resources needed to conduct and analyze an experiment properly. This also includes aspects like boundary conditions for advanced analysis methods, which we plan to apply to the data, because they might impose restriction on paradigm designs, as well as pre- or post-processing strategies. This chapter aims to provide some general background and working knowledge that is needed to plan, conduct, and analyze fMRI experiments, and it also covers the morphometric analysis of structural MRI data.

12.2 Physiological Foundations of fMRI

While several functional MRI techniques have developed in recent years, there is one aspect they have in common: They exploit hemodynamic responses that are triggered by changes in neural activation. When a focal brain activity occurs, the energy demand increases, and a plethora of physiological processes are triggered to ensure that sufficient energy is provided to support brain cell function (i.e., to keep the ATP concentration constant and the active ion channels up and running). In order to avoid any energy shortage, the vascular system reacts in this situation with a local vasodilatation, which leads to an increase of the local blood flow up to 40%. This temporary increase of regional cerebral blood flow (rCBF) in activated brain regions is a key process for all fMRI imaging techniques, and provides the physiological basis of *perfusion-based MRI* techniques (e.g., arterial spin labeling).

Yet, the short-term changes in rCBF have additional consequences (Fig. 12.1): In general, autoregulatory processes keep the global and local blood flow constant. The ratio C between the concentration of oxygenated and deoxygenated hemoglobin ($[HbO_2]/[dHbO_2]$) is also kept within constant margins during rest. However, when a certain brain region becomes (more) active, local oxygen consumption increases. Therefore, one observes a decrease of $[HbO_2]$, whereas $[dHbO_2]$ increases, and consequently, the ratio C between both decreases as well. Due to the drastic local flow increase in the activated brain area, much more oxygenated HbO_2 is actually delivered than consumed by the increased neuronal activity. This overcompensation leads to an increase of the ratio C, which exceeds the baseline level and remains elevated even after the local brain activation already went back to its initial level. This situation persists for up to 20–30 s before the whole system returns back to baseline values.

These short-lived changes in local blood oxygenation provide the physical basis for a second class of techniques: *BOLD fMRI*. As pointed out in Chap. 11, HbO_2 and

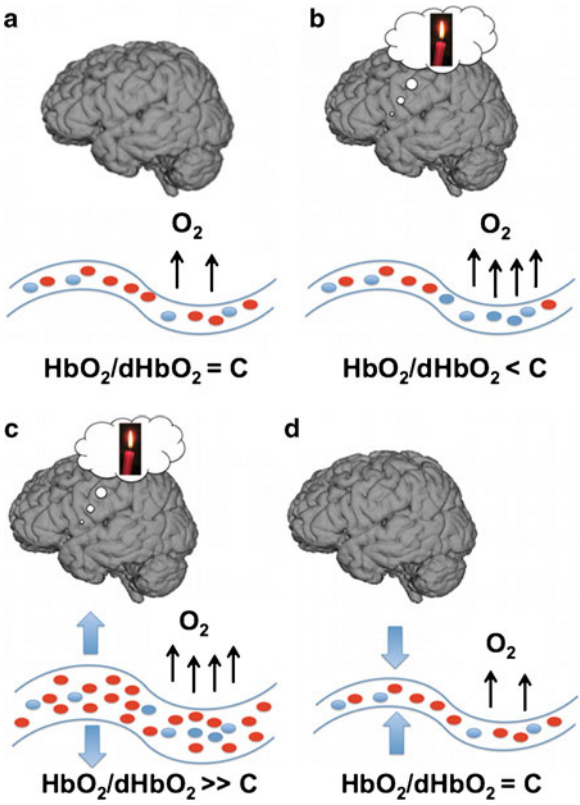

Fig. 12.1 *BOLD Effect.* During "rest" the ratio between oxygenated and deoxygenated hemoglobin is fairly stable: $[HbO_2]/[dHbO_2] = C$ (**a**). When brain activity increases locally, this raises oxygen extraction, and therefore $[HbO_2]/[dHbO_2] < C$ (**b**). This is followed by vasodilation, leading to increased local blood flow and blood volume. As the increased blood flow delivers more oxygen than needed: $[HbO_2]/[dHbO_2] >> C$ (**c**). After the locally increased brain activity stopped, the system slowly returns back to baseline again: $[HbO_2]/[dHbO_2] = C$ (**d**)

$dHbO_2$ have different magnetic properties. $dHbO_2$ is more paramagnetic and increases the local field, whereas HbO_2 is diamagnetic as the surrounding tissue (Pauling and Coryell 1936). These magnetic differences can have a profound effect on the MR signal of cerebral blood, which are mainly caused by $dHbO_2$. The higher the $dHbO_2$ concentration in a blood vessel is, the more the local magnetic field is disturbed in the vessel and in the surrounding tissue. These magnetic field disturbances can be detected by using a T2-(Thulborn et al. 1982) or T2*-weighted sequence (Ogawa et al. 1990), because local field inhomogeneities cause a rapid dephasing of the transversal magnetization, which causes signal loss in these sequence types. In other words: If the $dHbO_2$ concentration increases, the local signal in T2- or T2*-sensitive sequences decreases, and vice versa—a phenomenon that is referred to as the BOLD effect.

12.2.1 Hemodynamic Response Function

As outlined above, local cerebral activity is followed by a local vasodilatation that causes an increased regional cerebral blood flow, which in turn induces local changes of blood oxygenation that are measurable via signal changes (i.e., BOLD responses) in T2- and T2*-weighted images. The signal changes that are induced by brain

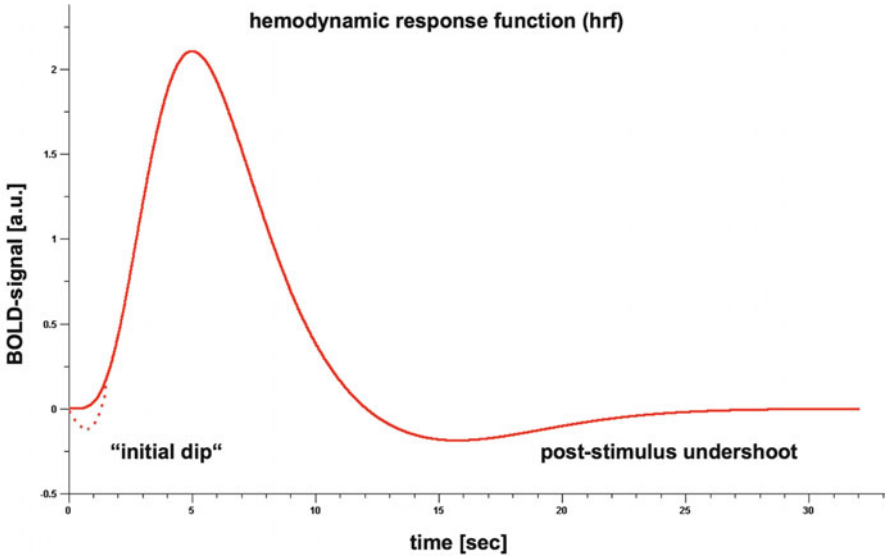

Fig. 12.2 *Hemodynamic response function (hrf).* Following a brief stimulus, [HbO_2] decreases, which might lead to an initial signal decrease (initial dip). The main signal change is driven by the large-scale increase in cerebral blood flow and blood volume that increases the [HbO_2]/[$dHbO_2$]-ratio and hence the signal intensity of the bold signal. Because the blood flow returns faster to baseline values than the regional blood volume one observes the poststimulus undershoot

activations (e.g., following a brief sensory stimulus) show specific temporal characteristics, which are usually referred to as *hemodynamic response function* (hrf: Fig. 12.2).

For a brief stimulus, one might observe an initial decrease of BOLD signal intensity within the first 1–2 s after the stimulus onset, which is often referred to as the "initial dip" (Ernst and Hennig 1994; Menon et al. 1995). It was suggested that the rapid increase of neuronal activity leads to a higher oxygen extraction fraction, which results in a decreased local [HbO_2]/[$dHbO_2$] ratio, and therefore an initial BOLD signal decrease. Yet, the initial dip is very low in amplitude, and often hard to detect: Thus, its existence is still under debate (Behzadi and Liu 2006; Buxton 2001; Nirkko 2003; Vanzetta and Grinvald 2001; Yacoub et al. 2001b). However, recent data indicate that it might depend on the microscopic properties of the tissue and may therefore be not always and ubiquitously observable (Tian et al. 2010).

Meanwhile, the subsequent temporary hyperperfusion that is triggered by brain activation supplies the respective brain region with more oxygenated blood than is actually needed, resulting in a drastic increase of the local blood oxygenation. This change is reflected by a steady BOLD signal increase, which takes about 2–5 s after stimulus onset to reach its maximum. Thereafter, the BOLD signal slowly returns back to baseline (which takes up to 12–18 s), and even experiences a temporary decline below this level (the so-called poststimulus undershoot), lasting about 4–10 s. The poststimulus undershoot is thought to reflect the slow recovery of the cerebral

blood volume: In the so-called *Balloon model* (Buxton and Frank 1997; Buxton et al. 1998), which aims to provide a physiological model of the hrf, the shape of the hrf is described with the help of an input-state-output model, using the blood flow as input parameter, blood volume and the amount of deoxyhemoglobin as state variable, and the BOLD signal as output variable. The venous part of the vascular system is considered as a balloon, which is inflated by the arterial blood flow. In this model, the poststimulus undershoot results from a reduced clearance and dilution of the deoxygenated hemoglobin after the balloon has relaxed. The "balloon model" is simple and capable to explain the whole shape of the hrf, including the initial dip. However, it should be mentioned here that also alternative models exist, like the "windkessel model" (Mandeville et al. 1999) or the "steady-state model" (Hoge et al. 1999a, b).

12.2.2 Properties of the hrf

Even though the hemodynamic response to a brief stimulus can elicit rather long BOLD fMRI signal changes (which can last up to 30 s to return to baseline levels), it has three properties which are basically responsible for the success of this method in the context of brain activation studies: (1) It allows the detection of very short stimuli. (2) Its shape is fairly stable and therefore predictable across events, regions, and volunteers. (3) It is linear across a broad range of stimulus durations.

At the beginning of fMRI, especially the first point was a matter of debate. The early stimulation designs were conducted with rather long stimulus durations (around 30 s) that only elicited very small signal changes (about 2–5%). For this reason, it appeared very unlikely that much shorter stimulus durations would elicit any detectable signal. However, this conclusion proved to be false. Blamire and colleagues (1992) showed that a visual stimulus as short as 2 s was capable to induce a measureable signal change. Savoy et al. reduced the stimulus duration further down to 34 ms and was still able to detect an activation in the primary visual cortex (Savoy et al. 1994), while a motor activity of 500 ms duration was shown to be sufficient to elicit a BOLD response in the primary motor cortex (Bandettini et al. 1993). Within a stimulus range between 1 and 5 s the amplitude of the BOLD signal appeared to be linear (Dale and Buckner 1997), and it was suggested that the "responses to long-duration stimuli can be predicted from responses to shorter duration stimuli" (Boynton et al. 1996) because of its stability and reproducibility. Yet, the amplitude seems to be stable below 500 ms, and does not depend on the stimulus duration (Savoy et al. 1994): Hence, it cannot be considered being linear anymore. However, in general, the hrf is considered to be linear and time-invariant. In fact, the linear aspects explain up to 70% of the variance in fMRI data, depending on the exact mathematical shape, which is used to model the hrf. It might be modeled by a Poisson function (Friston et al. 1994b), gamma function (Boynton et al. 1996; Kruggel and von Cramon 1999), Gaussian function (Kruggel and von Cramon 1999), or a mix of Gaussian functions (Gossl et al. 2000). In practice, the implemented hrf

model is not actively chosen by the researcher, but hard-coded by the software package used to analyze the data. However, there are tools available to customize the hrf function (Woolrich et al. 2004b), which might be used to model it on an individual basis, to integrate pharmacological models into an fMRI analysis, to account for developmental changes or for the aging process, or for differences in the hemodynamic coupling itself, or to simply improve the model accuracy. In fact, the accuracy can be improved (up to 92%) if one considers the inter-subject variability of the human BOLD response. Aguirre, Zahran, and D'Esposito showed that shape of the hrf varies significantly between subjects, but was highly consistent within subject across scanning sessions if the same region is examined (Aguirre et al. 1998). Also significant variations can be observed between brain regions (Buckner et al. 1996; Miezin et al. 2000). So far, it remains unclear whether such differences are caused by vasculature differences, processing latencies, or by any factor influencing the hemodynamic coupling, as summarized by Muthukumaraswamy et al. (2011).

Having said that, one might wonder whether fMRI can be conducted robustly at all, but it has to be kept in mind that the influence of variability of the hrf is small compared to the share of variance that is successfully explained by (one of) the "standard" or "canonical" hrf functions. Those "unwanted effects" might even be useful to address very special questions like, for example, mental chronometry (Menon and Kim 1999 for review; Menon et al. 1998). However, for most designs it will be of less importance and can be ignored. The same holds true for the above-mentioned nonlinearity issues. They are mainly of relevance if the stimulus duration is short (<1 s) and/or the time between successive stimuli is below 2 s. On the other hand, these nonlinearities are of outermost importance if physiological models are investigated (Friston 2005; Valdes-Sosa et al. 2009), the neurovascular coupling is of interest (Magri et al. 2011), or causal models are used to explain fMRI data (Stephan and Friston 2010) or might be of interest for more advanced analysis methods like the investigation of graph theoretical models (Hartman et al. 2011).

12.2.3 Hemodynamic Coupling

As outlined above, local cerebral activity is followed by a vasodilatation leading to an increased regional cerebral blood flow and consecutively to (hopefully) measurable BOLD response. At first sight, this seems to be a very simple mechanism. But it raises the important questions: What exactly triggers the response, and what are the underlying cellular mechanisms? In other words: What does fMRI measure?

First of all, it must be emphasized that functional MRI techniques do not measure brain activity by itself, but capture hemodynamic response phenomena that are triggered by brain activation, which means that fMRI does not provide a direct measure for the metabolic demand caused by neuronal activity or of spiking activity. While the former notion holds true for both perfusion-based and BOLD fMRI, there are additional considerations that are specific for BOLD fMRI: Currently, it is assumed that the BOLD signal basically reflects the excitatory component of local

neuronal activity (Attwell and Iadecola 2002; Logothetis et al. 2001). However, transmitter release in the synaptic cleft itself can modify the local perfusion. So far, three mechanisms are known: (1) via nitric oxide triggered by glutamate release (Akgoren et al. 1996), (2) via astrocytes (Figley and Stroman 2011; for review), and (3) via neurotransmitters (noradrenalin, dopamine, serotonin (5-HT); see Harris et al. (2011) for review). A thorough treatise of these physiological mechanisms would be beyond the scope of this chapter, but there are helpful discussions in recent review papers (Attwell et al. 2010; Logothetis 2008; Mangia et al. 2009). Thus, differences in BOLD signal might not reflect differences in brain activity, which is a general problem of fMRI (Harris et al. 2011). And this is the crucial question when interpreting or better scrutinizing own results, because BOLD changes can be induced by every mechanism that influences the regional cerebral blood flow and oxygenation. Specifically, in the context of exercise-related studies, one has to keep in mind that exercise might interact with any mechanism on a cellular level, which might change the hemodynamic coupling and might mimic changes on a functional level.

However, this issue was raised since the first fMRI manuscripts were submitted for review and "shedding new light on the regulation of cerebral hemodynamics and metabolism by neural activity is still an ongoing effort and cherished goal in the fMRI community" (Kwong 2011), and should not hinder any researcher from using this methodology to answer research questions.

12.3 Paradigm Design and Optimization

There are several methodological issues that have to be considered while planning task-related fMRI experiments, which will be discussed in the following section. Beyond the general issue of appropriate task selection, the utilized MRI technique itself determines a couple of boundary conditions that constrain the experimental design. For example, there are technical requirements dictated by MRI data acquisition itself. Moreover, the signal properties of the hemodynamic responses that are measured with fMRI techniques impose certain constraints regarding the temporal characteristics of brain activations that should be met to detect these activations efficiently. Thus, the timing, duration, and presentation order of the different task conditions—usually referred to as experimental design—need to be optimized to enable a sufficient detection of the expected brain activations.

12.3.1 General Considerations

Because the amplitude of any induced signal changes is very small, the stimuli have to be repeated many times. The technical conditions that are present during the scanning of fMRI sequences add general constraints to the experimental design: For example, head motion could lead to image artifacts, which means that volunteer

movements need to be restricted as much as possible. As a consequence, responses are typically limited to simple button presses or tiny joystick movement. Spoken responses are difficult to record due to the noise emitted by the MRI system. Even though MRI-compatible microphones are commercially available, the mandibular motion causes image artifacts and should be avoided. Moreover, the scanner noise during image acquisition makes it is easier to deliver stimuli or commands visually than acoustically, even though it should be noted that dedicated headphones are available.

12.3.2 Selection of Appropriate Task Conditions

In a nutshell, fMRI experiments make inferences about the neural underpinnings of psychological processes by provoking psychological states under controlled conditions (usually by presenting standardized tasks) and by observing correlated changes in brain activity. Thus, the foremost challenge in conducting an fMRI study is the construction of experiments that are able to activate the psychological processes of interest. Usually, this is accomplished by comparing the brain activation level during an "active" task (that is assumed to activate the psychological process of interest) with the brain activation level during "baseline" or "control" conditions. The control condition might be either a low-level rest period (like fixation of a cross on screen), or an additional active condition. Optimally, the (active) control condition would differ from a condition of interest only regarding the key process of interest, whereas every other aspect is kept the same. For example, if one is interested to find a brain region that specifically activates when face stimuli are presented, one could present a reference condition with stimulus objects that have a similar shape, information content, image contrast, and colors as the target stimuli (e.g., scrambled faces), which are presented in the same frequency and for the same duration as the face stimuli. Even though not mandatory, an additional low-level baseline is helpful, because it resolves ambiguities. For example, the difference Faces (F)—NonFaces (NF) can yield positive results (i.e., stronger relative activation for faces) in the following constellations (where 0 refers to the low-level baseline condition):

1. $F > NF, F > 0, NF > 0$
2. $F > 0, NF = 0$
3. $F = 0, NF > 0$
4. $F < NF, F < 0, NF < 0$
5. $F = 0, NF < 0$

Noteworthy, only the second constellation reveals a truly face-specific activation. However, in order to decide whether one of the stimulus classes activated a region, one has to compare it against a (low level) baseline. The comparison with active control conditions aims to control for the possibility that at least some of the observed brain activations are triggered by other psychological processes that became co-activated during task completion.

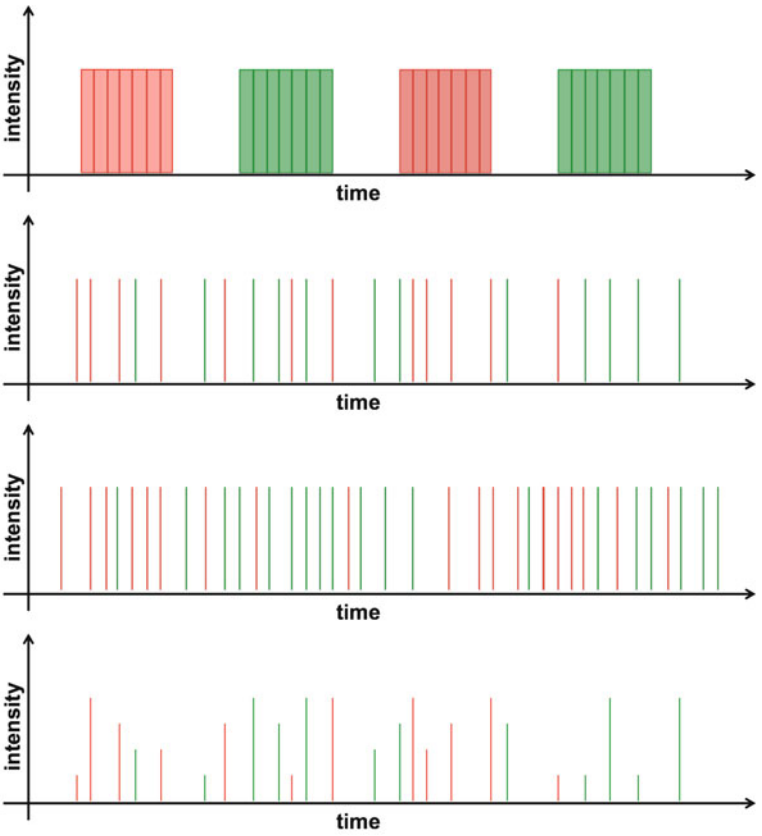

Fig. 12.3 *Paradigm design*. Four different paradigms are illustrated. From *top* to *bottom*: block design, randomized event-related design, mixed design, parametric design. Each paradigm consists of two event classes colored in red and green. In all cases, the low-level baseline is implicitly given by time periods without stimulus presentation (i.e., stimulus intensity equals zero)

12.3.3 Experimental Design Types

In general, task fMRI studies utilize two main classes of experimental design, the so-called block design and the event-related design (although there are also hybrid forms, so-called mixed designs, Fig. 12.3). Both design types differ regarding timing, order, and duration of stimulus presentation.

In a block design, stimuli of experimental and control conditions are concatenated into blocks of 10–30 s length, which are usually repeated about 4–6 times per condition. In this kind of design, the single stimuli presented within a block are not considered to be separate events, but are interpreted as a homogenous steady-state stimulation entity. Classical fMRI experiments to provoke motor

system (finger-opposition or finger-tapping task) or the visual system activation ("checkerboard stimulation") are performed in this fashion.

The advantage of the block design is its simplicity and its power for detecting focal brain activation. As it will be discussed below, a block design leads to the highest signal changes and should be the first choice when designing an fMRI experiment. Since blocked designs aim to provoke a prolonged and continuous increase of fMRI signal intensity, they are most appropriate for investigating psychological processes that can be assumed to be continuously active during the task block. Moreover, block designs are most appropriate for experimental tasks where frequent switches between task conditions would disrupt attention and impair task performance (in fact, task switching may even cause an unintended activation of psychological control processes: see also Chap. 6). However, block designs have a couple of drawbacks, like habituation and predictability: The latter aspect is especially problematic for task paradigms that are critically dependent on the unpredictability of the trial order. For example, motor inhibition paradigms often present a larger proportion of go reaction trials which are randomly interspersed with a smaller number of inhibition trials in order to induce a prepotent go response tendency that has to be actively suppressed during the few inhibition trials (see also Chap. 6): Here, a massed presentation of inhibition trials makes their appearance predictable, and will probably reduce the activation of inhibitory processes. Moreover, the narrow spacing of single stimulus events at a fixed pace, which is typically found in block designs, will amalgamate the hemodynamic responses that are elicited by these singular events. This guarantees an extended continuous period of elevated fMRI signal, but the averaging character of this design type does not allow for extracting the hrf, or for detecting brain activity associated with events that are unpredictable in time, as, for example, the time point when the visual perception of a switch figure changes from one state to the other, like in a Rubin vase–face illusion image.

The second prototypical design type, the event-related design (ER-design), overcomes many of the latter obstacles. As the name already implies, such paradigms focus on brain activations elicited by single stimulus events, instead of fusing the responses of several stimuli, as it is found in block designs. Thus, event-related fMRI designs are especially appropriate for investigating phasic brain responses that are closely time-locked to specific stimulus events.

In their most basic form, event-related designs separate the presentation of successive events by long pauses of, say, 12 s or longer, so-called slow event-related designs. Due to these long intertrial intervals (ITI), the hrf that is elicited by individual stimuli can evolve and return to baseline before the next stimulus is presented, which means that there is no (or: few) overlap between the different hemodynamic responses. As such, slow event-related designs are especially useful for estimating the shape of the hrf.

Meanwhile, many event-related fMRI studies use rapid event-related designs. Here, much shorter ITI between successive stimuli are used than in slow event-related designs, increasing the subjective pace of the task. As a consequence, the hemodynamic responses elicited by the different events show a stronger overlap,

which makes it more difficult to identify the event-related signal peaks in the fMRI signal time series. To cope with this problem, rapid event-related designs vary the temporal distance between successive events, either by varying the ITI systematically (e.g., using a number of intervals in a range from, say, 1–5 s: "jittering"), or by adding so-called null events (i.e., by randomly interspersing blank trials with a fixed duration). The resulting variation in hrf overlap between successive trials can later be used in statistical analysis to isolate event-related signal changes.

Event-related paradigms allow for a maximum of design flexibility. For example, events for the different experimental conditions can be mixed in a random fashion, which means that habituation and predictability are minimized. Moreover, it is possible to perform a post hoc classification of the different events according to task performance (e.g., separate trials with correct and erroneous responses): A classical application of this strategy can be found in memory studies, where subjects can be scanned while they encode a series of items in an event-related design, and subsequently tested for their retention of this material. This way, it is possible to compare brain activation during the encoding of items which were subsequently remembered with the brain activation during the encoding of items that were subsequently forgotten, so-called subsequent memory effects (e.g., Brewer et al. 1998; Wagner et al. 1998). Another potential advantage of this design class is the opportunity to measure brain responses that are unpredictable in time, for example, the time point when the visual perception of a switch figure (e.g., a Rubin vase–face illusion image) changes from one state to the other.

Yet, the event-related design has the disadvantage of a reduced power to detect brain activation as compared with a block design, which means that longer experimental durations are necessary to achieve comparable results. This will become especially salient in slow event-related designs, but is also true for fast event-related designs. While the stimuli of different classes can be as close together in time as 2 s and can be still resolved, because the hrf is linear in this range (Dale and Buckner 1997), successive trials should not be spaced closer in time.

Both of the above-mentioned design types can be combined in a hybrid format, so-called mixed designs. Here, different experimental conditions are presented in a block-wise fashion, but the temporal spacing of single events within a task block is systematically varied, or different event classes are intermixed, which allows for a separation of event-specific responses in later statistical analysis. This approach is especially useful if researchers are interested in segregating tonic and phasic brain responses. For example, Donaldson et al. (2001) used a mixed design approach for a recognition memory task where subjects had to recognize items that they had learned before. The design enabled to differentiate between activations reflecting the "retrieval mode" (i.e., the attempt to remember the stimuli, which was tonically present across the whole task block), and phasic responses, which reflected the successful recognition of remembered items (which were time-locked to the singular events that were recognized successfully).

So far, the different design types differ regarding the timing of the stimuli. The conditions operationalize the independent variable of interest (i.e., a psychological process) in a categorical fashion, that is, as fixed factors, where task conditions are

treated as discrete on-off states (i.e., are either present, or absent). Yet, it is also possible to treat the independent variable as a continuous variable. If the stimulus intensity for a task condition (i.e., pain intensity, cognitive demand, and finger-tapping frequency) is modulated throughout an experiment, the design is called parametric design. This does allow for measuring not only linear relationships (i.e., the stronger the stimulus intensity, the stronger the brain activation), but also exponential or curvilinear relationships. This design pattern is applicable to both block and event-related designs.

A good review on fMRI design types is given by Amaro and Barker (2006) or Chein and Schneider (2003). Regarding potential pitfalls, the reader is also referred to the discussion by Savoy (2005).

12.3.4 Optimizing Paradigms

When designing an fMRI experiment, the first and most important decision to be made is the choice of the paradigm design type. As a general rule, it can be stated that a blocked design should be preferred over an event-related approach, because it provides the optimal statistical power to detect BOLD changes. However, it does not allow for an investigation of the hrf, the analysis of single stimuli, and might not be adequate for the underlying neuroscientific question, which is of course the most crucial aspect. The boundary conditions for the latter point are (1) a condition is represented by only two states, which can be switched on and off (for example: self paced finger tapping: yes or no), (2) there is no need to distinguish between single stimuli within a block, and (3) processes cannot be separated from another process by a couple of seconds. An in-depth discussion can be found in Zarahn et al. (1997).

If the shape of the hrf is known (Aguirre et al. 1998), the optimal duration of a block is 14–20 s (Zarahn et al. 1997); otherwise a duration between 30 and 40 s might be used. A block is usually repeated 4–8 times. Due to slow scanner drifts and low-frequency noise (with its 1/f characteristic), it is not advisable to use larger block durations than 30–40 s (Zarahn et al. 1997). In other words, longer block durations increase the risk of misinterpreting these non-task fluctuations in BOLD signal as task-induced changes in brain activation. Therefore, BOLD fMRI are problematic if researchers are interested in examining psychological processes that cannot be switched on and off within a few seconds (e.g., mood or pain states). However, in these situations perfusion-based fMRI (see below) may provide a useful alternative, since these techniques are less sensitive to these forms of low-frequency noise. Considering the stimulus presentation within a given block, the number of stimuli presented within a single block, and the spacing between these stimulus onsets (stimulus onset asynchrony, SOA) primarily depends on the nature of the experiment and the used stimuli. In most block designs, the conditions have a fixed order, in which the conditions alternate, and are interleaved by a low-level rest condition. Considering the ordering of the different task conditions, there are a variety

of different approaches, for example the classical "boxcar design" (where an active (A) and a control (C) condition are presented in alternation, e.g., A-C-A-C-A-C), or "castle designs" (where an active (A) and an active control (C) condition alternate with a low-level resting baseline (R), e.g., R-A-R-C-R-A-R-C-R). The advantages and pitfalls of these different variants are extensively reviewed in Chein and Schneider (2003).

Event-related designs provide the maximum degrees of freedom for the paradigm design, but are more difficult to optimize. The simplest design is built by events of only one category separated far enough to allow the hrf to return (almost fully) to baseline (i.e., in a slow event-related design). In this situation, the most sensitive setup (=statistical power/time) is reached if the time between two successive stimuli, the interstimulus interval (ISI), is about 16 s. If the scan time is not crucial, the sensitivity could be further increased if the ISI becomes larger than 20–30 s. If more than one stimulus categories are used, the power for intercategorical differences can be increased by reducing the ISI well below 16 s as long as they are in randomized order. However, the sensitivity for detecting the evoked response of a single category necessarily decreases. If the ISI is not fixed but "jittered" around a mean ISI, the sensitivity/time can be increased, but will be always below that of a block design. Designs with long ISIs can also be used to extract the shape of the hrf. Due to the small within-subject and within-trial variability of the hrf (Aguirre et al. 1998), this approach can be used to detect even small differences in the onset of neuronal activity between conditions, as long as stimulus order, ISI, and jitter are fully randomized. If the number of conditions increases ($n>2$), or the contrasts become more complex, it is almost impossible to optimize these parameters manually. However, algorithms and free software tools are available that help to generate stimulus sequences and timing parameters that are optimized to detect contrasts of interest (Wager and Nichols 2003).

The number of events per condition that are needed to gain a sufficient signal is difficult to determine in advance. If the sampling rate of the fMRI scanning sequence is sufficiently high, it might detect even a single event, while if a high-frequency rapid event-related design is chosen, even 50 events or more can be insufficient. As a rule of thumb, at least about 30–40 events per condition should be presented. Yet, the necessary number of events per condition depends on the design and the underlying question.

The same holds true for the number of different conditions: If the number of conditions becomes too large, the balancing and the optimization become increasingly difficult. Moreover, the experiment is simply at risk of becoming too long. From a practical point of view, a single fMRI run that lasts longer than, say, 30 min means a very high burden for a volunteer, not only due to the noise of the MR and the narrowness of the magnetic bore, but also due to the attentional demands of the task which may become increasingly fatiguing.

This section was only able to give a broad overview of the topic fMRI design optimization. For further details, we like to refer to more extensive treatises (Dale and Buckner 1997; Friston et al. 1996; Friston et al. 1999; Josephs and Henson 1999; Zarahn et al. 1997).

12.4 Acquisition of fMRI Time Series

12.4.1 Field Strength

While experimental design is a crucial issue for fMRI studies, adequate scanner equipment is another relevant topic, because the technical limits of these systems necessarily will often restrict the signal-to-noise ratio (SNR) for measuring the physiological signal changes that are evoked in an fMRI experiment.

The most expensive way to maximize the signal-to-noise ratio is to maximize the field strength. As noted above, the BOLD effect is a compound of both T2 and T2* effects, which have a distinct physical basis. T2 is more sensitive to the intravascular effects, whereas T2* is more relevant for the extravascular tissue. Ogawa was able to show that the effect of intravascular component scales linearly with the field strength, whereas the tissue component scales exponentially (Ogawa et al. 1993) and shifts therefore from the vessel compartment more and more to the surrounding tissue (Gati et al. 1997).

Unfortunately, field strength is not an upgrade option, and the system prices scale by a factor of about 1.000.000 US$/T. Meanwhile, higher field strengths also increase the risk of image artifacts, especially outside the brain. Therefore, it has to be critically discussed with all users of the system whether the higher price of a higher field strength system really pays off. Currently, 3T can be considered as the standard field strength for MRI systems used for humans, but it has to be pointed out that most fMRI experiments can also be performed sufficiently with 1.5T scanners. The MR physics at these field strengths is fully understood and the vendors solved most technical problems. They are highly optimized and the leeway for further improvements is limited.

On the other hand, ultra-high-field scanners (i.e., 7T or even higher) should primarily be considered as being experimental systems. They show a drastic increase in BOLD sensitivity, but they are still far from being optimized, and a dedicated staff of MR physicists and technicians should be (fully) available in order to keep the system up and running (including sequence optimization). An in-depth discussion of different aspects of high-field- and ultra-high-field fMRI is given elsewhere (Gati et al. 1997; Hoenig et al. 2005; Triantafyllou et al. 2005; van der Zwaag et al. 2009; Yacoub et al. 2001a).

12.4.2 MR Sequences

There are mainly two criteria for MRI sequences that have to be met for BOLD-based fMRI: They have (1) to be sensitive to T2 or T2* changes, and (2) to allow fast data acquisition, since the time course of BOLD signal changes needs to be

observed with reasonable temporal resolution. Both requirements are met for so-called Single-Shot Gradient Echo Planar Imaging sequences (sshGE-EPI), when TE~$T2^*$ for gray matter (see also Chap. 11). They are the "working horse" for fMRI. With this sequence type, it is possible to acquire a multi-slice scan volume that covers the entire brain, while maintaining an acceptable spatial resolution about 3 mm voxel size, within a time frame well below 3 s (usually referred to as Time of Repetition, TR). Since a scan volume is acquired slice by slice, this means that the BOLD signal measurement for each single voxel is repeated every TR. Depending on the goals of the study, researchers may wish to achieve a higher sampling rate. For this purpose, there are different strategies available: For example, we can increase imaging speed simply by reducing the number of slices acquired. However, this is necessarily paid off with reduced brain coverage. Another option to accelerate image acquisition is the use of half-Fourier imaging or parallel imaging (see Chap. 11). In combination with another sequence type, which is called PRESTO (PRinciple of Echo Shifting with a Train of Observations (Liu et al. 1993)), a whole brain coverage can be accomplished within 500 ms and an isotropic spatial resolution of 4 mm (Neggers et al. 2008). However, a slight disadvantage of the latter might be the drastic increased noise level accompanied with this sequence.

While optimizing an fMRI sequence, one has to bear in mind that a high sensitivity for the BOLD effect, i.e., T2*-sensitive sequences, also results in a high sensitivity for static susceptibility gradients, which are especially present at the skull base, or close to the mastoid process. These gradients lead to a signal void and huge image distortions in adjacent brain regions. Using standard sequences and setups for whole brain image acquisition, it is therefore almost impossible to reliably scan temporobasal structures, like the amygdala or the hippocampus, or the orbitofrontal cortex. However, there is a growing literature discussing methodological approaches that can help to reduce these effects, for example by increasing the spatial resolution, using oblique image acquisition planes (Weiskopf et al. 2007), and parallel image acquisition schemas (Schmiedeskamp et al. 2010) which reduce these artifacts to an acceptable degree. Homogenizing the local magnetic field by applying additional magnetic field gradients and preparation pulses (Deichmann et al. 2003) or the use of intra-oral shims (Osterbauer et al. 2006; Wilson and Jezzard 2003) can further improve the image quality.

If long experimental conditions are needed (e.g., blocks longer than 30 s), classical fMRI sequences may not be ideal solutions due to scanner drifts and the low-frequency noise profile. Here, arterial spin labeling should be considered (Aguirre et al. 2002; Detre and Wang 2002; Wang et al. 2003). ASL is also useful when investigating states, which cannot easily be switched on or off, such as tinnitus. ASL time series consists of a series of successively acquired image pairs (unlabeled + labeled). Therefore, they are less susceptible to scanner drifts and low-frequency noise, and can be considered as method of choice in such situations. However, it should be mentioned that ASL sequences are difficult to implement and demand exquisite scanner stability.

12.5 Preprocessing of fMRI Time Series

Before fMRI data can be analyzed statistically, there are a number of preprocessing steps that have to be performed. First of all, the data have to be corrected for temporal differences between image slices that are due to the sequential image acquisition character of single-shot sequences (*slice-timing correction*). Moreover, image preprocessing needs to remove head movement effects (*realignment*). The spatially low-resolution functional imaging time series should undergo a *coregistration* to a high-resolution anatomical scan, allowing for later anatomical assignment of any imaging result. For group analysis, the imaging data have to be spatially transformed into a standard anatomical space (*spatial normalization*) and finally undergo a *spatial smoothing*, which compensates for residual individual anatomic differences, and increases the SNR for subsequent statistical inference. These preprocessing steps will be explained in the following subsections:

12.5.1 Slice-Timing Correction

The standard fMRI sequence is a single-shot EPI, which means that an image volume is acquired slice by slice, which takes about 3 s, depending on echo time, spatial resolution, and number of slices acquired. In other words, there is a huge time gap between the first and the last slice acquired within a single volume. This means that the BOLD signals that are collected from voxels in different slices reflect the state of the brain at slightly different points in time (i.e., have a different slice timing). For a block design, such a time gap is usually of less importance, because the design aims to average across the blocks of the same condition. Event-related designs, however, are designed to analyze the time series on the basis of individual events, which means that they critically rely on an exact timing of the BOLD responses. Therefore, slice-timing differences should be corrected. For short TRs (<2 s), the small timing differences can be accounted for by adapting the model setup to analyze the data by introducing the first derivative of the hrf time course into the statistical model (see below). A disadvantage of this approach is a reduction of statistical power, which is accompanied with this method, and the limitation to the small TRs.

However, because of the temporal characteristic of the HRF (i.e., because it is slowly varying in time), this problem can easily be solved by interpolation. The simplest approach is linear interpolation: When the image intensity in a voxel is known at time point $t1$ and $t2$, the intensity within each time point in-between can be estimated by drawing a line through both time points, determining its equation, and calculating the image intensity at $t1 + \Delta t$. To minimize the time difference Δt that has to correct for, it is usually advisable to use the time point of the middle slice as a reference for the slice-timing correction. By doing this, the correction is limited to a maximum of ½ TR. Alternative methods are spline- or sinc-interpolation, which

differ simply with regard to the number of reference points needed for the interpolation process, and the fitted function. See Sladky et al. (2011) for a recent discussion of this topic.

It might be argued that in the presence of head motion (which more or less always exists in fMRI time series), this approach might be not applicable, because the method relies on a rigid model (= the voxel coordinate does not change between two time points), which is not valid in the presence of motion. Others suggest realigning (i.e., motion correction) first, before the slice timing is performed, which might violate the assumption that two voxels with the same spatial coordinate have the same time lag relative to the reference slice. However, both approaches rely on the assumption that the differences (either in time or in space) between two consecutive volumes are small and, hence, both methods are suboptimal. From a mathematical point of view, the best solution for this problem would be to combine both approaches in one algorithm. This was recently accomplished and, indeed, showed a more accurate image reconstruction (Roche 2011).

12.5.2 Motion Correction

The motion correction procedure corrects for head motion during and across fMRI sessions, which can result in slightly different spatial positions of the brain between adjacent image volumes. Since the procedure acts on the image data that are acquired with exactly the same image modality, the motion between successive acquired image volumes can be corrected using a rigid body transformation (with three rotations and three translations). The optimal transformation can be determined using a minimal least square algorithm, which minimizes the residual sum of squares of the difference between two image volumes (Ashburner and Friston 2007b). At the end of this procedure, the whole time series is realigned either to the first volume, or to the mean of the time series. The resulting motion correction parameter can be later used as covariates of no interest in the statistical analysis step: This helps to account for residual noise associated with head motion, which even after realignment is typically large compared to experimentally induced variance. Another option that reduces this source of variance is to use not solely a rigid body transformation but to add a deformation-based term. The rationale for introducing a deformation term is based on the fact that magnetic field is not homogeneous in the field. Consequently, T2* images are a bit distorted. The distortion depends on the orientation of the head in the external magnetic field, and hence, head motion leads to variable deformations of the EPI images along time. This can be corrected by estimating the field changes and corrected by applying appropriate deformations during the motion correction procedure (Andersson et al. 2001). This method, which is usually referred to as “unwarping”, provides a better reduction of the motion-induced (and therefore unwanted) residual variance.

12.5.3 Coregistration

The price that is paid for the fast image acquisition of fMRI time series is the low spatial resolution. For example, a standard voxel size at 3 T is about $3 \times 3 \times 3$ mm^3, which means that the intrinsic spatial resolution of the functional images is in general not sufficient for proper anatomical assignment of detected activation clusters. This problem can be solved by a coregistration of the fMRI time series onto a high-resolution anatomical scan of the participant. Typically, this is a T1-weighted dataset with a spatial resolution of about $1 \times 1 \times 1$ mm^3. Because the image contrast and the spatial resolution of both modalities are different, the rigid body algorithm mentioned above cannot be used. The most common algorithm to solve this problem is called "mutual information maximization". Mutual information is a measure of statistical dependency between two variables. It is zero if two variables are not associated with each other and maximized otherwise. When using the image intensity histograms of both modalities as variables, this method can be used to find the optimum transformation to overlay the one image modality on the other. Because histograms are used (i.e., counting the number of occurrences of voxel intensities within certain intervals), this method can be used independently of the spatial resolution of the compared modalities (Woods et al. 1993).

12.5.4 Spatial Normalization

The term spatial normalization refers to a spatial transformation procedure that transforms a brain dataset into a common frame of reference. Spatial normalization serves two purposes: (1) the compensation of individual anatomical differences between subjects, which is relevant for group analyses, and (2) the simplification of anatomical orientation, when finally assigning activation foci to specific anatomical structures (Brett et al. 2002). The latter aspect also simplifies the comparison with research results published in the literature, even across the imaging modalities. This is achieved by spatially transforming the data into a common space of reference. The most popular frame of reference is provided by the atlas from Talairach and Tournoux (TTA) (Talairach and Tournoux 1988), which was based on detailed anatomical dissection of the 60-year-old women. Usually referred to as "Talairach space", the authors proposed a coordinate system where the origin is located in the anterior commissure, and the brain is oriented in a way that the x-axis runs through the posterior commissure. With appropriate scaling applied, the atlas can be used as a lookup table, assigning coordinates to major cortex structures, including Brodmann areas. In the last years, an atlas developed by Montreal Neurological Institute (MNI) largely replaced the TTA. It was created by averaging 152 high-resolution T1-weighted MRI datasets, using the same origin and axis orientation as defined by the TTA. The averaged datasets serve as a template, which can be used for coregistration of individual datasets to a common reference space. A large number of normalization algorithms and reference atlases have been published for the normalization process (Ashburner and Friston 2007a).

In a recent publication, different algorithms and atlases were compared against each other (Klein et al. 2009) and showed stable and reliable results irrespective of study populations and utilized algorithms.

A completely different approach is used by Anders M. Dale, Bruce Fischl, and colleagues, which does not aim to optimize the superposition of complete datasets onto a 3D template but to perform a cortical surface-based inter-subject alignment (Dale et al. 1999; Fischl et al. 1999a, b). This method is highly accurate, but restricted to the cortical surface, that is, does not cover subcortical regions or cerebellum. For comparison of the different spatial normalization procedures, we also refer to Gholipour et al. (2007).

12.5.5 Spatial Smoothing

Spatial smoothing refers to a procedure where signal intensities are averaged across neighboring voxels. Hereby, the voxels far away contribute less to the average, as compared to the direct neighbors of a voxel. The weighting function is usually a Gaussian bell curve, called Gaussian smoothing kernel, which is specified by its full width at half maximum (FWHM).

The advantage of the smoothing process is fourfold. First of all, it further increases the anatomical reliability of group studies, because the activation clusters are spread out in space, which increases the probability of overlap across subjects. Secondly, smoothing increases the signal-to-noise ratio, as every averaging process reduces noise components in the data. Thirdly, regarding the analysis of time series, the smoothing process has the advantage that it "normalizes" the noise structure of the BOLD signal (central limit theorem). The fourth rationale for smoothing lies in the statistical inference procedure. It reduces the number of independent comparisons within a dataset, and allows for less conservative statistical thresholding. As a rule of thumb, the smoothing kernel is chosen to be twice to three times larger than the spatial resolution of the dataset. However, if small structures are primarily of interest (e.g., amygdala, hippocampus, or brain stem structures), smaller smoothing kernels should be chosen (because the "matched filter theorem" dictates that the width of smoothing kernel should match the spatial dimensions of the structure of interest).

12.6 Analysis of fMRI Time Series

The easiest way to analyze fMRI time series is to average the images for the different conditions, and to perform a voxel-wise *t*-test to find all those voxels whose signal intensity (or brain activity level) differs significantly between the conditions. In this analysis strategy, the shape of the hrf is not taken into account, and it is difficult to extend this method to analyze event-related designs. An alternative approach is to model the *expected* time course of a condition and calculate

voxel-wise cross-correlation coefficients between the expected time course and the model time course (Bandettini et al. 1992). The resulting cross-correlation map provides information which voxels show condition-dependent BOLD changes. Even though these maps can be calculated very easily and can be applied to block and event-related designs, this approach has the disadvantage that it is difficult to directly compare two conditions with each other. Moreover, the cross-correlation takes only the shape into account, but ignores the amplitude of the respective activation.

12.6.1 The General Linear Model

The most flexible approach, which can be considered the current "gold standard" for fMRI analyses, is the use of the general linear model, which was initially proposed by Karl Friston and colleagues (Friston et al. 1994a; key concept). The main idea behind this approach is to model the time course for each condition in each voxel, and to estimate the response magnitudes by minimizing the residual error. Having done this, the differential effect of two conditions can be calculated by comparing the two amplitudes. The significance of the difference is estimated by comparing the amplitude difference with the residual error. To illustrate the procedure, let's consider the following *gedankenexperiment* which is outlined in Fig. 12.4: Imagine a block design paradigm with two active conditions (A and B), which are repeated eight times in alternating order. A low-level baseline separates both conditions. The block duration is 15 s. 160 volumes are acquired (TR = 3 s). The time course for each condition can be modeled by setting the value of the model function $X_{A/B}(t) = 1$ for those time points when the corresponding condition is "active" and $X_{A/B}(t) = 0$ for all other time points. In this case, we do not need to model the baseline condition explicitly. Now we can try to express the observed time course $Y_n(t)$ for any given voxel as a linear superposition of both model time courses plus an error term $\varepsilon(t)$:

$$Y_n(t) = \beta_{A,n} X_A(t) + \beta_{B,n} X_B(t) + \varepsilon_n(t). \tag{12.1}$$

Hereby, epsilon is assumed to follow a normal distribution. β represents the amplitude and has to be estimated for each condition and voxel separately. β can be estimated by minimizing the sum of squared errors, that is, by minimizing the term:

$$\sum \varepsilon^2{}_n = \sum (Y_n - (\beta_{A,n} X_A + \beta_{B,n} X_B))^2) = \min! \tag{12.2}$$

Equation (12.1) can be rewritten using matrix notation:

$$Y = X\beta + \varepsilon. \tag{12.3}$$

Because X contains the experimental design, or in statistical terms the "predictors", it is called design matrix. Y represents the real measured data or the response, whereas β are the unknown coefficient predictors and ε the error term. Figure 12.4

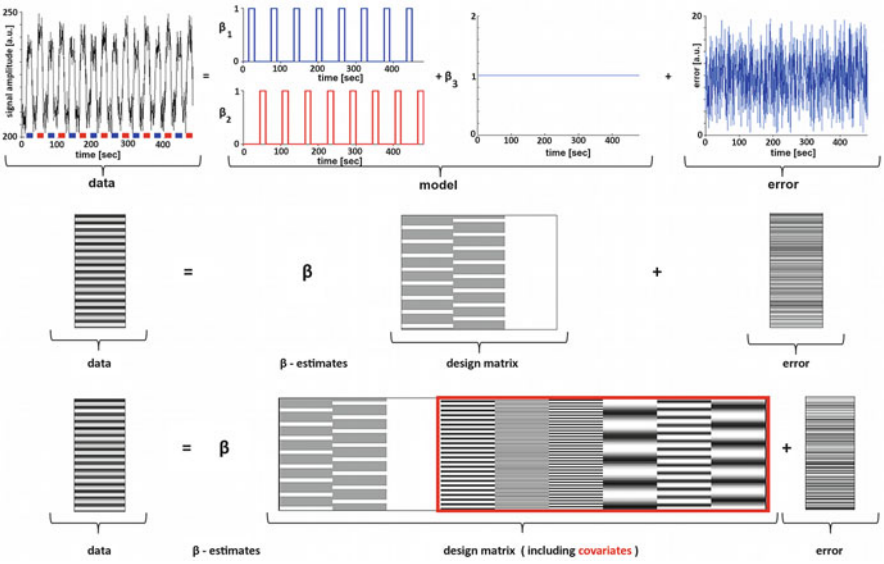

Fig. 12.4 *General Linear Model (GLM)*. The main idea behind the GLM is to explain as much variance of the measured data as possible by fitting a model to the observed data (*top row*). Each condition (Condition *A*: *blue*; Condition *B*: *red*) is modeled by a separate regressor. Both conditions superimpose linearly onto the mean signal intensity, which is represented by the third term. The optimal model parameters, the beta estimates, are found when the residual error term is minimal (*top row*). The model can be rewritten by concatenating the conditions into a so-called design matrix. Each column represents a single regressor. Time is coded along the row. Its graphical representation is shown in the middle row. The major advantage of the general linear model is its flexibility. Additional conditions can be added easily by adding an additional regressor. Moreover, covariates of no interest can be added as outlined in the *bottom row*

shows a graphical representation of the design matrix of the described experiment. The design matrix decodes each time point in a different line, whereas each condition is coded column-wise. The beauty of the General Linear Model (GLM) is its simplicity and extensibility. One can easily add covariates by just adding an additional term. A linear term (over time) might be added to compensate for linear drifts, or the motion parameters, derived from the motion correction procedure, to correct for head motion during the experiment:

$$Y_n(t) = \beta_{\mathrm{A},n} X_{\mathrm{A}}(t) + \beta_{\mathrm{B},n} X_{\mathrm{B}}(t) + \beta_{\mathrm{drift},n} + \beta_{\mathrm{motion},n} X_{\mathrm{motion}}(t) + \varepsilon_n(t). \qquad (12.4)$$

However, using the GLM as described here presumes a couple of assumptions: (1) the same model time course can be used for all regions activated by a certain condition, (2) all voxels are independent in time and space, and (3) the error term is normally distributed (mean = 0; variance σ^2), and its distribution is constant.

12.6.2 Detecting Brain Activations

So far, it was described how the data can be modeled using the GLM. However, the most crucial point is not answered yet, that is, how one can detect those regions activated by a task or which regions are activated stronger by task *A* compared to task *B*. Using the GLM, this questions can be properly addressed by comparing the estimated parameters $\beta_A - \beta_B$. If the difference is large compared with the unexplained variance, this would usually be considered significant. This so-called effect can be calculated formally by multiplying β with a contrast vector C. This vector depicts the β—estimates of interest. In the given example (12.4), the question which voxels are more activated under condition *A* as compared to condition *B* could be accessed by the $C = [1\ -1\ 0\ 0]$. The multiplication $C^*\beta$ yields: $\beta_A - \beta_B$. In order to address $B > 0$ (i.e., condition *B* activated above baseline), *C* would be $C = [0\ 1\ 0\ 0]$, or $C = [0\ 0\ 1\ 0]$ for the linear drift term accordingly. It should be noted here that $B > 0$ could also be expressed as differential contrast if the rest condition is explicitly modeled.

The statistical significance of any effect can be tested either using T- or F-statistics (generally implemented in all fMRI software packages; see below), which will depend on the specific contrast in question: Both tests compare the effect explained by the contrast with the residual variance and calculate a corresponding T- or F-value. Because this procedure is performed for every voxel of the brain, a corresponding T- or F-value is obtained for every voxel yielding a statistical three-dimensional map, which is thresholded depending on a chosen significance level. For better localization of the activated foci, the result can be overlaid as a color-coded map onto a high-resolution structural dataset (Fig. 12.5).

12.6.3 The Multiple Comparison Problem

One critical point for voxel-wise statistical analyses of imaging data is the large number of comparisons that are performed. A standard fMRI volume consists of $64 \times 64 = 4{,}096$ voxels/image, or 122,880 voxels if 30 slices were acquired. Each voxel is tested against the null hypothesis (i.e., that it is not activated), or that there is not a difference between two conditions, respectively. A significance level $p < 0.05$ means that if a difference is observed the probability of observing such a difference only by chance (= false positive) is less than 5%. However, it also means if 100,000 tests are performed, one could expect 5,000 false positives just by chance! The classical correction for this so-called multiple comparison problem is the Sidak correction or its approximation for large N, the Bonferroni correction, which divides the desired significance level by the number of independent tests performed. Even though the Bonferroni correction is easily calculated, it has a couple of disadvantages. If the significance level is chosen to be 0.05 and 100,000 voxels are tested, the Bonferroni corrected significance level would be $0.05/100{,}000 = 0.0000005$. Thus, it is very conservative from a practical point of view. To avoid making too many

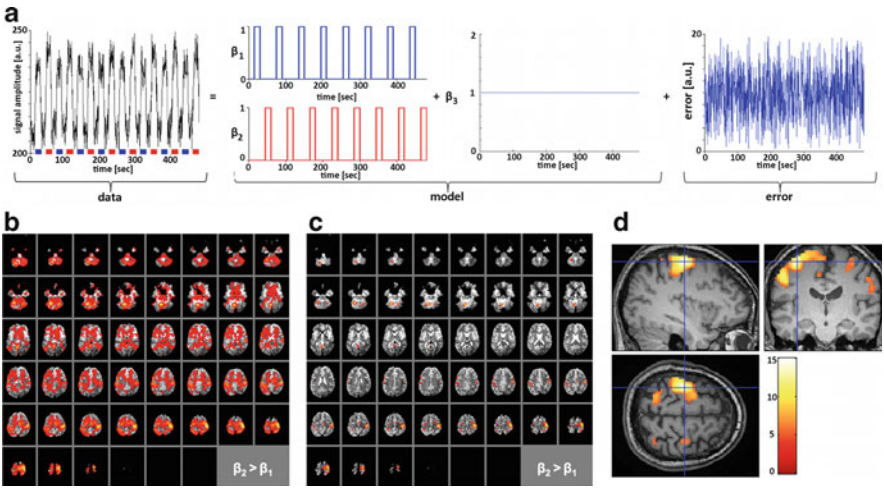

Fig. 12.5 *Statistical mapping*. Based on the general linear model (**a**), the parameters β_1, β_2, and β_3 are estimated. In order to access if and where condition *A* (*blue*) reveals a larger amplitude compared with condition *B* (*red*), the difference β_1–β_2 is calculated and compared with the residual error term. This leads to a color-coded statistical map showing all voxels, where β_1–$\beta_2 > 0$. The map is superimposed onto the mean-fMRI volume, which was constructed by averaging the whole time series after the realignment procedure. After applying an appropriate statistical threshold (in this case $p < 0.05$, FEW corrected) only the significant voxels are left over (**c**). By overlaying the data onto a high-resolution isotropic structural dataset, the anatomical assignment of the activated voxels can be improved (**d**). In the presented example, the subject performed a finger-tapping task. After appropriate thresholding, the sensory motor system is nicely depicted. The color-coding scheme for the *t*-values as given in (**d**) was used for all panels (**b**–**d**)

false-positive decisions, we risk missing true positives. Moreover, the Sidak or Bonferroni correction is not valid from a mathematical point of view, since neighboring voxels are not independent from each other, because activated regions are (usually) not confined to one voxel. Neighboring regions are heavily interconnected and supplied by the same vasculature, which means that it has to be assumed that the oxygenation level is similar in the close neighborhood. If one could calculate an effective number of "independent" voxels, the Bonferroni correction could be applied using a smaller N. The problem here is how to determine the number of independent voxels.

To some extent, this problem can be reduced by a spatial smoothing of the data, which was already discussed in Sect. 12.5.5: Worsley and colleagues showed that by smoothing the data with a Gaussian kernel, the number of independent comparisons can be estimated by replacing the number n of voxels by a number R of so-called RESELS (= resolution elements):

$$R = V / \mathrm{FWHM}^3, \tag{12.5}$$

V = volume to be analyzed, FWHM = FWHM of the Gaussian smoothing kernel (see Worsley et al. 1996 for details). As a rule of thumb, using smoothing kernels

with FWHM of 3× the voxel size reduces the multiple comparison problem by a factor about 30. This description is surely oversimplified, but should give an impression of the idea behind it. The mathematical theory applied here is called Gaussian Random Field Theory, and the correction for multiple comparisons family wise error correction (FWE).

Another approach to tackle the multiple comparison problem is to control the number of false-positive results (False Discovery Rate, FDR). Benjamini and Hochberg suggested to adjust the significance threshold in a way that the number of false positives in the thresholded map corresponds to the significance level (Benjamini and Hochberg 1995). Testing a dataset at a significance level of $p < 0.05$ FDR corrected means that no more than 5% of all above threshold voxels are false-positive results (Genovese et al. 2002).

Both methods (FDR and FWE) can be combined with an additional criterion, which takes the size of the activated clusters into account (Poline et al. 1997). Further approaches are permutation-based methods (Nichols and Holmes 2002) or simply restrict the search region to a (anatomically) well-defined and hypothesis-driven region of interest (ROI), which intrinsically reduces the number of comparisons performed. Further critical discussions of the statistical limitations in functional neuroimaging are presented elsewhere (Petersson et al. 1999a, b).

12.6.4 Group Analysis

Up to this point, all analytical issues were based on single subject data, which were acquired in one run.

To analyze multiple runs or subjects, the GLM can be easily extended by adding new blocks to the model, with each block containing a run of one subject. This so-called fixed-effect analysis assumes hereby that β is constant across runs, session, and subject, and takes only intra-subject variability into account, which is attributed to "noise" in the fMRI data. Consequently, fixed-effect models only ask whether an effect can be observed within the examined cohort.

However, we are usually more interested in the question whether the observed effects are representative for the whole population from which the cohort was drawn. This can only be addressed if the inter-subject variability—the variability of the effect sizes between different subjects—is considered as well. This is done in the so-called random effect (RFX) analysis. The random effect analysis in its simplest form assumes that the effect of each subject follows a normal distribution. The variance is assumed to be constant. Additionally, it is assumed that population(s) is (are) normal distributed. Both assumptions are questionable and lead to overly conservative test results. This can be overcome by either using multilevel approaches (Beckmann et al. 2003; Friston et al. 2002; Woolrich et al. 2004a) or nonparametric techniques (Holmes et al. 1996; Nichols and Holmes 2002).

12.7 Advanced Methods

12.7.1 Multivariate Analysis Methods

The data analysis method that was described in the preceding sections was "model-" or "hypothesis-" driven: Assumptions about the shape of the hrf and the putative time course for an active voxel during the presentation of experimental conditions are formulated and fed into the GLM to compare the hypothesized with the observed values for each single voxel. However, this approach might not always be adequate. For example, the hrf might not be known for a patient population, or a paradigm might not be suited to be divided easily into different conditions (e.g., during a car driving simulation). In fact, in so-called resting brain fMRI experiments, which became popular in recent years (see below), there is hardly an explicit task at all (except for the instruction to lie still and stay awake).

Data-driven approach does not rely on such a priori models, and does not have to account for every possible effect. Multivariate methods do not work on the single voxel level, but take the whole dataset and try to find common structures in space, time, or both space and time. Since a model does not have to be specified in advance, these approaches might be able to discover the unexpected, but they have the disadvantage to be nonspecific. A significant finding could be image artifact as well as a real finding.

The most popular multivariate method at present is the independent component analysis (ICA). The key idea behind ICA is that a mixture of independent sources is "more statistically dependent" than the sources itself. For example, take the classical "cocktail party problem" (Fig. 12.6). Imagine two guests during a cocktail party (or in a noisy environment) who are speaking at the same time (processing on the behavioral and the systemic (activation) level. Two microphones record this "conversation". Because the microphones are not exactly on the same position, both microphones record a slightly different mixture of the sources. ICA is capable to reconstruct the sources (= both speakers separately) from signals recorded by the microphones. If the conversations are denoted $S_1(t)$ and $S_2(t)$, and the recorded data $M_1(t)$ and $M_2(t)$, one could write

$$M_1(t) = a_{1,1}S_1(t) + a_{1,2}S_2(t), \tag{12.6}$$

$$M_2(t) = a_{2,1}S_1(t) + a_{2,2}S_2(t). \tag{12.7}$$

The coefficients $a_{i,j}$ form the mixing matrix **A**. **A** can be estimated with the assumptions that the $S_i(t)$ are non-normal, that the number of recorded tracks equals at least the number of independent components, and that the unmixing matrix consists of linear independent columns (Hyvarinen and Oja 2000). There are different approaches to solve this problem, but in the end, all are based on the idea that the

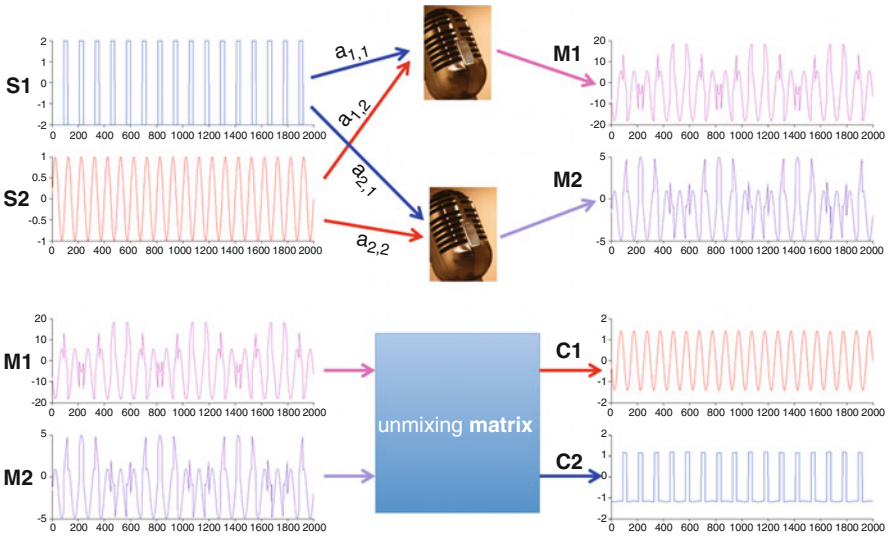

Fig. 12.6 *Cocktail Party Problem*. Two independent sources (*S*1, *S*2) are recorded by to independent microphones (*M*1, *M*2). They record different mixtures of both signals (*M*1, *M*2) depending on their position in space. Hereby it is assumed that the both signals mix linearly. Independent component analysis allows for calculating the so-called unmixing matrix, which is able to reconstruct two components (*C*1, *C*2) that represent the original sources (*S*1, *S*2). Please note that the numbering of the components does not (necessarily) correspond to the original numbering and that source and reconstructed independent component differ in amplitude and phase. This information is lost during the unmixing process

sources have to be less Gaussian than the mixed data. A nice introduction into the rationale of ICA can be found in a paper by Stone (2002).

ICAs are universally applicable, as long as the sources are linearly mixed and not perfectly Gaussian distributed. The result does not depend on the order of the entered data and reveals even useful results when the sources are correlated with each other. ICA can be used to detect and correct for artifacts in EEG data as well as to analyze fMRI data, or to find hidden factors in financial data. As a downside of this method, it has to be mentioned that ICA can only cope with linear mixtures of sources. Nonlinear interactions among modes are not detected by this method (see Friston 1998 for a critical discussion). It is also the job of the user to find the meaningful components and to identify the detected artifacts. In addition, ICA components have arbitrary amplitudes and even the sign is not defined, which means that a component might equally represent an activation or deactivation: In order to decide on the sign, one has to go back into the original data (see also Fig. 12.6).

Even though ICA can be used to analyze task fMRI data (McKeown et al. 1998), the most prominent use of ICA (in fMRI) is to analyze resting brain data. In resting brain experiments, volunteers are asked to relax and to keep their mind free of any thoughts (see also Chap. 16). By analyzing fMRI data acquired under such conditions, it has been shown that at least seven functionally and neuroanatomically

meaningful networks can be identified (Beckmann et al. 2005). These networks represent structures, which are anatomically connected, as can also be revealed using diffusion tensor imaging (Li et al. 2011; Skudlarski et al. 2008; Teipel et al. 2010, see below).

12.7.2 Connectivity Analysis

So far, we have primarily discussed how one could find certain brain regions. Unfortunately, focusing on functional segregation falls short of brain complexity. Every single brain region is embedded into a complex, interacting network. In order to understand brain function, functional pathology, or physiological changes due to interventions (which may also include exercise-related changes), it is also necessary to investigate the integration of brain regions into networks, as well as the interactions within and between networks. Currently, there are two distinct methods for characterizing the functional integration of brain areas within a network: functional and effective connectivity. Functional connectivity assesses functional integration by investigating the statistical dependencies between the activities of different brain regions. This is usually put into practice by calculating the cross-correlation coefficient between the time courses of preselected regions of interests. Even though functional connectivity is only descriptive, and it does not allow for distinguishing cause and effect, it is still very useful, for example, to classify groups. In this context, the correlation coefficient between well-defined regions can be used as an endophenotype distinguishing between populations (Craddock et al. 2009).

On the other hand, effective connectivity tries to directly access the influence between regions employing an explicit model of the coupling process. Effective connectivity is based on an anatomical model of regions that interact functionally and, in addition, on a model how this interaction takes place. In this sense, effective connectivity can be considered to be causative, whereas functional connectivity is more descriptive in nature. Yet, in both cases, the components of the network have to be specified. Currently, the most widely used approaches to access functional connectivity are structural equation modeling (SEM), dynamic causal modeling (DCM), and Granger causality. Within this troika, DCM is the most widely used method. Here a model is built, based on the neuronal level, and changes in neuronal activity are described by nonlinear differential equations. Applying a physiological model of the BOLD response (as the abovementioned balloon model) onto the neuronal model, the hidden neuronal states are transformed into a model for observable BOLD data. The connection strength between the a priori chosen regions is part of the model and can be estimated by comparing the predicted BOLD response with the experimental data. While the details cannot be discussed here, they are nicely covered in a recent review article by Karl Friston, in which the historical and conceptual, as well as the mathematical, background is discussed (Friston 2011).

Besides the above-mentioned approaches, there are a lot of alternative methods to analyze effective connectivity between brain regions, like coherence analysis,

generalized synchronization, or Patel's conditional dependence measure, and it is still an ongoing discussion which method might be best suited for analyzing brain connectivity. They differ in the sensitivity to detect network connections or directionality and therefore in their power to reveal causality within a given network (Smith et al. 2011). Interestingly, when comparing different modeling and analysis approaches, Smith and colleagues found that the most crucial parts in network modeling and effective connectivity analyses are the choice of functionally accurate ROIs. Connectivity analyses are extremely sensitive for inaccuracies in the initial step: network definition. Despite choosing the appropriate regions for the model itself, great care should be taken to identify these regions individually in each volunteer. The definition via a structural atlas seems not to be appropriate.

12.7.3 Network Analysis

An interesting question which is not addressed by the methods covered above is the *overall* network structure of the brain. How does information flow from one point to another? If information is transported between two regions, how many intermediate regions are needed? Do central relay structures exist, which are more important than others? Question of this kind can be investigated by a relatively new scientific field, called network science. Network sciences deal with properties of complex systems, and it applicability reaches from social sciences to physics, economy, and the description of ecosystems up to the evaluation of the properties of large neuronal cell populations as the human brain.

The mathematical theory behind network sciences is called graph theory. The mathematician Leonhard Euler founded graph theory when he tried to solve a popular puzzle in 1736. Königsberg, today Kaliningrad, was dissected into four parts by two branches of the river Pregel. Seven bridges connected the parts with each other. The question was whether a path exists that would allow make a walkabout, with each bridge being crossed only one time. Euler solved the problem by a graphical abstraction of the problem (Fig. 12.7). "Nodes" replaced the landmasses and "edges" replaced the bridges. By doing so, Euler was aware of the fact that the problem was independent of the actual distances or geographical shapes of Königsberg. Only the relative position of each part and its relation to the other part were of importance. He showed that the desired path does not exist and found a general solution that is applicable to an arbitrary number of nodes and edges.

Nodes and edges have a straightforward interpretation in the context of neuroscience: Nodes can be interpreted in terms of neurons, clusters of neurons, or brain regions, whereas edges are the connections between them. These connections can be directed or undirected and binary or weighted: as a consequence, directed/undirected and binary/weighted networks can be distinguished. Two different matrices, the connection matrix and adjacency matrix, are used to represent graphs mathematically. In these matrices, the columns and rows represent the nodes. For the connectivity matrix, the matrix entries represent the edges, and—in the case of the adjacency

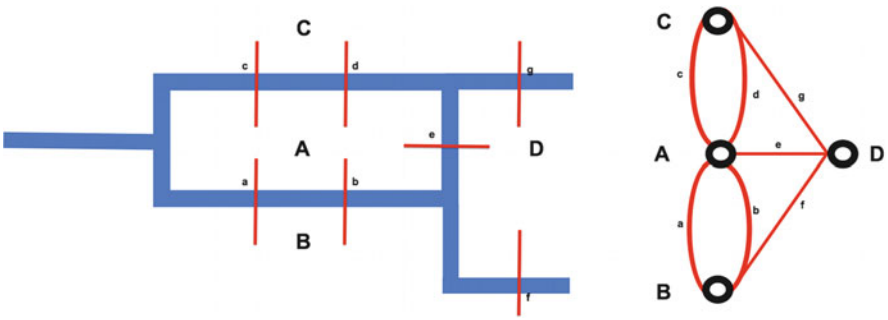

Fig. 12.7 *The Königsberg bridge problem*. Does a path exist that connects A–D via the bridges (*red*) a–g across the river Pregel (*blue*)? It is allowed to cross every bridge only one time and the end and starting point has to be the same. The geographical situation is schematically outlined on the left. Using the "graph representation" (drawn on the right), where the bridges are represented as a line, called "vertex", and the landmasses as dark circles, called "nodes", Leonard Euler was able to prove that such a path does not exist. He was even able to generalize the solution: A connecting path exists only if a graph contains exactly two nodes or no node with an uneven number of vertices. The drawings are based on Euler's work

matrix—the minimal number of edges needed to connect two nodes. An ordered sequence of edges that links two nodes is called "path", and the number of edges building a path is called "path length". With these two measures, it is possible to calculate global and local properties like "degree", which is the number of edges connected to a node or the average path length. Meanwhile, the adjacency matrix can be used to derive a third parameter, the "assortativity", which measures the tendency of nodes to link to nodes with similar degree. In terms of neuronal networks, these measures have a direct interpretation. A (brain) region with a high "degree" is directly influenced by a large number of other regions. Path length and distance matrices characterize the communication structure within the network. Using the degree parameter, one can also identify those regions, which are most important for the overall functioning of the network, because these are the nodes (so-called hubs), which are most highly connected. But a high connectivity does not necessarily mean that its breakdown will critically disturb the functioning of the network as a whole. This will critically depend on the network's overall architecture: If a network is built of subnetworks ("modes"), one can assume that the functioning of the network as a whole is not hampered, given that the critical hub only connects nodes within a mode. However, if a hub connects different modes, it might be crucial if it is taken out.

Networks can be classified with regarding to their construction process. Interestingly, this does also influence the properties of the network. There are two extremes: A purely random network, where each node is connected to other nodes by chance, and a regular lattice graph, which follows a predefined pattern (Fig. 12.8). Both types of networks have distinct features: Whereas random networks have small path lengths and a low level of clustering, the regular networks have a higher path length and a higher degree of clustering. It is not surprising that real-world networks

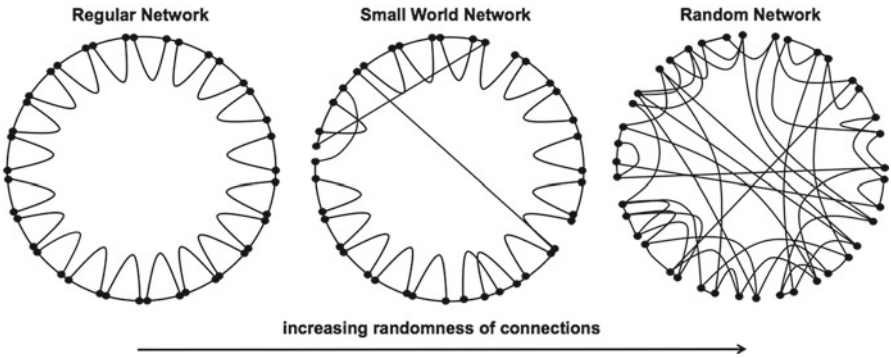

Fig. 12.8 *Network categories*. Three kinds of networks are distinguished: the regular network, the small world network, and the random network. By randomly rewiring a few connections, the regular network becomes a small-world network. If the number of randomly rewired connections increases, the network turns more and more a random network. The figure is adapted from Watts and Strogatz (1998)

are usually neither a pure random nor a regular lattice network; however, it is astonishing that most real-world networks seem to combine a high clustering coefficient with a short path length. Networks possessing this characteristic are called "small-world networks". Duncan Watts and Stephen Strogatz discovered that by randomly rewiring a regular network, a high degree of clustering can be combined with a small path length (Watts and Strogatz 1998). This behavior already occurs at very small rewire probabilities. Practically, a small-world network can be constructed by taking a regular network and replacing a few edges connecting nearby nodes with edges connecting randomly chosen nodes (Fig. 12.8). As far as we know it today, these kinds of networks represent a large variety of real-world networks, ranging from the internet to social networks. Small-world network architectures can be found in the biochemical network of the living cell, in river networks, as well as in the brain. Within the context of this book, it is not possible to discuss small-world properties in detail. Instead, we like to refer to the literature. Besides the seminal paper of Watts and Strogatz (1998), a book written by Olaf Sporns can be recommended here (Sporns 2011). It is a good introductory book if one likes to understand the brain in the view of network theory. The mathematics behind it is nicely covered in numerous review articles, for example, Rubinov and Sporns (2010), Bullmore and Sporns (2009), or van den Heuvel and Hulshoff Pol (2010).

12.8 Practical Aspects of fMRI

When designing an fMRI experiment, one has to decide on the overall paradigm design, and it is difficult to give general recommendations, except that a paradigm should be as simple and short as possible. The easiest design type for sure is the block design. It is easy to implement and to analyze and has a high SNR. These aspects

are appealing and might guide the decision. However, the leading guideline should always be the scientific question behind the paradigm. If it is essential to distinguish between single events, a block design is simply not appropriate. It is also advantageous to collect behavioral data during the fMRI experiment. By doing so, it can be checked whether the experiment was successfully performed by a volunteer, and it helps to decide if any fMRI activation differences between groups actually rely on group membership, or need to be attributed to coexisting performance differences. Considering the costs of scan time (about 500$/h), the paradigms should be tested beforehand. The positioning of the volunteer (supine), the restricted visual field, the handling of devices, age, and educational background of the volunteer (academic/nonacademic, children/adults/elderly etc.), and "click and feel" of the paradigm, should be evaluated during the testing phase. The optimum setup would be a mock scanner, which simulates the real scanner situation as close as possible (including scanner noise). The volunteers testing the final experiment should not be colleagues from the lab or students with a similar background, because they might anticipate the meaning of imprecise or misleading instructions, and might be familiar with experimental conditions, whereas a volunteer in general is not.

There are a plethora of software packages available for analyzing fMRI data (including preprocessing). Most of them are freely available and directly downloadable from the Internet. A good starting point is: http://www.nitrc.org/, where almost all freely available packages are linked. The most widely used packages are AFNI[1], BrainVISA[2], FSL[3], SPM[4], and the commercial package BrainVoyager[5]. Most vendors of MR scanners also have basic software packages available, but they usually provide only very basic preprocessing and analysis methods, which are rather designed for individual analyses than for group studies.

An important point that should be kept in mind when interpreting imaging results is that the large number of independent comparisons performed when analyzing data voxel-wise will produce false-positive results, no matter which correction method is used. Even if the location of activation fits perfectly into an a priori hypothesis, it does not automatically exclude the possibility that this finding might be a false-positive result. This was nicely illustrated by Craig Bennett and colleagues showing a brain activation of "dead salmon" (Bennett et al. 2009). The main lesson to learn from this paper is that one should not base a larger project on a single fMRI experiment, and consider a test-retest design, to validate the own data. Of course, this might not always be possible, but at least a split-half analysis may be feasible, especially when a larger project is planned based on a single fMRI experiment. A more general discussion on the reliability of fMRI results might also be found in a recent paper by Bennett and Miller (2010).

[1] http://afni.nimh.nih.gov/afni.

[2] http://brainvisa.info/.

[3] http://www.fmrib.ox.ac.uk/fsl/.

[4] http://www.fil.ion.ucl.ac.uk/spm/.

[5] http://www.brainvoyager.com/.

12.9 Structural Analysis of the Brain

MRI allows for the acquisition of high-resolution structural images with an excellent image contrast between white matter, gray matter, and cerebrospinal fluid. This enables researchers to investigate structural differences (volume or shape of anatomical structures) between populations of interest. Until the development of automatic methods, morphometric analyses were performed by delineating anatomical structures manually, which is of course an extremely time-consuming and personnel-intense business. As a consequence, those analyses were limited to small group sizes and to well-defined anatomical structures like the hippocampus, the ventricles, or the corpus callosum. An exploratory data analysis on large datasets is generally not feasible. This changed when automatic methods like voxel-based morphometry become available. Here, one can distinguish between voxel-based and surface-based methods (Ashburner et al. 2003). The development of diffusion imaging methods has opened additional venues for the analysis of structural differences in the white matter, which extend beyond classic volumetric approaches, by either analyzing the fractional anisotropy or the structural connectivity by reconstructing white matter tracts. The following sections introduce the key ideas of the most widely used morphometric methods.

12.9.1 Manual Morphometry

Manual morphometry is based on the manual delineation of anatomical structures on MR images and can be considered the classical region of interest (ROI) approach. In general, it can be applied to every brain structure that can be unambiguously identified on structural images. The key point here is the definition and standardization of landmarks that establish the border to neighboring structures. The easiest measure here is the volume and the surface of a structure. Another popular measure is the gyrification index, which compares the inner contour length following the sulci/gyri with the outer contour length enfolding the outer surface of the gyri.

Several software packages are available which can be used for this purpose (i.e., free packages: MRIcron[6], Mango[7], MeVisLab[8], fslview[9], or, as a commercial package, ANALYZE[10]. Yet, it should be pointed out that manual morphometry is not only extremely time-consuming, but also personnel-intense, because more than one person should perform the measurements. The researchers should be rigorously trained to ensure a high (inter-)rater reliability (e.g., Inter-rater Correlation Coefficient

[6] http://www.cabiatl.com/mricro/mricron/index.html.

[7] http://ric.uthscsa.edu/mango/.

[8] http://www.mevislab.de/.

[9] http://www.fmrib.ox.ac.uk/fsl/fslview/index.html.

[10] http://www.mayo.edu/bir/Software/Analyze/Analyze.html.

ICC > 0.85). The operators who conduct the analyses must be blinded for subject characteristics (and investigated hemisphere, if possible). The reliability should be reestablished during ongoing studies, and all definitions should be checked by at least one other person knowing the procedure. Usually, editors and reviewers want to see the actual quality control numbers if they are familiar with manual morphometry.

Despite the fact that manual morphometry demands a lot of resources, it also has a couple of advantages compared with automated measures. For example, it acts in native space of the data, which means that the datasets do not have to be spatially transformed or preprocessed, as it is the case for the automated methods (see below). It delivers unambiguous measures like volumes or surface areas and has, by definition, a high anatomical validity, which still has to be proven for many automatic methods. To conclude, if the resources are available and a clear a priori hypothesis can be defined, manual morphometry should be the method of choice to access structural differences in the brain.

12.9.2 Automated Methods

The automated methods have the advantage that almost no user interaction is necessary to analyze morphological differences between or within populations. Because no anatomical a priori hypothesis is needed, these methods can be used to conduct exploratory analyses of huge datasets. Meanwhile, unlike manual morphometry, automated morphometric methods do not work on data in native space. They have to be preprocessed before the analysis can be conducted. The preprocessing stream for all methods is more or less the same: skull stripping, intensity normalization to remove spatial intensity inhomogeneities, segmentation into gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF), and normalization into a common space. Applying filters like anisotropic diffusion filters or taking into account neighborhood relations might additionally improve the segmentation quality (Cuadra et al. 2005). The validity of the results crucially depends on the segmentation quality. This holds true for all automated methods.

12.9.2.1 Voxel-Based Morphometry

Voxel-based morphometry (VBM) was the first automated method that was available to the neuroscience community. Though it was introduced 15 years ago by Wright and colleagues (1995), it took about 5 years before it became a popular methodology for assessing structural brain differences. Its popularity increase might be attributed to the publication of three papers: Two of them were covered extensively by the popular press, showing that even the adult human brain is capable of structural adaption to external challenges. The first one indicated that the hippocampal volume of taxi drivers increases depending on the amount of time spent as a taxi driver (Maguire et al. 2000), and the other one proved that even a short intervention of

jiggling training over 3 months leads to a transient GM volume increase in regions relevant for visuo-motor processing (Draganski et al. 2004). The third paper published by Ashburner and Friston (2000) extensively explained the method and made clear that the whole procedure could be performed within the framework of SPM (one of the most widely used fMRI preprocessing and analysis packages). Further programming was neither needed, nor special MRI sequences were used. The method works well with conventional isotropic T1-weighted datasets, which are usually acquired along with fMRI experiments.

When segmenting brain images into its three classes (GM, WM, CSF), one assigns each voxel a probability of belonging to one of these classes. Voxel-based morphometry is based on the idea that these probability maps of the segmented brain images contain local volume information. As outlined by John Ashburner and Karl Friston, these probability maps can be used to make voxel-wise comparisons of local volume differences across groups, given that gross anatomical differences between the brains are compensated (Ashburner and Friston 2000). The latter can be realized by the normalization process, which was already outlined in Sect. 12.5.4 for functional imaging data. Good et al. optimized this method by recursively constructing a study-specific template and by adding an additional preprocessing step, called "modulation" (Good et al. 2001). Modulation compensates for local volume changes by scaling the image intensities by the amount of contraction or dilatation applied when normalizing the dataset. By doing so, the total amount of gray matter remains the same as in the original image. Figure 12.9 outlines the processing stream of VBM and "optimized VBM". The most recent improvement in VBM was to increase the amount of deformations allowed during the normalization process, which improves the realignment quality of small structures (Ashburner 2007). The newly developed algorithm is called Diffeomorphic Anatomical Registration using Exponentiated Lie algebra (DARTEL). Figure 12.10 compares the results of both methods (VBM with and without DARTEL).

12.9.2.2 Deformation-Based Morphometry

A further development of the VBM method is the deformation-based morphometry (DBM). It differs from VBM in the following points: the spatial normalization into a common space is performed using nonlinear deformations, and DBM does not compare the obtained normalized probability map for GM, WM, or CSF, but the transformation fields which are used to normalize the data (Ashburner et al. 1998). Because these deformations generally correct for global size and shape differences, DBM acts on a different spatial scale as compared to VBM. Therefore, it can be considered as complementary to VBM. Because deformation fields are multidimensional measures, a multivariate approach has to be applied to analyze the data statistically. This can be avoided by extracting a scalar measure from the deformation field. A common way is to calculate the determinant of the Jacobian matrix. The Jacobian matrix is built by the partial derivatives of a vector field. Its determinant is a measure for the magnitude of local deformations. This approach is also referred to in the literature as tensor-based morphometry (TBM).

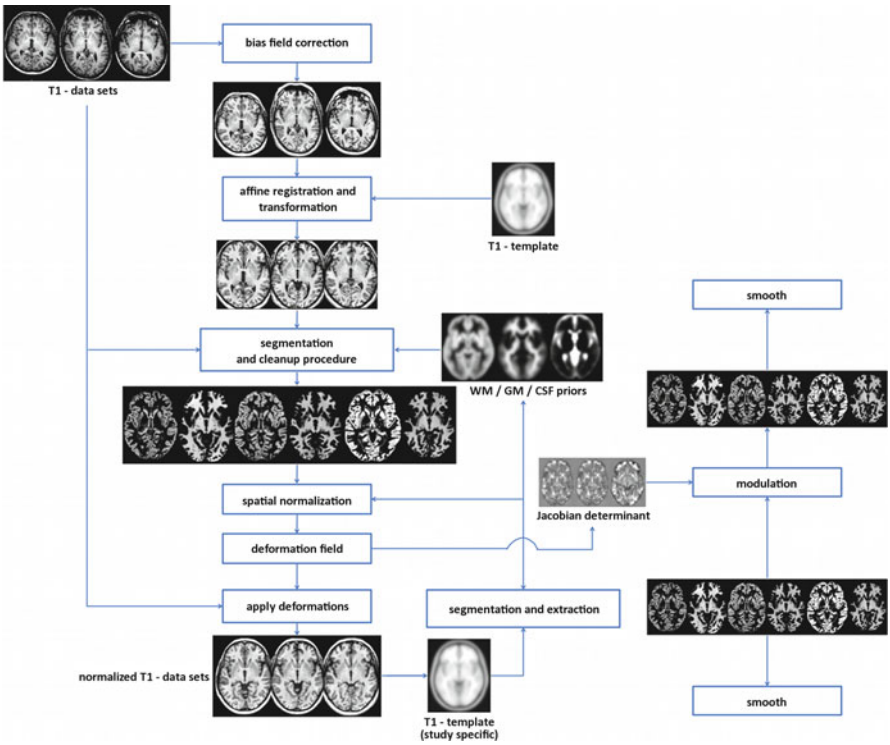

Fig. 12.9 *Processing scheme optimized VBM*. The key idea behind optimized VBM is to improve the quality of the segmentation and the normalization process. This is achieved by an iteratively constructed study-specific T1-template, and probability maps for GM and WM segmentations (GM-/WM-priors). An additional improvement of spatial normalization results is achieved by using the GM/WM segmentations for normalization procedure, instead using solely a T1-weighted dataset itself. After this initial normalization and segmentation, a study-specific template and segmentation class priors can be constructed. They are then used for the final normalization and segmentation. The "modulation" step (=voxel-wise multiplication with the Jacobian determinate) keeps the total amount of GM/WM constant. The bias-field correction corrects for large-scale intensity variation caused by inhomogeneous RF-deposition, which especially is seen at higher field strengths. The cleanup procedure(s) consist(s) of spatial filters. Both procedures (bias-field correction and cleanup) additionally improve the segmentation quality. The figure is adapted from Good et al. (2001)

12.9.2.3 Surface-Based Morphometry

Voxel-based or deformation-based methods measure morphological changes indirectly by analyzing either probability maps of a segmentation class or deformation fields. A more direct approach is to access geometric measures like cortical thickness, curvature, or sulcal depth. For this purpose, it is necessary to reconstruct the cortical sheet. It is defined by two boundaries: the inner boundary between the WM and GM, and the outer boundary between GM and CSF. The outer boundary corresponds anatomically to the pial surface, which can be reconstructed after successful

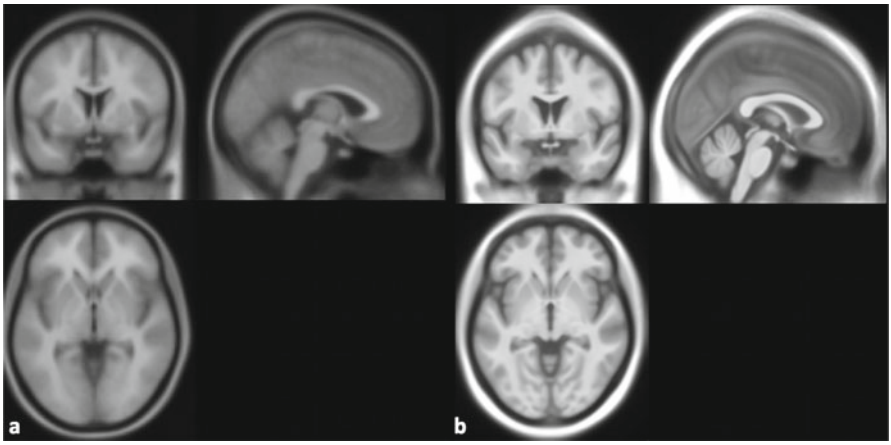

Fig. 12.10 *Comparison between two normalization procedures*. Resulting mean datasets after averaging the normalized T1-datasets of 20 healthy volunteers following either the "optimized-VBM" protocol (**a**) or the high-dimensional DARTEL normalization procedure (**b**). Please note the fine anatomical details preserved in (**b**)

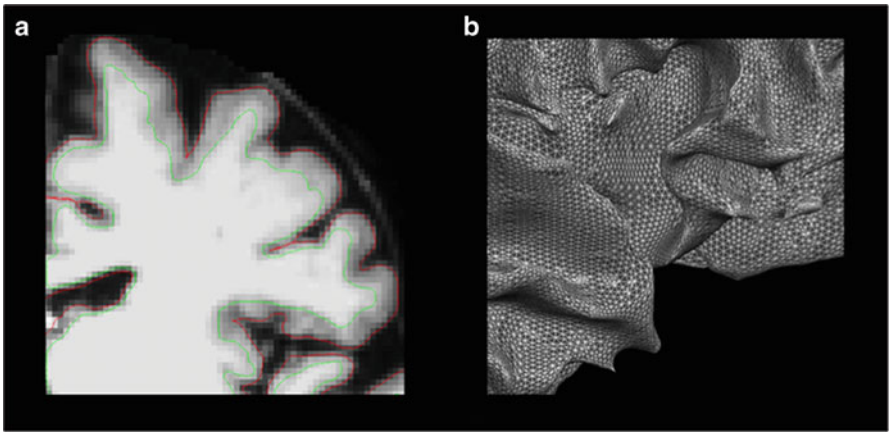

Fig. 12.11 *Mesh reconstruction*. Determination of the WM–GM (*red*) and GM–CSF(*green*) boundary by FreeSurfer (*right*). On the left, the triangulation of the WM surface is shown

skull stripping using the "Brain Extraction Tool" (BET, Smith 2002) or more advanced methods that combine watershed algorithms and deformable surface models (Segonne et al. 2004). The white matter is segmented based on its intensity. When both boundaries are determined, the surfaces can be parameterized using triangulation. Doing so, a dense mesh is constructed around the cortical sheet (Dale et al. 1999; see also Fig. 12.11). Using this mesh, measures like cortical thickness, curvature, or gyrification index can be directly calculated.

Besides the availability of direct measures for local and global geometric properties of the cortex, the reconstruction of the cortical sheet has an additional advantage. It allows for inter-subject registration using a surface-based coordinate system (Fischl et al. 1999a), which is more accurate compared with the voxel-based methods described above.

12.9.2.4 Practical Aspects

The preceding section gave an overview on the most common analysis approaches and is far away from being complete. But which method should be used? The gold standard is still manual morphometry. The advantage is its anatomical validity, and that it does not request any kind of preprocessing. However, it is extremely time-consuming and should be based on a priori hypotheses for anatomically well-defined structures. Usually, only small cohorts can be analyzed using this method. The automatic methods have the advantage that they are fast and need less human resources. They work on the whole brain or, at least, on the whole cortex. As a consequence, it is not necessary to define a priori hypotheses and methods can be applied to large cohorts, even in an exploratory manner. Cortex-based analyses provide anatomically meaningful measures like cortical thickness or cortex curvature. Group averaging can be performed on the cortical surface minimizing the sulcal variability within and across groups. Therefore, any effect that is found in cortical thickness maps (or curvature, etc.) can be clearly attributed to differences in this measure. Voxel-based and deformation-based morphometry are less specific in this respect. They use indirect measures, like probability maps or deformation fields, to find structural differences. Even though most authors of morphometry papers refer to GM/WM density, these methods do not assess GM/WM density or volume, but assess the probability for a certain voxel to be GM/WM: This is an ambiguous information, because this probability does not only depend on GM/WM content but also on the average shape of this structure across groups. However, VBM has the practical advantage that it can be used within the software used for fMRI analyses, and it is much faster as compared to the cortex-based methods. Meanwhile, VBM has the disadvantage that it is not optimal for longitudinal studies. As a recent study showed, drift effects in scanner hardware and inter-scanner variability lead to global and regional effects mimicking real brain volume changes (Takao et al. 2011). Surface-based and deformation-based methods seem to be less vulnerable to such effects. Both methods can also be applied to longitudinal case studies whereas VBM generally needs large cohorts.

However, it should be also noted at this point that if one is specially interested in a certain structure, optimized methods might exist that outperform the approaches outlined above. Most of them are semi-automated, combining manual delineation of a structure with automated analysis protocols. For example, there are specialized methods for analyzing the regional hippocampal thickness (Zeineh et al. 2001) or shape (Tepest et al. 2008).

Software for morphometric analysis is freely available in most of the cases. Voxel-based morphometry can be performed with any software package that

provides segmentation and normalization, like SPM, FSL, AFNI, or BrainVoyager. Surface-based analyses can be performed, for example, by FreeSurfer[11], CARET[12], mrVista/itkGray[13], SUMA[14], BrainVoyager, or BrainVISA/Anatomist[15]. The latter also contains toolboxes for sulcal recognition and morphometry, including gyrification index, sulcal length, and depth.

12.9.3 Analysis of Diffusion-Weighted Images

Diffusion-weighted imaging (DWI) permits the investigation of microstructure and integrity of the white matter and its anatomical connectivity. As pointed out in Chap. 11, it is based on the diffusion (= random motion or Brownian motion) of water molecules. Since the motion of water in axons is restricted perpendicular to the main direction of an axon, the main direction of axon bundles can be inferred by applying multiple diffusion gradients in different directions and strengths. Unfortunately, running diffusion-weighted MR sequences do not result in a single image volume that already contains parameters for diffusion direction and strength on a voxel-by-voxel basis. Instead, one obtains a series of image volumes. The amount of diffusion weighting in one image volume depends on the strength of the diffusion gradient applied when the volume was acquired and its directional sensitivity in the gradient direction. In the following sections, it will be explained how diffusion-related quantities are calculated and analyzed. As in the preceding sections, the following discussion has to be restricted to the main ideas. A nice introduction into the mathematics in diffusion tensor imaging can be found in three papers written by Kingsley (2006a, b, c).

12.9.3.1 Calculation of Diffusion Properties

The diffusion of water molecules in a homogenous volume does not prefer any spatial direction. The motion is isotropic. If the water is confined in a small tube, this motion is restricted perpendicular to the long axis of this tube, whereas it is unrestricted parallel to the long axis. The diffusion motion can be quantified using the diffusion coefficient as introduced by Einstein. The mean displacement $\left\langle X_i^2 \right\rangle$ of molecules in a liquid three-dimensional space over time t can be expressed as

$$\left\langle X_i^2 \right\rangle = 6 * D * t, \tag{12.8}$$

where D denotes the diffusion coefficient, and X_i the displacement vector of the ith molecule in the liquid. In the isotropic case, no preferred direction exists. If all displacement vectors X_i would be drawn after the time t, they would approximate a

[11] http://surfer.nmr.mgh.harvard.edu/.

[12] http://brainvis.wustl.edu/wiki/index.php/Main_Page.

[13] http://white.stanford.edu/software/.

[14] http://afni.nimh.nih.gov/afni/suma.

[15] http://brainvisa.info/.

sphere whose radius depends on D and t. However, if the diffusion was restricted, i.e., by a tube (like an axon), the displacement vectors would shape an ellipsoid with its long axis parallel to the long axis of the tube, because the diffusion is restricted perpendicular to this axis. While it is not sufficient to use a single value to characterize the diffusion, however, it would be sufficient to measure the diffusion coefficient along the three main axes of the ellipsoid. In the more general case, a diffusion tensor **D** is needed to describe the diffusion:

$$\mathbf{D} = \begin{pmatrix} d_{xx} & d_{xy} & d_{xz} \\ d_{yx} & d_{yy} & d_{yz} \\ d_{zx} & d_{zy} & d_{zz} \end{pmatrix} \tag{12.9}$$

The indices refer to the axes of any user-defined coordinate system (xx = x-axis, xy = diagonal between x- and y-axis, etc.). Because **D** is symmetric ($d_{xz} = d_{zx} \ldots$), it is sufficient to determine six elements to construct the complete tensor. This can be afforded by applying diffusion gradients in six different directions. Having done this, the diffusion is specified in the frame of reference defined by the gradient directions (usually the scanner reference frame). However, it can be mathematically transformed into the optimal frame of reference, where the coordinate axes are oriented parallel to the main- or principal axis of the diffusion ellipsoid.

$$\mathbf{D} = \begin{pmatrix} d_{xx} & d_{xy} & d_{xz} \\ d_{yx} & d_{yy} & d_{yz} \\ d_{zx} & d_{zy} & d_{zz} \end{pmatrix} \Rightarrow \text{diagonalize} \begin{pmatrix} \lambda_1 & 0 & 0 \\ 0 & \lambda_2 & 0 \\ 0 & 0 & \lambda_3 \end{pmatrix}. \tag{12.10}$$

The values λ_1, λ_2, and λ_3 refer to the diffusibility along the principal diffusion directions Λ_1, Λ_2, and Λ_3. They are determined when **D** is diagonalized. Practically, this means that one can determine direction and amount of the diffusion when the diffusion is measured in (at least) six directions.

Everything stated so far does not completely account for the situation in biological tissue. Additional components exist which influence the molecular motion, like capillary flow or plasma flow in axons. Because these effects cannot be separated from the Brownian motion, the measured diffusion coefficients are considered as "apparent diffusion coefficient", and called ADC accordingly.

12.9.3.2 Quantitative Diffusion Maps

The diagonalized diffusion tensor allows for calculating two measures, the fractional anisotropy (FA) and the mean diffusibility (MD). They are defined as follows:

$$\text{FA} = \sqrt{\frac{3\sum_{i=1}^{3}\left(\lambda_i - \bar{\lambda}\right)^2}{2\sum_{i=1}^{3}\lambda_i}} \tag{12.11}$$

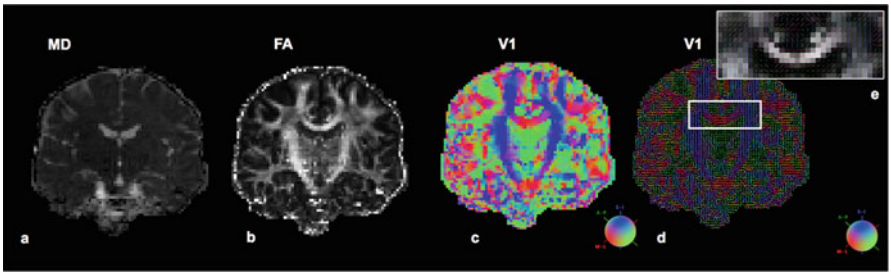

Fig. 12.12 *Reconstruction of different diffusion measures*. Mean diffusivity (**a**), fractional anisotropy (**b**), and the first eigenvector (V1) of the diffusion tensor are shown (**c/d**). The orientation of the eigenvector can be either visualized by using a certain colors for certain direction (*red*: medial—lateral, *blue*: superior-inferior, *green*: anterior—posterior) as outlined in (**c**), or by representing the directions by "lines" as it is commonly done for "vector fields". "Lines" are often used instead of "vectors", because only the orientation in space is meaningful (and not the direction). (**d**) Combines both approaches. The "vector field" representation can be superimposed onto structural data or, as shown in (**e**), onto any diffusion measure. Here, the first eigenvector is projected onto the FA map. Please note the high anisotropy of the capsula interna and the corpus callosum

and

$$\mathrm{MD} = \frac{\lambda_1 + \lambda_2 + \lambda_3}{3}. \tag{12.12}$$

FA can take values between 0 (isotropy) and 1 (maximal anisotropy). It measures how strongly directional diffusion is in a given voxel, and is thought to provide a good marker for WM integrity. In contrast, MD is simply a measure of the amount of diffusion within a voxel irrespective of direction (Fig. 12.12).

A straightforward approach for the within- or across-group analysis of FA and MD maps seems to be the application of those procedures that we already have described for VBM: normalization, smoothing, and univariate voxel-wise analysis. Indeed, this procedure has already led to valuable results (for example, Buchel et al. 2004), but it is problematic because the alignment of corresponding structures in the white matter (=fiber bundles) is very difficult across groups. Even small spatial shifts across subjects in a group can reduce the mean FA, which are then misinterpreted as real FA. Smoothing could help in this situation, but it is difficult to determine the amount of smoothing needed. One way to overcome this problem is a ROI-based approach, or to analyze the FA or MD values along reconstructed fiber tracts (see below). However, both methods do not allow for a whole brain analysis. An alternative method that was developed by Steven Smith and colleagues (Smith et al. 2006) is called tract-based spatial statistics (TBSS). The main idea is to perform voxel-wise cross-subject statistics on a WM skeleton, which represents the centers of all fiber tracts. These skeletons are constructed on the basis of the FA maps. After construction of these skeletons, the mean FA values can be projected onto them and compared across groups (Fig. 12.13).

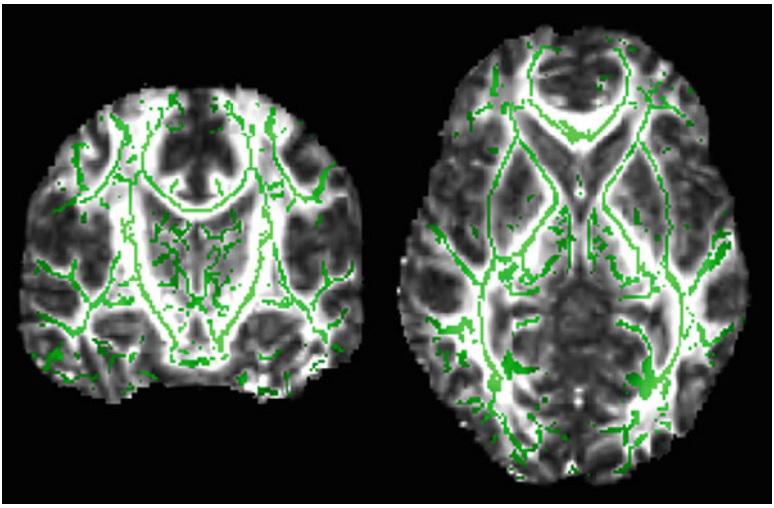

Fig. 12.13 *Skeleton*. Reconstruction of the "skeleton" for the main white matter tracts (*green*). As it can be depicted nicely from the images, the skeleton projects always onto the middle of the large fiber tracts. The FSL course test datasets were used to generate these images. (http://www.fmrib.ox.ac.uk/fslcourse/fsl_course_data2.tar.gz)

12.9.3.3 Analysis of Diffusion Tensors

So far, only scalar measures were used, ignoring the directional information that the diffusion tensor contains. This information can be used to reveal the large fiber bundles in the brain, assuming that the direction of the maximum diffusivity represents the major fiber orientation within a voxel. By plotting the principal diffusion direction (which can be indicated by a vector or using a color coding scheme), the gross structure of the white matter can be visualized on a voxel-by-voxel basis (Fig. 12.12).

Whereas these maps give a broad overview about the bundle orientation within the white matter, it is difficult to extract concrete information on single fiber bundles. This can be achieved by starting at a seed point and following the main direction voxel by voxel until it reaches gray matter. Mathematically this problem can be expressed by a differential equation:

$$\frac{d\vec{r}(s)}{ds} = \vec{v}\left(\vec{r}(s)\right), \tag{12.13}$$

where $\vec{r}$ denotes a position along a curve and $\vec{v}$ the main principal direction. Usually, additional boundary conditions are employed to avoid wrong assignments, like FA thresholds to ensure that the "fibers" only propagate in regions with meaningful anisotropy, or a maximum curvature to avoid kinks and extremely bended paths. The success of this "deterministic fiber tracking" approach to extract the main fiber bundles is nicely shown by Catani and Thiebaut de Schotten (2008).

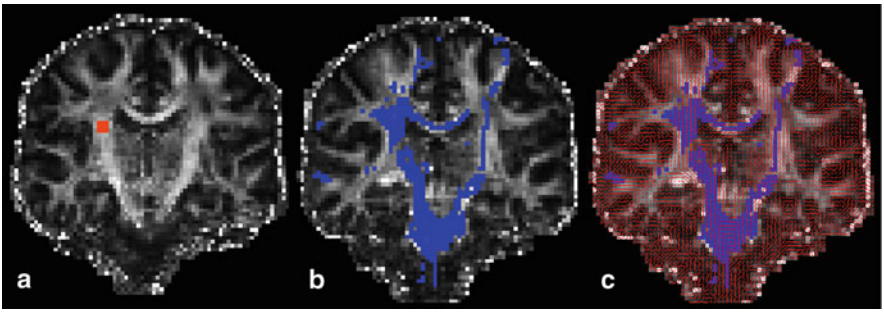

Fig. 12.14 *Tensor-tracking*. Using seed voxel(s) (**a**), the major connections (*blue*) between the seed voxel(s) and the rest of the WM voxels can be reconstructed with probabilistic fiber tracking approaches (**b**, **c**). In comparison to simple approaches that follow only the main directions within the tensor field (not shown), the probabilistic tracking approach also finds more complex pathways like the fibers that cross the corpus callosum and or run through the contralateral capsula interna. The relation between the tensor field and the tracks is shown in (**c**)

An alternative approach to derive white matter tracts is probabilistic tracking, which assigns each diffusion direction in a given voxel with a probability. The probability is based on the directional information of the tensor and the measurement error of the tensor. The error term describes the uncertainty of the calculated main diffusion direction. Combining both parameters, one can construct all possible paths starting from a given seed region. It results in a probabilistic map that assigns every voxel (in the brain) a probability of being reached via a fiber bundle running through the seed region (Behrens et al. 2003b; Parker and Alexander 2003; Parker et al. 2003; see also Fig. 12.14). One of the advantages of the probabilistic tracking method is that it also allows to access regions with low FA values, and that it does not rely on artificial thresholds like the FA threshold or maximum-curvature criterion, as it can be found for deterministic tractography. By comparing all paths through a voxel with all possible paths, also quantification is possible. Moreover, because no FA threshold has to be applied, the method can be used to track the white matter paths right into the gray matter: This has been impressively shown by Tim Behrens, Heidi Johanson-Berg, and colleagues, who were able to distinguish thalamic subnuclei by analyzing their cortical connectivity (Behrens et al. 2003a).

12.9.3.4 Crossing Fibers

One issue that we have not discussed so far is the problem of ambiguity of the diffusion tensor in regions with crossing or kissing fiber bundles. At the commonly used spatial resolution ($2 \times 2 \times 2$ mm^3), DTI does not resolve a single fiber but average across a vast amount of axons. The calculation based on the measurement of six diffusion directions does not account for crossing or kissing fibers, which can lead to wrong path assignments or artificially low FA values. This issue can be resolved by measuring a higher number of diffusion directions. This allows for calculating higher-order tensor terms that can account for additional preferred diffusion directions.

The more diffusion directions are acquired, the better crossing fiber regions can be evaluated. However, it increases also the measurement time and, hence, the probability of motion artifacts (Alexander 2005).

12.9.3.5 Practical Aspects

A couple of practical aspects have to be considered when DTI is performed. The strength of the diffusion gradients should be chosen between 1,000 and 1,500 s/mm^2. To compensate for motion, it is of advantage to acquire additional volumes without diffusion weighting. It also has to be decided how many directions have to be measured. The optimum number of diffusion directions is still under debate. To calculate FA values, 6–12 directions or more give stable results. For tractography, 30–60 diffusion directions seem to be appropriate, but this depends on the scientific question: The major fiber bundles can be already tracked using 12–30 diffusion directions, but for probabilistic tractography frequently a higher number of directions are used (60+). Independent of the number of directions, the direction should be evenly distributed on a sphere. The optimal parameters are also hardware dependent and should be discussed with the local physicist group.

The next obstacle when doing DTI is to extract the diffusion direction. The diffusion directions are needed in image space. The directions cannot be directly gained from the sequence protocol, because the image space depends on the patient position, whereas the gradient directions are defined using the scanner coordinate system as frame of reference. However, the information can be directly extracted from the DICOM[16] header of the DTI volumes, i.e., using MRIcron[17]. Most software packages that are capable of extracting the diffusion direction (and gradient amplitude) on the basis of DICOM data are also able to convert the DTI data into an appropriate data format, like Nifti[18]. The preprocessing steps (motion correction and so-called eddy-current compensation) can be performed within the same framework as the calculation of the ADC and FA maps. The most widely used free software packages for DTI analyses are FSL, DTI-studio, and BrainVISA, or BrainVoyager as the commercial counterpart. A good starting point to look for tools and free software packages is http://www.nitrc.org.

References

Aguirre GK, Zarahn E, D'Esposito M (1998) The variability of human, BOLD hemodynamic responses. Neuroimage 8:360–369

Aguirre GK, Detre JA, Zarahn E, Alsop DC (2002) Experimental design and the relative sensitivity of BOLD and perfusion fMRI. Neuroimage 15:488–500

[16] DICOM is a standard data format for medical images and available on every MR-scanner.

[17] http://www.cabiatl.com/mricro/mricron/index.html.

[18] http://nifti.nimh.nih.gov/.

Akgoren N, Dalgaard P, Lauritzen M (1996) Cerebral blood flow increases evoked by electrical stimulation of rat cerebellar cortex: relation to excitatory synaptic activity and nitric oxide synthesis. Brain Res 710:204–214

Alexander DC (2005) Multiple-fiber reconstruction algorithms for diffusion MRI. Ann N Y Acad Sci 1064:113–133

Amaro E Jr, Barker GJ (2006) Study design in fMRI: basic principles. Brain Cogn 60:220–232

Andersson JL, Hutton C, Ashburner J, Turner R, Friston K (2001) Modeling geometric deformations in EPI time series. Neuroimage 13:903–919

Ashburner J (2007) A fast diffeomorphic image registration algorithm. Neuroimage 38:95–113

Ashburner J, Friston KJ (2000) Voxel-based morphometry–the methods. Neuroimage 11:805–821

Ashburner J, Friston K (2007a) Non-linear registration. In: Friston KJ, Ashburner J, Kiebel S, Nichols TE, Penny W (eds) Statistical parametric mapping: the analysis of functional brain images. Academic, London, pp 63–80

Ashburner J, Friston KJ (2007b) Rigid body registration. In: Friston KJ, Ashburner J, Kiebel S, Nichols TE, Penny W (eds) Statistical parametric mapping: the analysis of functional brain images. Academic Press, London, pp 49–60

Ashburner J, Hutton C, Frackowiak R, Johnsrude I, Price C, Friston K (1998) Identifying global anatomical differences: deformation-based morphometry. Hum Brain Mapp 6:348–357

Ashburner J, Csernansky JG, Davatzikos C, Fox NC, Frisoni GB, Thompson PM (2003) Computer-assisted imaging to assess brain structure in healthy and diseased brains. Lancet Neurol 2:79–88

Attwell D, Iadecola C (2002) The neural basis of functional brain imaging signals. Trends Neurosci 25:621–625

Attwell D, Buchan AM, Charpak S, Lauritzen M, Macvicar BA, Newman EA (2010) Glial and neuronal control of brain blood flow. Nature 468:232–243

Bandettini PA, Wong EC, Hinks RS, Tikofsky RS, Hyde JS (1992) Time course EPI of human brain function during task activation. Magn Reson Med 25:390–397

Bandettini PA, Wong EC, DeYoe EA, Binder JR, Rao SM, Birzer D (1993) The functional dynamics of blood oxygenlevel dependent contrast in the motor cortex. Proc Int Soc Magn Reson Med, New York, p 1382

Beckmann CF, Jenkinson M, Smith SM (2003) General multilevel linear modeling for group analysis in FMRI. Neuroimage 20:1052–1063

Beckmann CF, DeLuca M, Devlin JT, Smith SM (2005) Investigations into resting-state connectivity using independent component analysis. Phil Trans R Soc Lond B Biol Sci 360:1001–1013

Behrens TE, Johansen-Berg H, Woolrich MW, Smith SM, Wheeler-Kingshott CA, Boulby PA, Barker GJ, Sillery EL, Sheehan K, Ciccarelli O, Thompson AJ, Brady JM, Matthews PM (2003a) Non-invasive mapping of connections between human thalamus and cortex using diffusion imaging. Nat Neurosci 6:750–757

Behrens TE, Woolrich MW, Jenkinson M, Johansen-Berg H, Nunes RG, Clare S, Matthews PM, Brady JM, Smith SM (2003b) Characterization and propagation of uncertainty in diffusion-weighted MR imaging. Magn Reson Med 50:1077–1088

Behzadi Y, Liu TT (2006) Caffeine reduces the initial dip in the visual BOLD response at 3 T. Neuroimage 32:9–15

Benjamini Y, Hochberg Y (1995) Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc Series B (Methodological) 57:289–300

Bennett CM, Miller MB (2010) How reliable are the results from functional magnetic resonance imaging? Ann N Y Acad Sci 1191:133–155

Bennett CM, Miller MB, Wolford GL (2009) Neural correlates of interspecies perspective taking in the post-mortem Atlantic Salmon: an argument for multiple comparisons correction. NeuroImage 47(Suppl 1):S125

Blamire AM, Ogawa S, Ugurbil K, Rothman D, McCarthy G, Ellermann JM, Hyder F, Rattner Z, Shulman RG (1992) Dynamic mapping of the human visual cortex by high-speed magnetic resonance imaging. Proc Natl Acad Sci USA 89:11069–11073

Boynton GM, Engel SA, Glover GH, Heeger DJ (1996) Linear systems analysis of functional magnetic resonance imaging in human V1. J Neurosci 16:4207–4221
Brett M, Johnsrude IS, Owen AM (2002) The problem of functional localization in the human brain. Nat Rev Neurosci 3:243–249
Brewer JB, Zhao Z, Desmond JE, Glover GH, Gabrieli JD (1998) Making memories: brain activity that predicts how well visual experience will be remembered. Science 281:1185–1187
Buchel C, Raedler T, Sommer M, Sach M, Weiller C, Koch MA (2004) White matter asymmetry in the human brain: a diffusion tensor MRI study. Cereb Cortex 14:945–951
Buckner RL, Bandettini PA, O'Craven KM, Savoy RL, Petersen SE, Raichle ME, Rosen BR (1996) Detection of cortical activation during averaged single trials of a cognitive task using functional magnetic resonance imaging. Proc Natl Acad Sci USA 93:14878–14883
Bullmore E, Sporns O (2009) Complex brain networks: graph theoretical analysis of structural and functional systems. Nat Rev Neurosci 10:186–198
Buxton RB (2001) The elusive initial dip. Neuroimage 13:953–958
Buxton RB, Frank LR (1997) A model for the coupling between cerebral blood flow and oxygen metabolism during neural stimulation. J Cereb Blood Flow Metab 17:64–72
Buxton RB, Wong EC, Frank LR (1998) Dynamics of blood flow and oxygenation changes during brain activation: the balloon model. Magn Reson Med 39:855–864
Catani M, Thiebaut de Schotten M (2008) A diffusion tensor imaging tractography atlas for virtual in vivo dissections. Cortex 44:1105–1132, A journal devoted to the study of the nervous system and behavior
Chein JM, Schneider W (2003) Designing Efficient fMRI Experiments. In: Grafman J, Robertson IH (eds) Handbook of neuropsychology. Elsevier, Amsterdam, pp 299–326
Craddock RC, Holtzheimer PE 3rd, Hu XP, Mayberg HS (2009) Disease state prediction from resting state functional connectivity. Magn Reson Med 62:1619–1628
Cuadra MB, Cammoun L, Butz T, Cuisenaire O, Thiran JP (2005) Comparison and validation of tissue modelization and statistical classification methods in T1-weighted MR brain images. IEEE Trans Med Imaging 24:1548–1565
Dale AM, Buckner RL (1997) Selective averaging of rapidly presented individual trials using fMRI. Hum Brain Mapp 5:329–340
Dale AM, Fischl B, Sereno MI (1999) Cortical surface-based analysis. I. Segmentation and surface reconstruction. NeuroImage 9:179–194
Deichmann R, Gottfried JA, Hutton C, Turner R (2003) Optimized EPI for fMRI studies of the orbitofrontal cortex. Neuroimage 19:430–441
Detre JA, Wang J (2002) Technical aspects and utility of fMRI using BOLD and ASL. Clinical Neurophysiol 113:621–634
Donaldson DI, Petersen SE, Ollinger JM, Buckner RL (2001) Dissociating state and item components of recognition memory using fMRI. NeuroImage 13:129–142
Draganski B, Gaser C, Busch V, Schuierer G, Bogdahn U, May A (2004) Neuroplasticity: changes in grey matter induced by training. Nature 427:311–312
Ernst T, Hennig J (1994) Observation of a fast response in functional MR. Magn Reson Med 32:146–149
Figley CR, Stroman PW (2011) The role(s) of astrocytes and astrocyte activity in neurometabolism, neurovascular coupling, and the production of functional neuroimaging signals. Eur J Neurosci 33:577–588
Fischl B, Sereno MI, Dale AM (1999a) Cortical surface-based analysis. II: Inflation, flattening, and a surface-based coordinate system. Neuroimage 9:195–207
Fischl B, Sereno MI, Tootell RB, Dale AM (1999b) High-resolution intersubject averaging and a coordinate system for the cortical surface. Hum Brain Mapp 8:272–284
Friston KJ (1998) Modes or models: a critique on independent component analysis for fMRI. Trends Cogn Sci 2:373–375
Friston KJ (2005) Models of brain function in neuroimaging. Annu Rev Psychol 56:57–87
Friston K (2011) Functional and effective connectivity: a review. Brain Connectivity 1:13–36

Friston KJ, Holmes AP, Worsley KJ, Poline JP, Frith CD, Frackowiak RSJ (1994a) Statistical parametric maps in functional imaging: a general linear approach. Hum Brain Mapp 2:189–210

Friston KJ, Tononi G, Reeke GN Jr, Sporns O, Edelman GM (1994b) Value-dependent selection in the brain: simulation in a synthetic neural model. Neuroscience 59:229–243

Friston KJ, Price CJ, Fletcher P, Moore C, Frackowiak RS, Dolan RJ (1996) The trouble with cognitive subtraction. Neuroimage 4:97–104

Friston KJ, Zarahn E, Josephs O, Henson RN, Dale AM (1999) Stochastic designs in event-related fMRI. Neuroimage 10:607–619

Friston KJ, Glaser DE, Henson RN, Kiebel S, Phillips C, Ashburner J (2002) Classical and Bayesian inference in neuroimaging: applications. Neuroimage 16:484–512

Gati JS, Menon RS, Ugurbil K, Rutt BK (1997) Experimental determination of the BOLD field strength dependence in vessels and tissue. Magn Reson Med 38:296–302, Official journal of the Society of Magnetic Resonance in Medicine/Society of Magnetic Resonance in Medicine

Genovese CR, Lazar NA, Nichols T (2002) Thresholding of statistical maps in functional neuroimaging using the false discovery rate. Neuroimage 15:870–878

Gholipour A, Kehtarnavaz N, Briggs R, Devous M, Gopinath K (2007) Brain functional localization: a survey of image registration techniques. IEEE Trans Med Imaging 26:427–451

Good CD, Johnsrude IS, Ashburner J, Henson RN, Friston KJ, Frackowiak RS (2001) A voxel-based morphometric study of ageing in 465 normal adult human brains. Neuroimage 14:21–36

Gossl C, Auer DP, Fahrmeir L (2000) Dynamic models in fMRI. Magn Reson Med 43:72–81

Harris JJ, Reynell C, Attwell D (2011) The physiology of developmental changes in BOLD functional imaging signals. Dev Cogn Neurosci 1:199–216

Hartman D, Hlinka J, Palus M, Mantini D, Corbetta M (2011) The role of nonlinearity in computing graph-theoretical properties of resting-state functional magnetic resonance imaging brain networks. Chaos 21:013119

Hoenig K, Kuhl CK, Scheef L (2005) Functional 3.0-T MR assessment of higher cognitive function: are there advantages over 1.5-T imaging? Radiology 234:860–868

Hoge RD, Atkinson J, Gill B, Crelier GR, Marrett S, Pike GB (1999a) Investigation of BOLD signal dependence on cerebral blood flow and oxygen consumption: the deoxyhemoglobin dilution model. Magn Reson Med 42:849–863

Hoge RD, Atkinson J, Gill B, Crelier GR, Marrett S, Pike GB (1999b) Linear coupling between cerebral blood flow and oxygen consumption in activated human cortex. Proc Natl Acad Sci USA 96:9403–9408

Holmes AP, Blair RC, Watson JD, Ford I (1996) Nonparametric analysis of statistic images from functional mapping experiments. J Cereb Blood Flow Metab 16:7–22

Hyvarinen A, Oja E (2000) Independent component analysis: algorithms and applications. Neural Netw 13:411–430

Josephs O, Henson RN (1999) Event-related functional magnetic resonance imaging: modelling, inference and optimization. Phil Trans R Soc Lond B Biol Sci 354:1215–1228

Kingsley PB (2006a) Introduction to diffusion tensor imaging mathematics: Part I. Tensors, rotations, and eigenvectors. Concept Magn Reson A 28A:101–122

Kingsley PB (2006b) Introduction to diffusion tensor imaging mathematics: Part II. Anisotropy, diffusion-weighting factors, and gradient encoding schemes. Concept Magn Reson A 28A:123–154

Kingsley PB (2006c) Introduction to diffusion tensor imaging mathematics: Part III. Tensor calculation, noise, simulations, and optimization. Concept Magn Reson A 28A:155–179

Klein A, Andersson J, Ardekani BA, Ashburner J, Avants B, Chiang MC, Christensen GE, Collins DL, Gee J, Hellier P, Song JH, Jenkinson M, Lepage C, Rueckert D, Thompson P, Vercauteren T, Woods RP, Mann JJ, Parsey RV (2009) Evaluation of 14 nonlinear deformation algorithms applied to human brain MRI registration. Neuroimage 46:786–802

Kruggel F, von Cramon DY (1999) Modeling the hemodynamic response in single-trial functional MRI experiments. Magn Reson Med 42:787–797

Kwong KK (2011) Record of a single fMRI experiment in May of 1991. Neuroimage. doi:10.1016/j.neuroimage.2011.07.089 [Epub ahead of print]
Li YO, Yang FG, Nguyen CT, Cooper SR, Lahue SC, Venugopal S, Mukherjee P (2011) Independent component analysis of DTI reveals multivariate microstructural correlations of white matter in the human brain. Hum Brain Mapp. doi:10.1002/hbm.21292 [Epub ahead of print]
Liu G, Sobering G, Duyn J, Moonen CT (1993) A functional MRI technique combining principles of echo-shifting with a train of observations (PRESTO). Magn Reson Med 30:764–768
Logothetis NK (2008) What we can do and what we cannot do with fMRI. Nature 453:869–878
Logothetis NK, Pauls J, Augath M, Trinath T, Oeltermann A (2001) Neurophysiological investigation of the basis of the fMRI signal. Nature 412:150–157
Magri C, Logothetis NK, Panzeri S (2011) Investigating static nonlinearities in neurovascular coupling. Magn Reson Imaging 29:1358–1364
Maguire EA, Gadian DG, Johnsrude IS, Good CD, Ashburner J, Frackowiak RS, Frith CD (2000) Navigation-related structural change in the hippocampi of taxi drivers. Proc Natl Acad Sci USA 97:4398–4403
Mandeville JB, Marota JJ, Ayata C, Zaharchuk G, Moskowitz MA, Rosen BR, Weisskoff RM (1999) Evidence of a cerebrovascular postarteriole windkessel with delayed compliance. J Cereb Blood Flow Metab 19:679–689
Mangia S, Giove F, Tkac I, Logothetis NK, Henry PG, Olman CA, Maraviglia B, Di Salle F, Ugurbil K (2009) Metabolic and hemodynamic events after changes in neuronal activity: current hypotheses, theoretical predictions and in vivo NMR experimental findings. J Cereb Blood Flow Metab 29:441–463
McKeown MJ, Makeig S, Brown GG, Jung TP, Kindermann SS, Bell AJ, Sejnowski TJ (1998) Analysis of fMRI data by blind separation into independent spatial components. Hum Brain Mapp 6:160–188
Menon RS, Kim SG (1999) Spatial and temporal limits in cognitive neuroimaging with fMRI. Trends Cogn Sci 3:207–216
Menon RS, Ogawa S, Hu X, Strupp JP, Anderson P, Ugurbil K (1995) BOLD based functional MRI at 4 Tesla includes a capillary bed contribution: echo-planar imaging correlates with previous optical imaging using intrinsic signals. Magn Reson Med 33:453–459
Menon RS, Luknowsky DC, Gati JS (1998) Mental chronometry using latency-resolved functional MRI. Proc Natl Acad Sci USA 95:10902–10907
Miezin FM, Maccotta L, Ollinger JM, Petersen SE, Buckner RL (2000) Characterizing the hemodynamic response: effects of presentation rate, sampling procedure, and the possibility of ordering brain activity based on relative timing. Neuroimage 11:735–759
Muthukumaraswamy SD, Evans CJ, Edden RA, Wise RG, Singh KD (2011) Individual variability in the shape and amplitude of the BOLD-HRF correlates with endogenous GABAergic inhibition. Hum Brain Mapp 33:455–465
Neggers SF, Hermans EJ, Ramsey NF (2008) Enhanced sensitivity with fast three-dimensional blood-oxygen-level-dependent functional MRI: comparison of SENSE-PRESTO and 2D-EPI at 3 T. NMR Biomed 21:663–676
Nichols TE, Holmes AP (2002) Nonparametric permutation tests for functional neuroimaging: a primer with examples. Hum Brain Mapp 15:1–25
Nirkko AC (2003) Nitric oxide-an endogenous contrast agent contributing to “the elusive initial dip?”. NeuroImage 20:611–612
Ogawa S, Lee TM, Kay AR, Tank DW (1990) Brain magnetic resonance imaging with contrast dependent on blood oxygenation. Proc Natl Acad Sci USA 87:9868–9872
Ogawa S, Menon RS, Tank DW, Kim SG, Merkle H, Ellermann JM, Ugurbil K (1993) Functional brain mapping by blood oxygenation level-dependent contrast magnetic resonance imaging. A comparison of signal characteristics with a biophysical model. Biophys J 64:803–812
Osterbauer RA, Wilson JL, Calvert GA, Jezzard P (2006) Physical and physiological consequences of passive intra-oral shimming. Neuroimage 29:245–253

Parker GJ, Alexander DC (2003) Probabilistic Monte Carlo based mapping of cerebral connections utilising whole-brain crossing fibre information. Inf Process Med Imaging 18:684–695

Parker GJ, Haroon HA, Wheeler-Kingshott CA (2003) A framework for a streamline-based probabilistic index of connectivity (PICo) using a structural interpretation of MRI diffusion measurements. J Magn Reson Imaging: JMRI 18:242–254

Pauling L, Coryell CD (1936) The magnetic properties and structure of hemoglobin, oxyhemoglobin and carbonmonoxyhemoglobin. Proc Natl Acad Sci USA 22:210–216

Petersson KM, Nichols TE, Poline JB, Holmes AP (1999a) Statistical limitations in functional neuroimaging. I. Non-inferential methods and statistical models. Phil Trans R Soc Lond B Biol Sci 354:1239–1260

Petersson KM, Nichols TE, Poline JB, Holmes AP (1999b) Statistical limitations in functional neuroimaging. II. Signal detection and statistical inference. Philos Trans R Soc Lond B Biol Sci 354:1261–1281

Poline JB, Worsley KJ, Evans AC, Friston KJ (1997) Combining spatial extent and peak intensity to test for activations in functional imaging. Neuroimage 5:83–96

Roche A (2011) A four-dimensional registration algorithm with application to joint correction of motion and slice timing in FMRI. IEEE Trans Med Imaging 30:1546–1554

Rubinov M, Sporns O (2010) Complex network measures of brain connectivity: uses and interpretations. Neuroimage 52:1059–1069

Savoy RL (2005) Experimental design in brain activation MRI: cautionary tales. Brain Res Bull 67:361–367

Savoy RL, O'Craven KM, Weisskoff RM, Davis TL, Baker J, Rosen BR (1994) Exploring the tempral boundaries of fMRI: measuring responses to very brief stimuli. 24th. Annual Meeting of the Society of Neuroscience, Miami, p 1264

Schmiedeskamp H, Newbould RD, Pisani LJ, Skare S, Glover GH, Pruessmann KP, Bammer R (2010) Improvements in parallel imaging accelerated functional MRI using multiecho echo-planar imaging. Magn Reson Med 63:959–969

Segonne F, Dale AM, Busa E, Glessner M, Salat D, Hahn HK, Fischl B (2004) A hybrid approach to the skull stripping problem in MRI. Neuroimage 22:1060–1075

Skudlarski P, Jagannathan K, Calhoun VD, Hampson M, Skudlarska BA, Pearlson G (2008) Measuring brain connectivity: diffusion tensor imaging validates resting state temporal correlations. Neuroimage 43:554–561

Sladky R, Friston KJ, Trostl J, Cunnington R, Moser E, Windischberger C (2011) Slice-timing effects and their correction in functional MRI. NeuroImage 58:588–594

Smith SM (2002) Fast robust automated brain extraction. Hum Brain Mapp 17:143–155

Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, Watkins KE, Ciccarelli O, Cader MZ, Matthews PM, Behrens TE (2006) Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. Neuroimage 31:1487–1505

Smith SM, Miller KL, Salimi-Khorshidi G, Webster M, Beckmann CF, Nichols TE, Ramsey JD, Woolrich MW (2011) Network modelling methods for FMRI. Neuroimage 54:875–891

Sporns O (2011) Networks of the brain. MIT Press, Cambridge, MA

Stephan KE, Friston KJ (2010) Analyzing effective connectivity with fMRI. Wiley interdisciplinary reviews. Cogn Sci 1:446–459

Stone JV (2002) Independent component analysis: an introduction. Trends Cogn Sci 6:59–64

Takao H, Hayashi N, Ohtomo K (2011) Effect of scanner in longitudinal studies of brain volume changes. J Magn Reson Imaging: JMRI 34:438–444

Talairach J, Tournoux P (1988) Co-planar stereotaxic Atlas of the human brain. Thieme, Stuttgard

Teipel SJ, Bokde AL, Meindl T, Amaro E Jr, Soldner J, Reiser MF, Herpertz SC, Moller HJ, Hampel H (2010) White matter microstructure underlying default mode network connectivity in the human brain. Neuroimage 49:2021–2032

Tepest R, Wang L, Csernansky JG, Neubert P, Heun R, Scheef L, Jessen F (2008) Hippocampal surface analysis in subjective memory impairment, mild cognitive impairment and Alzheimer's dementia. Dement Geriatr Cogn Disord 26:323–329

Thulborn KR, Waterton JC, Matthews PM, Radda GK (1982) Oxygenation dependence of the transverse relaxation time of water protons in whole blood at high field. Biochim Biophys Acta 714:265–270

Tian P, Teng IC, May LD, Kurz R, Lu K, Scadeng M, Hillman EM, De Crespigny AJ, D'Arceuil HE, Mandeville JB, Marota JJ, Rosen BR, Liu TT, Boas DA, Buxton RB, Dale AM, Devor A (2010) Cortical depth-specific microvascular dilation underlies laminar differences in blood oxygenation level-dependent functional MRI signal. Proc Natl Acad Sci USA 107:15246–15251

Triantafyllou C, Hoge RD, Krueger G, Wiggins CJ, Potthast A, Wiggins GC, Wald LL (2005) Comparison of physiological noise at 1.5 T, 3 T and 7 T and optimization of fMRI acquisition parameters. Neuroimage 26:243–250

Valdes-Sosa PA, Sanchez-Bornot JM, Sotero RC, Iturria-Medina Y, Aleman-Gomez Y, Bosch-Bayard J, Carbonell F, Ozaki T (2009) Model driven EEG/fMRI fusion of brain oscillations. Hum Brain Mapp 30:2701–2721

van den Heuvel MP, Hulshoff Pol HE (2010) Exploring the brain network: a review on resting-state fMRI functional connectivity. Eur Neuropsychopharmacol 20:519–534

van der Zwaag W, Francis S, Head K, Peters A, Gowland P, Morris P, Bowtell R (2009) fMRI at 1.5, 3 and 7 T: characterising BOLD signal changes. Neuroimage 47:1425–1434

Vanzetta I, Grinvald A (2001) Evidence and lack of evidence for the initial dip in the anesthetized rat: implications for human functional brain imaging. Neuroimage 13:959–967

Wager TD, Nichols TE (2003) Optimization of experimental design in fMRI: a general framework using a genetic algorithm. Neuroimage 18:293–309

Wagner AD, Schacter DL, Rotte M, Koutstaal W, Maril A, Dale AM, Rosen BR, Buckner RL (1998) Building memories: remembering and forgetting of verbal experiences as predicted by brain activity. Science 281:1188–1191

Wang J, Aguirre GK, Kimberg DY, Roc AC, Li L, Detre JA (2003) Arterial spin labeling perfusion fMRI with very low task frequency. Magn Reson Med 49:796–802

Watts DJ, Strogatz SH (1998) Collective dynamics of 'small-world' networks. Nature 393:440–442

Weiskopf N, Hutton C, Josephs O, Turner R, Deichmann R (2007) Optimized EPI for fMRI studies of the orbitofrontal cortex: compensation of susceptibility-induced gradients in the readout direction. MAGMA 20:39–49

Wilson JL, Jezzard P (2003) Utilization of an intra-oral diamagnetic passive shim in functional MRI of the inferior frontal cortex. Magn Reson Med 50:1089–1094

Woods RP, Mazziotta JC, Cherry SR (1993) MRI-PET registration with automated algorithm. J Comput Assist Tomogr 17:536–546

Woolrich MW, Behrens TE, Beckmann CF, Jenkinson M, Smith SM (2004a) Multilevel linear modelling for FMRI group analysis using Bayesian inference. Neuroimage 21:1732–1747

Woolrich MW, Behrens TE, Smith SM (2004b) Constrained linear basis sets for HRF modelling using Variational Bayes. Neuroimage 21:1748–1761

Worsley KJ, Marrett S, Neelin P, Vandal AC, Friston KJ, Evans AC (1996) A unified statistical approach for determining significant signals in images of cerebral activation. Hum Brain Mapp 4:58–73

Wright IC, McGuire PK, Poline JB, Travere JM, Murray RM, Frith CD, Frackowiak RS, Friston KJ (1995) A voxel-based method for the statistical analysis of gray and white matter density applied to schizophrenia. Neuroimage 2:244–252

Yacoub E, Shmuel A, Pfeuffer J, Van De Moortele PF, Adriany G, Andersen P, Vaughan JT, Merkle H, Ugurbil K, Hu X (2001a) Imaging brain function in humans at 7 Tesla. Magn Reson Med 45:588–594

Yacoub E, Shmuel A, Pfeuffer J, Van De Moortele PF, Adriany G, Ugurbil K, Hu X (2001b) Investigation of the initial dip in fMRI at 7 Tesla. NMR Biomed 14:408–412

Zarahn E, Aguirre G, D'Esposito M (1997) A trial-based experimental design for fMRI. Neuroimage 6:122–138

Zeineh MM, Engel SA, Thompson PM, Bookheimer SY (2001) Unfolding the human hippocampus with high resolution structural and functional MRI. Anat Rec 265:111–120

Chapter 13
PET: Theoretical Background and Practical Aspects

Isabelle Miederer and Henning Boecker

Abstract Positron emission tomography (PET) is a nuclear medicine imaging tool utilized for investigation of physiological processes in vivo. PET uses the decay characteristics of positron-emitting radionuclides which are produced in a cyclotron and then used to label compounds involved in physiological processes. Usually, the labeled compound—the tracer—is administered intravenously and distributed in the tissue. The radionuclide decays and the emitted photons are detected by the PET scanner. PET then offers the possibility to compute three-dimensional images of the biodistribution and kinetics of the regional radioactivity concentration. There are several options to analyze reconstructed PET images, i.e., they can be analyzed using qualitative approaches or more sophisticated methods such as pharmacokinetic modeling approaches. Here, the main focus is on pharmacokinetic modeling approaches as they deliver quantitative parameters describing uptake and metabolism of the administered radioactive tracer. In the context of sport and exercise sciences, it is of particular interest to quantify the cerebral metabolic rate of glucose consumption with the tracer ^{18}F-FDG or to assess endogenous neurotransmitter trafficking using dedicated tracers and the applications are based on the methodology described here.

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13.1 Introduction

Positron emission tomography (PET) is a nuclear medicine imaging tool for investigation of cellular and molecular processes in vivo. After injection of a positron-emitting tracer into humans or animals, PET produces three-dimensional images of the biodistribution and kinetics of the regional radioactivity concentration.

The initial contributions that influenced the development of PET were made by Rankowitz et al. (1962) by introducing a circular arrangement to scan brain sections in the 1960s. However, at that time, universal application of image reconstruction algorithms was not feasible. Useful algorithms could not be developed until the invention of computed tomography (CT) by Cormack (1964) and Hounsfield (1973). First PET scanners were introduced in research environments where cyclotrons and radiochemistry facilities were available to produce short-lived positron emitters like ^{15}O and with ^{11}C. These devices used ring or ringlike detector systems surrounding a patient in supine position. In the middle 1970s, [^{18}F]-fluorodeoxyglucose ([^{18}F]-FDG)—radiolabeled deoxyglucose—was introduced to image regional tissue glucose utilization. In the late 1970s and early 1980s, the quantitative accuracy of PET scanners was high enough and measurements of blood flow, oxygen utilization, and oxygen extraction could be obtained using tracers such as oxygen and water labeled with ^{15}O in conjunction with pharmacokinetic models. Furthermore, in the 1980s neuroreceptor ligands were introduced and it was shown that PET can be used to image neurotransmitter systems (e.g., the dopaminergic system using [^{18}F]-fluoro-L-DOPA (Garnett et al. 1983) or the opiate receptor system using [^{11}C]-diprenorphine (Jones et al. 1985). Parallel to neuroreceptor studies, repeated measurements of regional cerebral blood flow (rCBF) with [^{15}O]-H_2O were performed to detect changes in flow in response to experimental stimuli. In the early 1990s, PET-based rCBF studies for brain activation were replaced by functional magnetic resonance imaging (fMRI) studies (see also Chap. 12). Regarding spatial resolution and sensitivity of detectors, there has been a permanent advancement of PET systems by developing components like scintillators, by constructing detector assemblies, and by introducing acquisition modes with removed septa and new 3D reconstruction algorithms. A detailed overview of the historical development of positron-emitting tracers and PET is given in Jones (2003) and Ziegler (2005).

In general, a tracer is a substance that follows a physiological or biochemical process. It has to be given in small amounts ensuring that the system under investigation is not perturbed. A PET-tracer is a radiolabeled compound that contains a positron-emitting isotope. Depending on the radiochemical process, a tracer shows the same physiological or biochemical characteristics as compared to the naturally occurring compound, as for example chemical identical ^{15}O analogues (e.g., [^{15}O]-H_2O). On the other hand, tracers might have deviating properties, for example substituting the carboxyl group by ^{18}F (e.g., [^{18}F]-FDG). In neuroreceptor studies, a tracer is also called ligand to underline that it is a (radiolabeled) substance that is able to bind to a receptor and form a complex with it. By this one can follow a physiological process (e.g., [^{11}C]-diprenorphine).

Using dedicated tracers, PET offers the possibility to, e.g., measure diffusion across cell membranes, substrate metabolism, or receptor density/affinity. Hence, PET significantly differs from other tomographic methods like computed tomography (CT) and magnetic resonance tomography (MRI) as the latter images physical properties of the underlying organism whereas PET also images biochemical properties. The strength of these methods lies in the depiction of anatomical structures which is a principal limitation of PET. A combination of PET and CT or PET and MR devices are now available and include both physiological and structural information.

In PET studies of the human brain, there are several options to analyze PET images. For a given tracer, PET images can be analyzed using qualitative approaches or more sophisticated quantitative methods such as mathematical modeling approaches. Qualitative approaches are among those that deliver indices of tissue measurements rather than absolute quantitative values. Visual inspection gives a first estimate for the experienced reader; however, it is limited by the resolution of PET images and the lack of a standardized scale. Qualitative measures are calculated based on absolute radioactivity values, radioactivity values corrected for dose and/or weight (e.g., SUV, %ID), and radioactivity values between target and reference regions or based on the ratio of a tissue region to blood. Qualitative approaches are simple but have disadvantages as indices of tissue measurements may only allow indirect conclusion concerning the underlying physiology. Furthermore, they often require additional assumptions, such as true equilibrium conditions. Mathematical modeling methods provide more information. They enable the definition of a relationship between the measurement data and physiological parameters, which describe uptake of the tracer and its metabolism. Mathematical modeling methods are superior to qualitative methods as they deliver absolute quantitative parameters, but they usually require complex study protocols. For a detailed introduction, see Carson (2003). This chapter provides an account of the current application of PET ligand studies in the sport and exercise sciences, and all the applications are based on the methodology described here.

13.2 Physical and Technical Basics

13.2.1 Physical Basics

Positron emission tomography (PET) is a nuclear medicine imaging tool that uses the decay characteristics of positron-emitting radionuclides, which are produced in a cyclotron and are then used to label compounds taking part in physiological processes. Usually, the labeled compound is administered intravenously into the body and distributed in the tissue.

Once the radioactive nuclide decays, it emits a positron that loses energy to the surrounding tissue through ionization and excitation processes. When it has expended all its kinetic energy, it combines with an electron, its antiparticle, to a positronium. This annihilates immediately by converting all its mass into energy and forms two

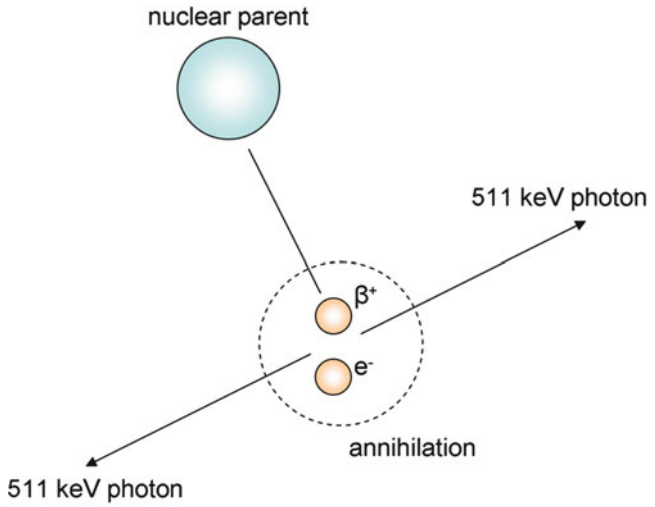

Fig. 13.1 Schematic representation of the annihilation of a positron and an electron. This process results in two 511 keV photons emitted nearly 180° apart. The positron range, i.e., the distance between positron emission and positron annihilation is dependent on the energy of the positron

511 keV photons, which are emitted in nearly opposite directions (Fig. 13.1). In PET, the two most important interactions of photons with matter are the photoelectric effect and the Compton scattering. The photoelectric effect is relevant to detection of 511 keV photons, and Compton scattering is the predominant interaction in tissue. Compton scattering can cause loss of sensitivity and resolution of the final image.

13.2.2 PET Scanner

A part of the emitted photons is registered by a detector system surrounding the object to be imaged. Any detector of the ring can be in coincidence with any other detector on the opposite side of the ring. Only those events are counted that are recorded by the two detectors within a time interval (coincidence window) of 4–20 ns. The line between the detectors is called line of response (LOR). Most systems also use an energy window of 350–650 keV to separate between scattered and non-scattered photons. Most PET cameras are full-ring systems with a patient opening of about 50–70 cm and an axial field of view of 100–200 mm. However, current development is leading to devices with larger openings and/or FOV. The elementary components of a detector are a scintillation detector and a photodetector. There are a wide variety of inorganic scintillation detectors, which have a relatively high density and atomic number such that their coefficient of interaction is high enough for detection of 511 keV photons. The incident photon interacts in the scintillator whereby light is emitted that produces a pulse in the detector. The emitted light is proportional to the energy deposited in the material.

A photodetector can be a photomultiplier tube (PMT), avalanche photodiode (APD), or silicone photomultiplier (SiPM). Normally PET cameras utilize a modular detector arrangement consisting of multiple block detectors arranged in a ring. Each block is cut into 8×8 crystals, which are read out by 2×2 photomultipliers. Cuts are made in the surface of the crystal on the inside of the ring to produce a square or rectangular array of crystal elements. These sections in the block define separate detector elements. A detailed description about PET detectors is given in Lecomte (2009).

13.2.3 Data Acquisition

The detection of events is based on electronic collimation, i.e., by collinearly aligned detector pairs which are operated in coincidence. An event is regarded as valid if (1) two detected photons occur in a coincidence window, (2) the LOR is within a valid angle of the tomograph, and (3) the energy deposited in the crystal by the two photons occurs within a predefined energy window.

These coincidences are often referred to as prompt events (or "prompts"). A distinction is drawn between five different kinds of prompts: (1) A true coincidence is an event that arises from a positron annihilation on the LOR under the assumption that the photons are not further disturbed. These events carry the information about the location of the positron emitter. (2) A random or accidental coincidence occurs when two unrelated photons are detected by two opposing detectors within the coincidence time window. These "randoms" do not carry any spatial information about the activity distribution within the body. They are part of the background noise and cause a nearly flat background. (3) Scattered coincidences are those in which at least one annihilation photon is diverted from its original path. This means that two detectors that are not opposite to each other register valid events. Scattering results from Compton interactions with electrons in the surrounding tissue. This causes a low-frequency background decreasing the image contrast. (4) Multiple coincidences occur if more than one positron annihilates during the coincidence time window, so that it is possible that three or more detectors are involved registering a valid coincidence. These coincidences only occur at high counting rates and are normally discarded. (5) A single event occurs if the detector records only one photon of the annihilated photons. The measured single count rate may be increased if much activity is located outside the scanner's field of view. They increase the random coincidences as well as the dead time.

Thus, not only true coincidences are recorded but also random and scattered coincidences so that the total count rate reads: $R_{\text{total}} = R_{\text{true}} + R_{\text{random}} + R_{\text{scatter}}$. Random and scattered coincidences have to be corrected, in order to accurately quantify the tracer distribution.

At the completion of data acquisition, the coincidence events are stored as two-dimensional matrices. The horizontal direction describes the offset s from the center

of the field of view and the vertical direction describes the projection angle (ϕ). These two-dimensional matrices are referred to as a "sinogram". One row in a sinogram represents the accumulated events of a LOR at a particular angle (ϕ). The number of columns corresponds to the number of bins at each projection angle.

If the study design envisages the use of mathematical models, then a number of three-dimensional images (i.e., a four-dimensional image volume) in units of Bq/ml covering the full time course of radioactivity in tissue can be acquired. They build the basis for compartmental modeling approaches aiming at measuring physiological parameters such as uptake of tracer and metabolic rates. More about data acquisition is depicted in Bailey (2003).

13.2.4 Image Reconstruction

To calculate the underlying activity distribution, the detected events are reconstructed into three-dimensional images by means of mathematical algorithms like filtered backprojection (FBP) or statistical iterative reconstruction algorithms. Using filtered backprojection means that the data are acquired from many views around the body and reprojected into an image matrix. However, the superposition of the backprojected data yields a blurred image. To account for this effect, the data have to be sharpened by using filter methods.

In many cases, iterative reconstruction algorithms have become the method of choice as they are fast and deliver images of superior quality. Basically, an initial guess concerning the activity distribution is made and the data are forward projected with regard to the scanner geometry. These calculated projections are compared to the measured projections. The resulting error-projections are used for correcting the estimate yielding a new estimate. In turn, this new estimate is then forward projected and the comparison between estimated and measured projections is conducted. This loop is iterated until some error criterion is achieved. In clinical routine, fast algorithms like ordered subset expectation maximization (OSEM) are used (Hudson and Larkin 1994). The spatial resolution of a PET image, which can reach approximately 2–3 mm, is principally limited due to the positron range and photon non-collinearity. For more information about reconstruction methods, see Defrise et al. (2003).

13.2.5 Data Correction Procedures

As described above, the emitted photons may be distorted in several ways before they reach the scintillation detectors. On their way through the tissue they can be scattered and/or absorbed. Some coincidences may be of random nature. Furthermore, the dead time of the detectors has to be considered and attenuation correction and detector normalization has to be applied. Attenuation correction is the most complex

correction and requires the knowledge of regional attenuation factors from the subject. They can be derived either from a CT scan or alternatively from external rotating radioactive pin sources. In order to accurately quantify the tracer distribution, these effects have to be corrected and the scanner count rate has to be calibrated in relation to the true activity concentration. A full description about quantitative techniques can be found in Meikle and Badawi (2003). A detailed description about the physical and technical basics can also be found in Cherry and Dahlbom (2009).

13.3 Image Analysis

In in vivo PET studies, mathematical models are used to describe the relation between the measurement data and physiological parameters that determine uptake of a tracer and its metabolism. The most commonly used modes are compartmental models. In the field of pharmacokinetics, compartments are usually considered as physiologically distinct pools of tracer, in which rate constants describe the rate of exchange of tracer between them. Mainly two datasets are necessary to determine the physiological parameters of interest: first, the blood time course calculated from blood samples drawn during the PET scan (input function (IF)), and second, the tissue activity time course (time–activity curve (TAC)) measured by the PET scanner.

13.3.1 Compartmental Models

A compartment defines a possible state of the tracer, i.e., every compartment defines a physical space (e.g., intracellular space) or chemical state (e.g., metabolic state or binding to receptors) within which the tracer becomes uniform distributed rapidly. Often, compartments are lumped together into a single compartment. Here, blood is not counted as a compartment. Furthermore, the compartmental model describes the rate of tracer transformation from one state to another. The transport of the tracer to a different compartment within a specified time is defined by the fractional rate of change of tracer concentration in one compartment. The related rate constant is expressed as "k" in units of min^{-1}. K_1 is capitalized as it is usually expressed in units of ml ml^{-1} min^{-1} (ml plasma per ml tissue per min).[1] The meaning of the rate constants depends on the interpretation of the source and destination compartments. The goal of all modeling approaches is to estimate one or more rate constants (or a ratio of them) from blood and tissue radioactivity measurements.

[1] The radioactivity in blood is usually measured in units of ml plasma, whereas in non-imaging studies, the radioactivity in tissue is measured per ml tissue. Therefore, compartment 1 (C_1) has units of Bq/ml tissue and plasma (C_p) has units of Bq/ml; hence, K_1 has units of ml plasma per ml tissue per min.

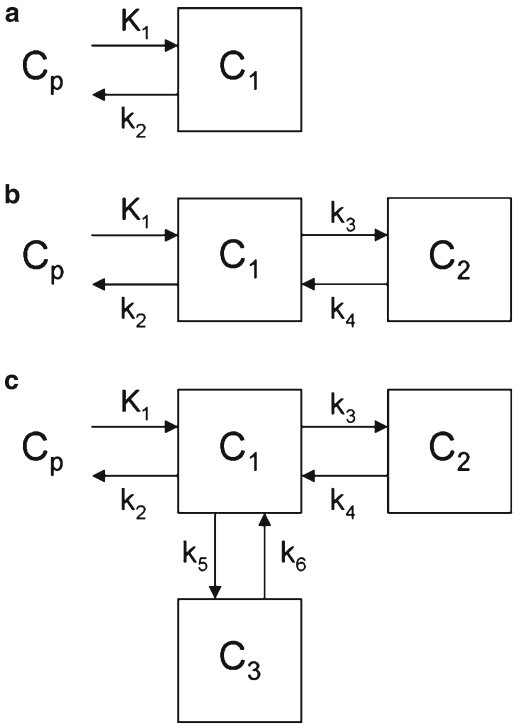

Fig. 13.2 Frequently used compartment models: (**a**) shows a one-tissue compartment suitable for inert tracers that are used to measure local blood flow such as ^{15}O; (**b**) depicts a model with two compartments used for describing the metabolism of deoxyglucose ([^{18}F]-FDG) assuming that k_4 can be neglected; (**c**) illustrates a three-compartment model for a receptor-binding ligand. C_p represents the concentration of tracer in arterial blood, $C_{1–3}$ is the concentration of tracer in the compartment, and "*k*" is the rate constants describing tracer movement from one compartment to the other

13.3.2 Model Configurations

Figure 13.2a shows a one-tissue compartment model. It is suitable for a tracer that returns back to blood. The rate constant K_1 symbolizes the rate at which the tracer is moving from blood to the compartment and k_2 symbolizes the rate in the opposite direction. Such a model is appropriate for inert tracers that are used to measure local blood flow such as ^{15}O.

Figure 13.2b shows a model with two compartments. This model is used for tracers that enter the tissue from blood, are either metabolized and trapped in tissue (at a rate by k_3), or return to blood (at a rate by k_2). Compartment 1 presents the unmetabolized tracer and compartment 2 the metabolized tracer. The most common example is the metabolism of deoxyglucose ([^{18}F]-FDG) assuming that k_4 can be neglected. Figure 13.2c illustrates a three-compartment model. This is a model for a receptor-binding ligand where compartment 1 represents the free tracer, compartment 2 the tracer specially bound to the receptor, and compartment 3 the tracer nonspecifically bound to other tissue elements. Often, a number of possible states are lumped together and described by a single compartment, e.g., tracer nonspecifically bound and free in tissue water.

13.3.3 Model Assumptions

The application of compartmental models requires that a number of assumptions are valid. It is assumed that the injected tracer concentration is negligible and does not influence the system under investigation. It is also presumed that the physiological processes under investigation are in steady state, i.e., that for example metabolic processes remain constant during a study. Furthermore, it is also assumed that there are no concentration gradients within a given compartment. These assumptions are typically not completely true and it depends on the amount of error in the model parameters if a dedicated model can be utilized.

13.3.4 Model Parameters

The interpretation of individual rate constants is dependent on the meaning of the source and destination compartments and on the particular model configuration and number of compartments. However, there are other model parameters, which are independent of the underlying model structure. For reversible tracers, the rate constant describing transfer from blood to the compartment (K_1 in, e.g., Fig. 13.2a) and the *volume of distribution* are commonly used model parameters. The volume of distribution used in most imaging studies is the ratio of the concentration of radioligand in a region of tissue to that in plasma at equilibrium and has units of ml/cm^3. It can also be calculated from the individual model rate constants. For studies with radioligands that bind reversely to a receptor, the *binding potential* quantifies the equilibrium concentration of specific binding as a ratio to some other reference concentration. This is usually free plasma concentration, total plasma concentration, or nondisplaceable uptake.

Regarding irreversible systems, the "combined forward rate constant" K_1 is used to describe the net rate of irreversible transfer of tracer from blood to tissue. Besides K_1, this parameter is usually used in metabolic studies using glucose analogues.

13.3.5 Model Implementation

It is assumed that after intravenous (bolus) administration of a tracer (1) the concentration of the tracer in the arterial plasma C_P (metabolite-corrected), i.e., the input function, and arterial whole blood C_{WB} (metabolite-uncorrected) is provided by measurements of the arterial blood samples (approaches that do not require arterial blood samples are considered below), (2) radiolabeled metabolites of the parent tracer do not cross the blood–brain barrier, and (3) the concentration of the tracer in the tissue C_{PET}, i.e., the time–activity curve, can be determined by using a properly chosen volumes-of-interest (VOI) on reconstructed PET images or directly on a voxel-by-voxel level.

13.3.6 Input Function

The measurements of arterial blood samples are usually undertaken in blood drawn from the radial artery. From these samples, concentration of the tracer in plasma, whole blood, and the fraction of metabolites are determined. This induces delay and dispersion effects with respect to tracer in arterial blood in brain tissue. The arterial blood samples can be taken manually or automatically using an online detection system for continuous withdrawal. If a significant fraction of radioactive signal represents metabolites of the parent tracer, the arterial plasma input function has to be corrected. Thereby, a mono- or bi-exponential function is fitted to the fraction of intact tracer and multiplied with the total plasma curve. If metabolites cross the blood–brain barrier, the standard compartmental model may not be valid anymore.

13.3.7 Model Equations

Under the given assumptions (see Sect. 13.3.3), compartmental models are mathematically represented by coupled inhomogeneous linear first-order differential equations with constant coefficients. In the following, the model equations for a one- and a two-tissue compartmental model (Fig. 13.2a, b) for reversible tracers are considered. For the one-tissue compartmental model, the differential equation describing the rate of change of tissue concentration C_1 is given by

$$\frac{\mathrm{d}C_1}{\mathrm{d}t} = K_1 C_\mathrm{P} - k_2 C_1, \tag{13.1}$$

and the solution is given by

$$C_1 = K_1 \mathrm{e}^{-k_2 t} \otimes C_\mathrm{P}, \tag{13.2}$$

where the symbol ⊗ denotes convolution.[2]

For the two-tissue compartmental model, two differential equations are given to describe the rate of change of tissue concentration in C_1 and C_2:

$$\frac{\mathrm{d}C_1}{\mathrm{d}t} = K_1 C_\mathrm{P} - (k_2 + k_3) C_1 + k_4 C_2, \tag{13.3}$$

$$\frac{\mathrm{d}C_2}{\mathrm{d}t} = k_3 C_1 - k_4 C_2, \tag{13.4}$$

[2] Formula 2 represents an alternative notation for the solution of the differential equation: $C_1(t) = \int_0^t C_\mathrm{p}(s) K_1 \mathrm{e}^{-k_2 (t-s)} \mathrm{d}s$, where s is an integration variable. The interested reader is referred to the literature about the theory of linear time invariant systems, e.g., Godfrey (1983).

and the solution is given by

$$C_T = C_1 + C_2 = \left(\varphi_1 e^{-\theta_1 t} + \varphi_2 e^{-\theta_2 t}\right) \otimes C_P, \tag{13.5}$$

where φ and θ are functions of the rate constants K_1, k_2, k_3, and k_4.

Thus, the tissue time–activity curve C_i is given by convolution of the input function with the impulse response function (IRF). For this type of compartmental models, the IRF is a sum of exponentials corresponding to the number of compartments.

13.3.8 Parameter Estimation

The prior section presents the mathematical tools to solve the model equation, i.e., knowing the blood time course C_P, the model configuration, and its rate constants, the tissue concentration C_T can be calculated. However, using PET an inverse mathematical problem arises: given measurements of the tissue radioactivity C_T and the measurements of the blood samples C_P and a proposed model configuration, the aim is to estimate the underlying rate constants $K_1 - k_x$. There are several methods available to accomplish parameter estimation, depending on the model, sampling, and statistical quality of the data. The most commonly used method for parameter estimation using compartmental models is least-squares estimation. Along with initial estimates of the rate constants, the goal is hereby to minimize an optimization function, which is the sum of squared differences between the measured tissue radioactivity concentration and the model equation:

$$\sum_{i=1}^{n} \left(C_i - C(T_i)\right)^2. \tag{13.6}$$

C_i denotes the tissue measurements at times T_i and $C(T_i)$ is the model prediction at these time points. As the errors parameter estimation generally increases with increasing model complexity, most PET compartmental models contain two or three compartments.

13.3.9 Alternative Modeling Methods

Besides the model-driven approaches presented above, so-called data-driven methods exist that do not require a priori hypotheses regarding the underlying model structure. This information is solely obtained from the data. These methods include, e.g., graphical analyses (Cunningham and Jones 1993; Logan et al. 1990; Patlak et al. 1983) where the data are transformed into a straight-line plot and

whose terminal linear slope and intercept equal the parameter of interest which can be obtained by linear regression. Furthermore, spectral analysis is a data-driven modeling approach where a possible set of basis functions is defined which describes the expected behavior of the ligand. The tissue time–activity curve is then fitted to the sum of a subset of these basis functions. Convolutions of the input function with a sum of exponential terms characterize the data (Cunningham and Jones 1993).

In order to avoid the invasive arterial cannulation, reference tissue methods have been proposed whereby a time–activity curve from a reference region that is devoid of the relevant receptor(s) is used as an indirect input function to the target region. Using reference tissue models where the reference region can be characterized by a single compartment assumes that the reference region does not allow specific binding. Furthermore, it requires that the tissue concentration of free and nonspecifically bound ligand relative to the ligand in plasma is the same in the target region and in the reference region.

Data-driven methods do not necessarily require the definition of regions of interest. They allow the calculation of parameters at the voxel level to produce parametric images, yielding a high physiological spatial resolution. These methods are generally simpler than full parameter models and use additional assumptions on physiological parameters. However, they can provide accurate and reliable estimates. A comprehensive description about pharmacokinetic modeling in PET is referred to Carson (2003).

13.3.10 Conclusion and Potential Applications

The application of PET is a tool to study cellular and molecular processes in vivo. Compartmental modeling methods allow for the determination of the relationship between measurement data and physiological parameters like tracer uptake and metabolism. Alternative modeling approaches have been proposed that simplify the analysis protocol. In the context of the sport and exercise sciences, the application of PET as a means to study receptor binding is of particular interest, as the underlying neurochemistry of acute and chronic sport challenges can be investigated at the systems level and linked to psychological measures (see also Chap. 6). Another application in the context of long-term exercise is the quantification of the cerebral metabolic rate of glucose consumption with the tracer ^{18}F-FDG (see also Chap. 15). Indeed, ^{18}F-FDG may serve as an interesting biomarker, as it allows testing the assumption that exercise counteracts the physiological age-related metabolic decline in longitudinal designs. ^{18}F-FDG PET may be applied in healthy aging populations, or in (pre-) symptomatic disease states. Finally, the study of so-called ligand activation approaches, as discussed in (see also Chap. 22), provides a powerful means to assess endogenous neurotransmitter trafficking. This approach is based on computing the difference between specific ligand binding at rest and post-intervention and,

thereby, inferring upon endogenous neurotransmission: ligand binding can be either increased, compared to rest conditions, which indicates decreased endogenous neurotransmission, or decreased, indicating increased endogenous neurotransmission compared to the rest state.

References

Bailey LT (2003) Data acquisition and performance characterization in PET. In: Valk PE, Bailey DL, Townsend DW, Maisey MN (eds) Positron emission tomography: basic sciences: basic science and clinical practice. Springer, Berlin, pp 69–90

Carson RE (2003) Tracer kinetic modeling in PET. In: Valk PE, Bailey DL, Townsend DW, Maisey MN (eds) Positron emission tomography: basic sciences: basic science and clinical practice. Springer, Berlin, pp 147–179

Cherry SR, Dahlbom M (2009) PET: physics, instrumentation, and scanners. Springer, New York

Cormack AM (1964) Representation of a function by its line integrals, with some radiological applications. II. J Appl Phys 35:2908–2913

Cunningham VJ, Jones T (1993) Spectral analysis of dynamic PET studies. J Cereb Blood Flow Metab 13:15–23

Defrise MK, Kinahan PE, Michel C (2003) Image reconstruction algorithms in PET. In: Valk PE, Bailey DL, Townsend DW, Maisey MN (eds) Positron emission tomography: basic sciences: basic science and clinical practice. Springer, Berlin, pp 91–114

Garnett ES, Firnau G, Nahmias C (1983) Dopamine visualized in the basal ganglia of living man. Nature 305:137–138

Godfrey K (1983) Compartmental models and their application. Academic, London

Hounsfield GN (1973) Computerized transverse axial scanning (tomography). 1. Description of system. Br J Radiol 46:1016–1022

Hudson HM, Larkin RS (1994) Accelerated image reconstruction using ordered subsets of projection data. IEEE Trans Med Imaging 13:601–609

Jones T (2003) Historical development of functional *in vivo* studies using positron-emitting tracers. In: Valk PE, Bailey DL, Townsend DW, Maisey MN (eds) Positron emission tomography: basic sciences: basic science and clinical practice. Springer, Berlin, pp 3–40

Jones AK, Luthra SK, Pike VW, Herold S, Brady F (1985) New labelled ligand for in-vivo studies of opioid physiology. Lancet 2:665–666

Lecomte R (2009) Novel detector technology for clinical PET. Eur J Nucl Med Mol Imaging 36(Suppl 1):S69–S85

Logan J, Fowler JS, Volkow ND, Wolf AP, Dewey SL, Schlyer DJ, MacGregor RR, Hitzemann R, Bendriem B, Gatley SJ et al (1990) Graphical analysis of reversible radioligand binding from time-activity measurements applied to [N-11C-methyl]-(-)-cocaine PET studies in human subjects. J Cereb Blood Flow Metab 10:740–747

Meikle SR, Badawi RD (2003) Quantitative techniques in PET. In: Valk PE, Bailey DL, Townsend DW, Maisey MN (eds) Positron emission tomography: basic sciences: basic science and clinical practice. Springer, Berlin, pp 115–146

Patlak CS, Blasberg RG, Fenstermacher JD (1983) Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data. J Cereb Blood Flow Metab 3:1–7

Rankowitz S, Robertson JS, Higinbotham WA, Rosenblum MJ (1962) Positron scanner for locating brain tumors. IRE Int Conv Rec 9:49–56

Ziegler SI (2005) Positron emission tomography: principles, technology, and recent developments. Nucl Phys A 752:679c–687c

Part III
Effects of Exercise on Brain Perfusion, Metabolism, and Structure

Chapter 14
NIRS for Measuring Cerebral Hemodynamic Responses During Exercise

Stéphane Perrey

Abstract NIRS is ideally suited to perform brain imaging in various populations during movement as it represents several advantages over other methods (Perrey, Methods 45:289–299, 2008). Thus, it is not surprising that the last two decades have witnessed a considerable increase in the use of NIRS with healthy subjects and patients. This chapter first outlines typical hemodynamic changes measured with NIRS in responses to different exercise demands. Then, we describe its future prospective in neuroimaging clinical studies with emphasis on the fact that although there are still many problems to solve, the potential benefits of NIRS are considerable for obtaining further insights into brain functions during exercise.

14.1 Introduction

To date, several techniques to examine functional brain activity are available. Historically, electroencephalography (EEG) was the first available imaging method, followed by other technologies including positron emission tomography (PET) and single-positron emission computed tomography (SPECT), magnetoencephalography (MEG) and, most recently, functional magnetic resonance imaging (fMRI). A less-known technology for monitoring brain function, near-infrared spectroscopy (NIRS), uses the difference of absorption spectra of oxyhemoglobin (HbO_2) and reduced hemoglobin (HHb) as well as oxygenated cytochrome oxidase in mitochondria in the near-infrared light region. Optical spectroscopy is a long-established technique for the observation of oxygenation and hemodynamic effects in tissue (for methodological details, see Chap. 10). The specific interest in NIRS followed

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the initial description by Jöbsis (1977) in which he demonstrated that NIRS can be used as a new tool to noninvasively monitor cerebral blood oxygenation. Since that time, several NIRS studies conducted in the past 20 years have demonstrated that activation-induced changes in brain activity can be assessed noninvasively during the performance of motor activity (Hirth et al. 1996; Maki et al. 1995; Obrig et al. 1996). Main advantages of NIRS rely on the temporal resolution of the device and its better tolerance to head motion that precludes studies of higher-intensity exercise. NIRS as an optical technique is noninvasive, relatively inexpensive compared to PET or fMRI, highly portable, replicable (Kono et al. 2007), and offers real-time measurement of tissue oxygenation in the human brain under a "natural" setting, without any rigid fixation of the head as required in PET or fMRI setups. This suggests high suitability for using NIRS to investigate brain function during exercise. Brain function in the adult can be usefully probed by NIRS imaging techniques (functional NIRS for fNIRS) to a maximum depth of approximately 3 cm. Ongoing technological advances in NIRS imaging have made it possible to noninvasively extract information from the human brain regarding brain plasticity and site of action.

Exercise has fascinated people over hundreds of years. During exercise, there is a hyperbolic relationship between work intensity and endurance exercise performance. Yet it is the brain that makes the decision when to slow down or to stop exercise and from that perspective fatigue is considered of central origin (i.e., a progressive decline in the central neural drive to motor neurons; Gandevia 2001). Exercise-induced fatigue is usually defined as the reduction in force or power-generating capacity of the neuromuscular system (Bigland-Ritchie et al. 1986). Within recent years, physiologists have employed a vast array of experimental procedures and protocols to understand mechanisms of fatigue and potential limitations to exercise performance for various types of motor tasks. Reduction in cerebral oxygenation induced by exhaustive exercise is thought to be associated with impairments in central neural drive (Rasmussen et al. 2010). This effect is still poorly understood, and further progress has been limited. Indeed, regional measurements of cerebral blood flow and oxygenation are difficult to obtain during moderate to intense dynamic exercise. As a result, brain monitoring in tasks that require substantial motion, e.g., walking, running, and cycling, is generally precluded.

Until now, our understanding of human brain physiology under exercise conditions has depended primarily on indirect assessments or models derived from animal studies. However, the advent of fNIRS allows researchers to focus directly on human brain function while exercising. This chapter outlines typical hemodynamic changes measured with NIRS in responses to different exercise demands in humans and examines how this method has already been applied to the investigation of brain activity related to human motor performance from low- to high-intensity exercise, as well as how fNIRS might be applied in the future for clinical applications to detect cerebral activation during exercise. With these measurements, expected objectives are to understand targeted neurocircuitries in situ that may be compromised by physical challenges or neurological diseases for the purpose of developing plausible treatment strategies.

14.2 Typical Hemodynamic Changes in Responses to Motor Tasks

NIRS has been developed based on the principle that near-infrared light (700–1,000 nm), unlike visible light, easily passes through biological tissues and is mainly absorbed by molecules, such as hemoglobin. Thus, different absorption spectra can be detected depending on their oxygenation–deoxygenation state, and hemodynamic responses can be inferred. As regional brain activation leads to an increase in oxygen metabolism, initial deoxygenation of the tissue is followed by an effective enhancement of regional cerebral blood flow (rCBF). As rCBF compensates for the initial tissue deoxygenation, the end result of neural activation is an elevation of HbO_2 and a decrease in HHb (Obrig et al. 1996). Thus, the prototypical NIRS oxygenation response to be expected over an activated cortical area (see Fig. 14.1) consists of a slight or no decrease in HHb, accompanied by an increase in HbO_2 (of two- to three-fold magnitude), resulting in an increase in total hemoglobin (Hb_{tot}). Directions of changes in HbO_2 are always the same as those of rCBF, whereas the direction of changes in HHb is determined by changes in venous blood oxygenation and volume. Thus, HbO_2 is considered the most sensitive indicator of changes in rCBF in NIRS measurement, and the term activation has been operationally defined due to the focal increase in rCBF. Apparently, regional flow changes in activated brain regions are accompanied by much smaller increases in regional metabolism. The methodological background of NIRS is presented in Sect. 14.2 of this book (see Chap. 10).

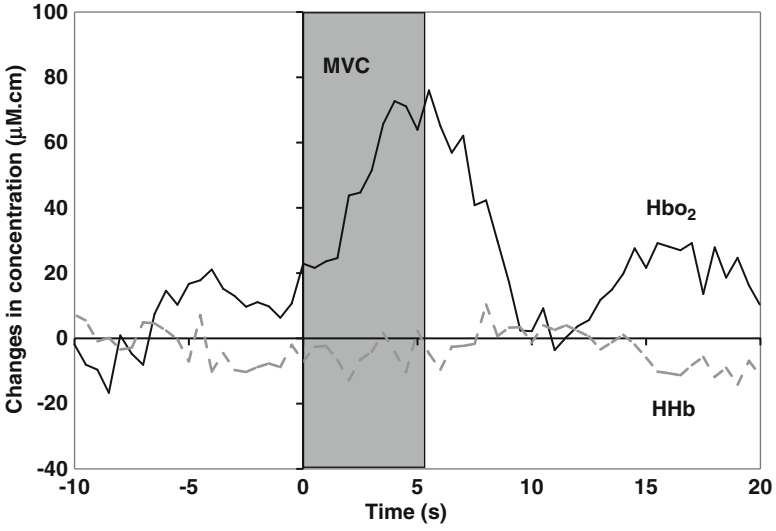


Fig. 14.1 Original hemodynamics time course plot illustrating the changes in oxygenated hemoglobin (*full line*, HbO_2) and desoxyhemoglobin (*dashed line*, HHb) in response to a sustained isometric maximal voluntary contraction (MVC) during a handgrip task in a right-handed subject. The optical probes were positioned over the left primary motor cortex. Data acquisition with the NIRO-300 system (Hamamatsu Photonics)

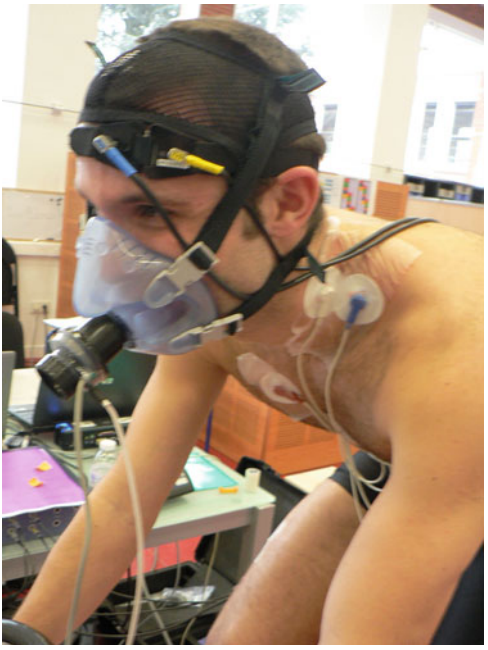
Here, we first summarize what information NIRS offers regarding the oxygenation status in responses to voluntary motor tasks. Global exercise does not affect whole-brain blood flow or O_2 uptake (Madsen 1993) even during vigorous exercise. But with enhanced flow velocity of the middle cerebral artery (Jørgensen 1995), rCBF increases during exercise. It was proposed that regional increases in CBF are not reflected in the global values, perhaps due to downregulation of activity in nonactivated brain regions or to the variation in anatomy of the cerebral venous drainage with respect to both the cerebral regions of interest and whether the exercising subjects is supine or upright (Dalsgaard 2006). Even with simple motor paradigms, such as unilateral finger opposition, oxygenation increases in the primary sensorimotor cortex (SMC), whereas blood oxygenation is reduced in other areas including the ipsilateral SMC (Kleinschmidt et al. 1996). Typically, more complex movements are associated with cortical activation increases in the supplementary motor area (SMA) and adjacent premotor areas (Orgogozo and Larsen 1979). As the cortical motor regions are located in close proximity to the scalp tissue, they are well accessible to optical measurements. Furthermore, NIRS seems ideally suited for assessing the function of the prefrontal cortex (PFC) through hemodynamic parameters over different whole-body exercise paradigms and intensities, as this noninvasive method is less associated with susceptibility artifacts that could impair fMRI studies especially for the orbitofrontal PFC region (see also Chap. 11). A variety of motor tasks have been studied with NIRS, including grasping, pinching, and tapping. Moreover, NIRS applications have been applied to exercise challenges, including dynamic whole-body exercise (cycling, rowing, walking with demands on general aerobic and anaerobic endurance), as well as strength exercise (isometric, isokinetic exercise) and will be summarized in the following (see also Chap. 5).

14.3 Application of NIRS During Ordinary Movements in Humans

Over the past 10 years, studies have convincingly demonstrated that NIRS assessments during dynamic whole-body exercise are feasible. It has been possible to monitor real-time regional cerebral oxygenation changes during strenuous cycling exercise through NIRS (Shibuya et al. 2004a; Fig. 14.2) and even during treadmill walking (Miyai et al. 2001; Suzuki et al. 2004). These studies suggest that the hemodynamic response to exercise can be modulated by the exercise intensity (Shibuya et al. 2008).

14.3.1 Walking

The ability to walk is an important determinant for human quality of life. Elderly people are particularly susceptible to gait disturbances. Recent technical advances in NIRS (Wolf et al. 2007) have enabled studying cortical activity during dynamic



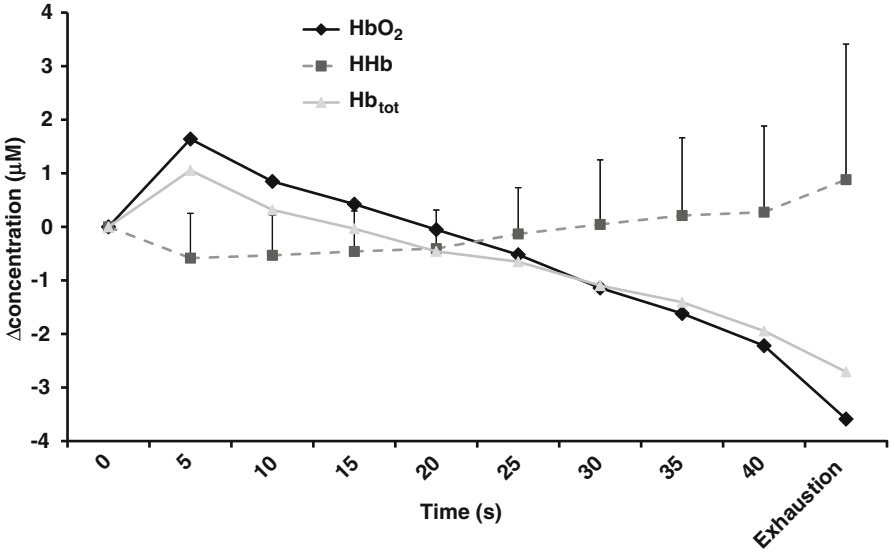


Fig. 14.2 Regional changes in cerebral oxygenation during supramaximal cycling exercise to exhaustion. Continuous recordings obtained are shown as change from resting value for oxygenated hemoglobin (HbO_2), deoxyhemoglobin (HHb), and total hemoglobin (Hb_{tot}) in left prefrontal cortex (see on the accompanied picture). Values are mean ± SD. Personal data acquisition with the Oxymon Mk III system (Artinis)

movements such as walking, allowing NIRS to illuminate the cortical processes responsible for upright human gait. Using fNIRS, researchers demonstrated increases in oxygenated hemoglobin in the PFC, the PMC, and the SMA during walking (Harada et al. 2009; Miyai et al. 2001; Suzuki et al. 2004, 2008). The first study by Miyai et al. (2001) using multichannel fNIRS (30 source-detector pairs) demonstrated significantly increased levels of HbO_2 and total Hb in bilateral SMA and SMC during upright treadmill walking (with arm swing) at 1 km/h. This study was the first to show cortical activation patterns in human gait. Importantly, their study showed that NIRS was able to reliably measure artifact-free signals. By walking at 3 and 4 km/h, Suzuki et al. (2004) reported evoked hemodynamic responses from the bilateral medial SMC, whereas running at 9 km/h led to additional oxygenation changes in PMC and especially in PFC. Hence, the PMC and the PFC were predominantly involved in adapting to increasing locomotor speed. These findings in humans indicated that areas involved in planning and allocating attentional resources play a crucial role in controlling locomotion, in particular, adapting to changes in speed. In elderly humans, increases in walking speed have also been shown to enhance cortical activation in the left PFC and the SMA (Harada et al. 2009; 42-channel system). Besides investigating cortical patterns related to different walking speeds, the influence of a verbal cue (i.e., prepared walking) leads to more profound PFC and PMC activation than walking without a verbal cue (i.e., simple walking) (Suzuki et al. 2008). This indicates that anticipated adaptations of gait to changes of treadmill speed readily affect regional activations in PFC, SMA, PMC, and SMC. Of note, particularly remarkable increases in left PFC activation were observed in subjects with low gait capacity, relative to subjects with high gait capacity (gait speed at 70% target heart rate>6 km/h; Harada et al. 2009). The aforementioned studies using multichannel settings also emphasize that NIRS is able to detect adaptations in cortical activity related to the normal aging. Therefore, treadmill walking studies (from light to fast speeds) will advance our understanding of cortical control of locomotor behaviors throughout different life spans.

14.3.2 Cycling and Rowing

Some studies using NIRS in the context of submaximal and/or maximal cycling exercise suggest that cortical oxygenation increases in the first few minutes following initiation of exercise (Shibuya et al. 2004a; Rupp and Perrey 2008; Subudhi et al. 2009). Specifically, cerebral oxygenation and blood volume increase for PFC and PMC regions in response to moderate-to-hard submaximal whole-body exercise, which is consistent with increased O_2 metabolic demand (Ide et al. 1999; Subudhi et al. 2009). There appears to be a threshold exercise intensity for detection of, e.g., PFC oxygenation increases, as can be determined by changes in HbO_2 and Hb_{tot}. In cycling, Ide et al. (1999) reported increases in HbO_2 and Hb_{tot} with 10 min at 30% maximal oxygen uptake ($\dot{V}O_2max$), whereas cycling for 3 min at 60% $\dot{V}O_2max$ or 15 min at 40% $\dot{V}O_2max$ did not produce significant oxygenation changes. Users

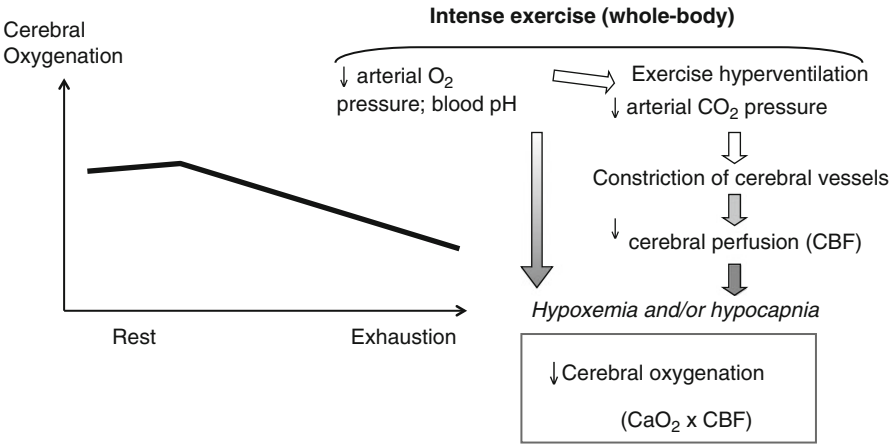


Fig. 14.3 Possible changes in brain blood flow that could contribute to fatigue and exhaustion. Increasing levels of arterial CO_2 pressure are accompanied by vasodilation and increased blood flow, while lowered arterial CO_2 pressure levels can lead to cerebral hypoperfusion and, in turn, to a decrease in cerebral oxygenation. See text for further details

should have in mind that the level of intensity at which cerebral oxygenation begins to increase varies considerably between individuals and is linked to the percentage of maximal aerobic capacity during whole-body exercise. With increasing exercise intensity, the rise in cerebral oxygenation follows a quadratic trend. Indeed, recent evidence from the literature shows that the increase in cerebral oxygenation does not continue linearly until exhaustion; instead, before the point of exhaustion when maximal exercise elicits significant arterial desaturation (Nielsen et al. 1999), the cerebral oxygenation decreases (Bhambhani et al. 2007; Rupp and Perrey 2008). Not only during incremental exercise but also during challenging physical exercise, such as 6 min of high-intensity rowing (Nielsen et al. 1999), cycling to exhaustion against a constant high resistance during 15 min (González-Alonso et al. 2004), or supramaximal exercises (successive intervals at 150% $\dot{V}O_2$max in Shibuya et al. 2004b; at 120% $\dot{V}O_2$max to exhaustion in Shibuya et al. 2004a; personal data in Fig. 14.2), a phase of decreasing cortical oxygenation can be identified. During highly intense exercise, it can be problematic to maintain the arterial oxygen saturation and also hyperventilation-induced lowering of the arterial carbon dioxide tension can occur (Rupp and Perrey 2008). The hypocapnia that accompanies hyperventilation during exhaustive exercise leads to cerebral vasoconstriction and, consequently, reduced cerebral blood flow (Nielsen et al. 1999) and decreased cerebral oxygenation (Fig. 14.3). At very challenging exercise intensities, limitations in cardiac output or decreasing $PaCO_2$ can limit the delivery of oxygen to the brain, or, increased neural activity at these intensities could exceed the delivery of oxygen to the brain such that oxygen levels in cerebral blood fall.

Based on pertinent NIRS investigations, this would suggest that during either incremental exercise tests to exhaustion or highly intense exercise of very short

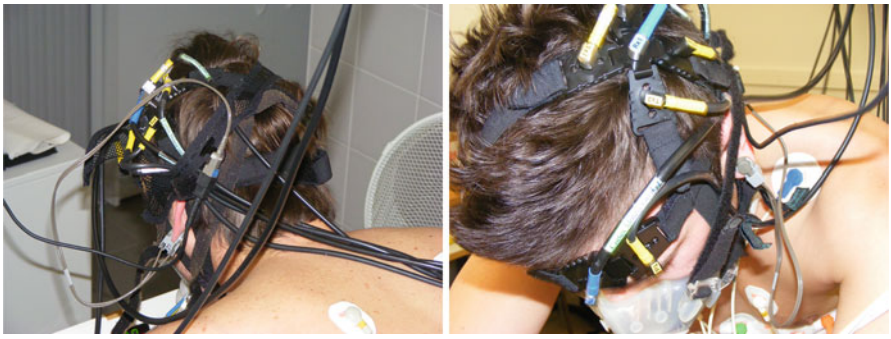


Fig. 14.4 Pictures showing head coverage setting (frontal and motor cortex) during cycling exercise with a multichannel instrument (Oxmon Mk III, Artinis)

duration (<15 min), there is inadequate delivery of oxygen, which could lead to compromised brain function, particularly influencing the PFC. In a recent review (Perrey 2008) pertaining to the application of NIRS on brain activation during exercise, we suggested that the PFC may be implicated in the onset of fatigue. The PFC projects to premotor areas and may be responsible for movement and planning strategies, as well as decision making. Several studies have used NIRS to evaluate the changes in cerebral and muscle oxygenation simultaneously during whole-body aerobic exercise such as cycling and rowing under normoxic, hypoxic, and hyperoxic conditions (Amann et al. 2006; González-Alonso et al. 2004; Ide et al. 1999; Subudhi et al. 2007). These findings clearly suggest that at exercise intensities above the respiratory compensation threshold, there is a systematic decline in cerebral oxygenation until exercise is terminated because of fatigue (Subudhi et al. 2007). This phenomenon is further amplified in hypoxia conditions (Subudhi et al. 2009). As well, the evidence suggests that when arterial hypoxemia is reversed by breathing a hyperoxic mixture (30% inspired fraction of oxygen) during maximal rowing exercise, performance is enhanced because of an increase in cerebral but not muscle oxygenation (Nielsen et al. 1999). This suggests that a decline in cerebral oxygenation is most likely implicated in fatigue during maximal exercise. However, the predominant application of NIRS only to the left PFC (placed on the forehead between areas F1 and F5 of the international 10-20 system) in the literature weakens more generalized conclusions about brain responses during exercise. Recently, cerebral hemodynamic parameters from multiple sites (premotor/motor cortices) across the full range of submaximal exercise intensity during incremental cycling have provided similar findings (Subudhi et al. 2009).

In conclusion, NIRS has sufficient selectivity to localize neural activity over different cortical areas triggered by exercise stimuli. Data suggest that the motor drive may be influenced by cerebral deoxygenation of certain motor cortical areas during high-intensity exercise. This provides new ideas of the role of cerebral activity in exhaustive whole-body exercise, but clearly, improved regional head coverage is needed in future NIRS studies on exercise (see some head coverage settings in Fig. 14.4).

14.3.3 Upper Body and Resistance Exercise

As for locomotor activities, it is evident that NIRS can reveal important information pertaining to the cerebral oxygenation and hemodynamics during static and dynamic resistance exercise. Currently, there is limited research using NIRS examining alterations in cerebral oxygenation and blood volume during sustained lower-body isometric contractions of a muscle group (Rupp and Perrey 2009). The findings of this study indicated that fatigue during submaximal isometric exercise (ankle extension performed at 40% of the maximal voluntary contraction) is not limited by neuronal activation but is most likely mediated peripherally in the activated muscle. Likewise, Pereira et al. (2007) found that the ability to sustain the maximal isometric knee extension (unilateral 1 RM contraction lasting approximately 20 s; for further explanation, see also Chap. 5) was not limited by central neuronal activation: none of the investigated subjects demonstrated a leveling off or decline in cerebral oxygenation during the contraction. The fact that cerebral blood volume also demonstrated a concomitant increase in almost all subjects supports this finding. Indeed, the nature of the muscle contraction (dynamic vs. static) as its intensity could influence the relative contribution of the anaerobic and aerobic energy pathways, thereby influencing metabolic factors implicated in skeletal muscle fatigue (Sirikul et al. 2007). It is possible that during the relaxation phase of the dynamic contraction, oxygenated blood perfuses the muscle, thereby increasing the availability of nutrients and oxygen and thus increasing the overall aerobic energy contribution. As well, the activation of the muscle pump during dynamic contractions could enhance venous return and cardiac output, facilitating the clearance of fatigue-inducing metabolites.

Examining upper body exercise with small muscle mass, there is considerable research on cortical activation in regions related to force exertion tasks. With the NIRS method, an increase in PFC cerebral oxygenation is classically used as an index of neuronal activation. Initial reports found during right-hand finger tapping in healthy subjects a significant increase in the cerebral oxygenation using NIRS recorded from the frontal lobe. The changes in cerebral oxygenation were proportional to the task intensity, and differences were evident when the NIRS measurements were taken from the contra- and ipsilateral sides (Obrig et al. 1996). During static handgrip tasks, some researchers have described a positive relationship between muscle force and the contralateral (Derosieres and Perrey 2012, Fig. 14.5) and ipsilateral (Shibuya et al. 2008) PMC using NIRS.

Because NIRS imposes fewer constraints than other imaging techniques, further application is warranted in some daily motor hand tasks in upright positions. The NIRS study of Shibuya et al. (2008) on a sustained handgrip motor task showed that the ipsilateral PMC activity increases depending on voluntary effort. Rasmussen et al. (2007) showed that a decrease in frontal cortex oxygenation was associated with reduced muscle force-generating capacity. Similar to whole-body exercise, a critical reduction in cerebral oxygenation may pose a central limitation to exercise performance by inhibiting cortical activation of efferent motor neurons (Nybo and Rasmussen 2007). A decline in oxygenation of the bilateral SMC was observed

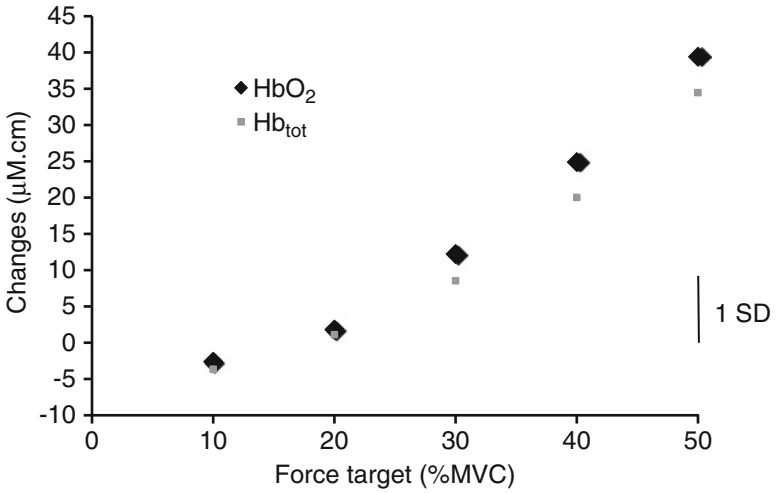


Fig. 14.5 Relationship (R^2>0.96) between muscle force and brain activation estimated by NIRS during right-hand 30-s contractions. The mean amplitude of the three contractions at each force level (% maximum voluntary contraction, MVC) is plotted against the mean amplitude of the accompanying brain activation changes (HbO_2 and Hb_{tot}) for the whole group. The optical probes were positioned over the left primary motor cortex. Data acquisition with the NIRO-300 system (Hamamatsu Photonics)

during a unimanual static-pinching task at 50–60% maximal voluntary contraction (MVC) performed to exhaustion (Shibuya and Kuboyama 2007).

In conclusion, although NIRS has been used extensively during dynamic exercise such as cycling, rowing, walking, or running, its application during resistance exercise and upper extremity tasks provides additional evidence on the central motor responses during exercise. Although reductions in the force-generating capacity of muscle fibers contribute to locomotor fatigue directly, some of the mechanisms of fatigue in whole-body locomotor exercise may differ from those associated with isolated muscle contractions. Further studies using NIRS in exercising tasks will be revealing as to whether NIRS can also be used as an adjunct to investigate central mechanisms of fatigue throughout the motor task.

14.4 Applications of NIRS in the Study of Central Fatigue Research and Muscular Performance

Whole-body exercise can provoke an inability of the central nervous system (CNS) to fully recruit the muscles involved in the physical challenge (Ross et al. 2007; Racinais et al. 2007; Millet and Lepers 2004). This may result from perturbations of cerebral oxygenation and metabolism as discussed above. Inadequate cerebral oxygenation impacts on neuronal activity (Hansen 1985). Advances in understanding

the roles of the brain in regulating central fatigue require the use of complementary technologies, such as NIRS, that allow for determining central and peripheral determinants of muscle performance. In that way, the role that the brain plays in regulating cardiovascular responses during maximal exercise and fatigue was studied by Dalsgaard and Secher (2007). Under some experimental conditions, it has been shown that central fatigue is elicited by low brain oxygenation, i.e., insufficient O_2 delivery and/or low pressure gradient to drive the diffusion of O_2 from the capillaries to the mitochondria. The CNS is highly sensitive to reductions in oxygenation, and consequently cerebral oxygenation is strongly defended by several homeostatic mechanisms. Low brain oxygenation may cause a mismatch between brain O_2 demand and O_2 supply. To what extent a reduction in the cerebral mitochondrial O_2 tension during maximal whole-body exercise affects brain function remains to be established. Multichannel NIRS is warranted to allow a better insight into what happens in the brain at the moment of exhaustion from intense effort.

14.5 Applications of NIRS for Brain Health Monitoring During Motor Task

It is important to consider how NIRS can be applied during exercise to advance our understanding of brain function in exercise practice. In the last 20 years, the promotion of exercise has become an important public health message. This can be attributed primarily to the impact of previous exercise on cardiorespiratory and metabolic parameters and their influence on physical health. But apart from those peripheral changes, recent evidence suggests that there is also a major influence of exercise on brain cortical function. It has been suggested that exercise improves brain functions by increasing cerebral blood volume (Timinkul et al. 2008); however, the exact mechanisms are still unknown. From a perspective of sports medicine, recent results covering the spectrum of mild to exhaustive exercise intensities in humans provide a more comprehensive view of cortical oxygenation levels relative to biomarkers of exercise stress, i.e., lactate accumulation or lactate threshold. However, there is as of yet no clear definition as to the minimal exercise sufficient to confer the advantages of cerebral oxygenation. Only one study from Timinkul et al. (2008) has provided some information on the threshold which may play an important role in improving brain function with exercise just above this threshold in healthy young men. They found that during incremental cycling exercise, cerebral oxygenation patterns (mainly observable in HbO_2) at the PFC area showed a nonlinear behavior, the threshold being at mild exercise intensity prior to the lactate threshold occurrence. Using NIRS, data from Neary et al. (2008) suggest that there is a link between impaired cerebral oxygenation and chronic fatigue during a maximal exercise challenge. Note that as for healthy and active individuals, cerebral HbO_2 and Hb_{tot} plateau at approximately 90% time to exhaustion, resulting from a decline in $PaCO_2$. These two studies show that during whole-body graded cycling exercise, cerebral

oxygenation changes occur quite similarly compared to young and active healthy subjects but at a lower threshold level. Collectively, these results suggest that health status involves altered CNS signals in controlling voluntary muscle activities, especially when the physical activities induce fatigue.

NIRS may also prove useful for treatment monitoring in stroke rehabilitation, for instance, during a force production task before, after, or during the intervention. In a seminal study, Saitou et al. (2000) employed NIRS to measure oxygenation in the affected prefrontal cortex in poststroke patients. They found that the technique might be useful for determining changes in oxygenation during exercises with affected lower limbs. Optical brain mapping with fNIRS was first used in six non-ambulatory patients during gait (with partial body weight support) on a treadmill (Miyai et al. 2002). Similar activations were found in the SMC and SMA as in healthy subjects, but PMC and pre-SMA activation was increased in the affected hemisphere. In a subsequent study (Miyai et al. 2006), less activation in the SMC was observed in six subcortical stroke patients during ambulation with body weight support (10%) training, compared to without. This technique of facilitation is thought to lower SMC activation since less effort has to be exerted during walking. A longitudinal study proposed by Miyai et al. (2003) studied the cortical maps based on changes in HbO_2 levels, during hemiplegic gait before and after 2 months of a regular rehabilitation program. Before rehabilitation, gait was associated with increased SMC activation that was greater in the unaffected versus the affected hemisphere, as well as increased activation in the PMC and SMA. After rehabilitation, fNIRS data revealed that the SMC activation became more equally distributed, along with an enhancement of PMC activation in the affected hemisphere. Again, asymmetrical cortical activation of SMC was significantly correlated with the increased symmetry of gait performance. These studies demonstrate that NIRS is a unique tool to monitor poststroke alterations in cortical motor functions during lower-limb exercise and has a role in providing clinical guidelines for the evaluation of rehabilitation treatment efficacy.

14.6 Conclusions: Vision for the Future of NIRS Neuroimaging in Exercise and Beyond

NIRS offers noninvasive monitoring of cerebral oxygenation in a wide range of exercise scenarios in humans. By acquiring multiple measurements simultaneously at numerous cortical sites, spatially resolved data enable studying the hemodynamic response across different cortical regions. Despite some genuine disadvantages (low spatial resolution, probe designs, and placement due to hair layer), its advantages over other functional imaging modalities (noninvasiveness, practicability, reduction of motion artifacts) position NIRS as an interesting tool to monitor brain activation patterns during gait in healthy and neurologically impaired patients. NIRS has also been extensively used to monitor cerebral physiology in exercise physiology studies,

allowing a better understanding of mechanisms mediating central fatigue. Finally, for all applications in health and disease, fNIRS may have further applications in the future as a complementary imaging method allying with, in particular, EEG and TMS modalities.

References

Amann M, Eldridge MW, Lovering AT, Stickland MK, Pegelow DF, Dempsey JA (2006) Arterial oxygenation influences central motor output and exercise performance via effects on peripheral locomotor muscle fatigue in humans. J Physiol 575:937–952

Bhambhani Y, Malik R, Mookerjee S (2007) Cerebral oxygenation declines at exercise intensities above the respiratory compensation threshold. Respir Physiol Neurobiol 156:196–202

Bigland-Ritchie B, Furbush F, Woods JJ (1986) Fatigue of intermittent submaximal voluntary contractions: central and peripheral factors. J Appl Physiol 61:421–429

Dalsgaard MK (2006) Fuelling cerebral activity in exercising man. J Cereb Blood Flow Metab 26:731–750

Dalsgaard MK, Secher NH (2007) The brain at work: a cerebral metabolic manifestation of central fatigue? J Neurosci Res 85:3334–3339

Derosieres G, Perrey S (2012) Relationship between submaximal handgrip muscle force and NIRS-measured motor cortical activation. Adv Exp Med Biol 737:269–274

Gandevia SC (2001) Spinal and supraspinal factors in human muscle fatigue. Physiol Rev 81:1725–1789

González-Alonso J, Dalsgaard MK, Osada T, Volianitis S, Dawson EA, Yoshiga CC, Secher NH (2004) Brain and central haemodynamics and oxygenation during maximal exercise in humans. J Physiol 557:331–342

Hansen AJ (1985) Effect of anoxia on ion distribution in the brain. Physiol Rev 65:101–148

Harada T, Miyai I, Suzuki M, Kubota K (2009) Gait capacity affects cortical activation patterns related to speed control in the elderly. Exp Brain Res 193:445–454

Hirth C, Obrig H, Villringer K, Thiel A, Bernarding J, Mühlnickel W, Flor H, Dirnagl U, Villringer A (1996) Non-invasive functional mapping of the human motor cortex using near-infrared spectroscopy. Neuroreport 7:1977–1981

Ide K, Horn A, Secher NH (1999) Cerebral metabolic response to submaximal exercise. J Appl Physiol 87:1604–1608

Jöbsis FF (1977) Noninvasive, infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. Science 198(4323):1264–1267

Jørgensen LG (1995) Transcranial Doppler ultrasound for cerebral perfusion. Acta Physiol Scand Suppl 625:1–44

Kleinschmidt A, Obrig H, Requardt M, Merboldt KD, Dirnagl U, Villringer A, Frahm J (1996) Simultaneous recording of cerebral blood oxygenation changes during human brain activation by magnetic resonance imaging and near-infrared spectroscopy. J Cereb Blood Flow Metab 16:817–826

Kono T, Matsuo K, Tsunashima K, Kasai K, Takizawa R, Rogers MA, Yamasue H, Yano T, Taketani Y, Kato N (2007) Multiple-time replicability of near-infrared spectroscopy recording during prefrontal activation task in healthy men. Neurosci Res 57:504–512

Madsen PL (1993) Blood flow and oxygen uptake in the human brain during various states of sleep and wakefulness. Acta Neurol Scand Suppl 148:3–27

Maki A, Yamashita Y, Ito Y, Watanabe E, Mayanagi Y, Koizumi H (1995) Spatial and temporal analysis of human motor activity using noninvasive NIR topography. Med Phys 22:1997–2005

Millet GY, Lepers R (2004) Alterations of neuromuscular function after prolonged running, cycling and skiing exercises. Sports Med 34:105–116

Miyai I, Tanabe HC, Sase I, Eda H, Oda I, Konishi I, Tsunazawa Y, Suzuki T, Yanagida T, Kubota K (2001) Cortical mapping of gait in humans: a near-infrared spectroscopic topography study. Neuroimage 14:1186–1192

Miyai I, Fujimoto Y, Yamamoto H, Ueda Y, Saito T, Nozaki S, Kang J (2002) Long-term effect of body weight-supported treadmill training in Parkinson's disease: a randomized controlled trial. Arch Phys Med Rehabil 83:1370–1373

Miyai I, Yagura H, Hatakenaka M, Oda I, Konishi I, Kubota K (2003) Longitudinal optical imaging study for locomotor recovery after stroke. Stroke 34:2866–2870

Miyai I, Suzuki M, Hatakenaka M, Kubota K (2006) Effect of body weight support on cortical activation during gait in patients with stroke. Exp Brain Res 169:85–91

Neary PJ, Roberts AD, Leavins N, Harrison MF, Croll JC, Sexsmith JR (2008) Prefrontal cortex oxygenation during incremental exercise in chronic fatigue syndrome. Clin Physiol Funct Imaging 28:364–372

Nielsen HB, Boushel R, Madsen P, Secher NH (1999) Cerebral desaturation during exercise reversed by O2 supplementation. Am J Physiol 277:H1045–H1052

Nybo L, Rasmussen P (2007) Inadequate cerebral oxygen delivery and central fatigue during strenuous exercise. Exerc Sport Sci Rev 35:110–118

Obrig H, Hirth C, Junge-Hülsing JG, Döge C, Wolf T, Dirnagl U, Villringer A (1996) Cerebral oxygenation changes in response to motor stimulation. J Appl Physiol 81:1174–1183

Orgogozo JM, Larsen B (1979) Activation of the supplementary motor area during voluntary movement in man suggests it works as a supramotor area. Science 206:847–850

Pereira MI, Gomes PS, Bhambhani YN (2007) A brief review of the use of near infrared spectroscopy with particular interest in resistance exercise. Sports Med 37:615–624

Perrey S (2008) Non-invasive NIR spectroscopy of human brain function during exercise. Methods 45:289–299

Racinais S, Girard O, Micallef JP, Perrey S (2007) Failed excitability of spinal motoneurons induced by prolonged running exercise. J Neurophysiol 97:596–603

Rasmussen P, Dawson EA, Nybo L, van Lieshout JJ, Secher NH, Gjedde A (2007) Capillary-oxygenation-level-dependent near-infrared spectrometry in frontal lobe of humans. J Cereb Blood Flow Metab 27:1082–1093

Rasmussen P, Nielsen J, Overgaard M, Krogh-Madsen R, Gjedde A, Secher NH, Petersen NC (2010) Reduced muscle activation during exercise related to brain oxygenation and metabolism in humans. J Physiol 588:1985–1995

Ross EZ, Middleton N, Shave R, George K, Nowicky A (2007) Corticomotor excitability contributes to neuromuscular fatigue following marathon running in man. Exp Physiol 92:417–426

Rupp T, Perrey S (2008) Prefrontal cortex oxygenation and neuromuscular responses to exhaustive exercise. Eur J Appl Physiol 102:153–163

Rupp T, Perrey S (2009) Effect of severe hypoxia on prefrontal cortex and muscle oxygenation responses at rest and during exhaustive exercise. Adv Exp Med Biol 645:329–334

Saitou H, Yanagi H, Hara S, Tscuchiya S, Tomura S (2000) Cerebral blood flow and oxygenation among poststroke hemiplegic patients: effects of 13 rehabilitation tasks measured by near-infrared spectroscopy. Arch Phys Med Rehab 81:1348–1356

Shibuya K, Kuboyama N (2007) Human motor cortex oxygenation during exhaustive pinching task. Brain Res 1156:120–124

Shibuya K, Tanaka J, Kuboyama N, Murai S, Ogaki T (2004a) Cerebral cortex activity during supramaximal exhaustive exercise. J Sports Med Phys Fitness 44:215–219

Shibuya K, Tanaka J, Kuboyama N, Ogaki T (2004b) Cerebral oxygenation during intermittent supramaximal exercise. Respir Physiol Neurobiol 140:165–172

Shibuya K, Sadamoto T, Sato K, Moriyama M, Iwadate M (2008) Quantification of delayed oxygenation in ipsilateral primary motor cortex compared with contralateral side during a unimanual dominant-hand motor task using near-infrared spectroscopy. Brain Res 1210:142–147

Sirikul B, Hunter GR, Larson-Meyer DE, Desmond R, Newcomer BR (2007) Relationship between metabolic function and skeletal muscle fatigue during a 90 s maximal isometric contraction. Appl Physiol Nutr Metab 32:394–399

Subudhi AW, Dimmen AC, Roach RC (2007) Effects of acute hypoxia on cerebral and muscle oxygenation during incremental exercise. J Appl Physiol 103:177–183
Subudhi AW, Miramon BR, Granger ME, Roach RC (2009) Frontal and motor cortex oxygenation during maximal exercise in normoxia and hypoxia. J Appl Physiol 106:1153–1158
Suzuki M, Miyai I, Ono T, Oda I, Konishi I, Kochiyama T, Kubota K (2004) Prefrontal and premotor cortices are involved in adapting walking and running speed on the treadmill: an optical imaging study. Neuroimage 23:1020–1026
Suzuki M, Miyai I, Ono T, Kubota K (2008) Activities in the frontal cortex and gait performance are modulated by preparation. An fNIRS study. Neuroimage 39:600–607
Timinkul A, Kato M, Omori T, Deocaris CC, Ito A, Kizuka T, Sakairi Y, Nishijima T, Asada T, Soya H (2008) Enhancing effect of cerebral blood volume by mild exercise in healthy young men: a near-infrared spectroscopy study. Neurosci Res 61:242–248
Wolf M, Ferrari M, Quaresima V (2007) Progress of near-infrared spectroscopy and topography for brain and muscle clinical applications. J Biomed Opt 12:062104

Chapter 15
PET Studies of Brain Metabolism in Exercise Research

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Abstract This chapter provides an accounting of studies using nuclear medicine techniques, especially positron emission tomography (PET), to measure regional brain activity induced by exercise. We describe the advantages and limitations of PET examinations using [^{18}F]fluorodeoxyglucose ([^{18}F]FDG). PET is an interesting method for the exercise sciences, as studied subjects can move freely during the

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Table 15.1 Physical half-lives of specific nuclides

Nuclide	Half-life[a]
^{11}C	20.40
^{15}O	2.07
^{13}N	9.96
^{18}F	109.70

[a]Physical half-lives of specific nuclides (radioisotopes) are shown in minutes

measurement due to the "metabolic trapping" property of [^{18}F]FDG. We also describe the molecular mechanisms of cerebral glucose consumption and cerebral blood flow regulation.

15.1 Introduction

Physical exercise is controlled by a sophisticated control system in the brain that is involved in the generation of motor outputs and in the perception and integration of various sensory inputs. Different methods are available for functional neuroimaging of exercise and sports, and the most suitable technique should be chosen depending on the purpose of a study.

15.2 Basic Principles of Nuclear Medicine Techniques

15.2.1 Overview

Nuclear medicine techniques such as positron emission tomography (PET) and single photon emission computed tomography (SPECT) are well-suited methods for functional neuroimaging of physical exercise. Nuclear medicine techniques date back to the early twentieth century, when they were originally developed as "tracer techniques" by Dr. George von Hevesy, a Nobel Laureate for Chemistry in 1943. Here, the term "tracer" refers to an injected radiopharmaceutical used for obtaining information (signals) about phenomena occurring in the body. The initial "planar scintigraphy" was progressively advanced technically and combined with computed tomography technology, thereby establishing PET and SPECT in the late twentieth century. Both techniques have become important tools for current functional and molecular imaging. One of the most important advantages of nuclear medicine is that it enables perfusion and metabolism to be quantified noninvasively. Metabolically active substances such as glucose, water, amino acids, or their analogues can be labeled with fluorine 18 (^{18}F), oxygen 15 (^{15}O), carbon 11 (^{11}C), and nitrogen 13 (^{13}N) nuclides, which have relatively short physical half-lives (Table 15.1; see also Chap. 13).

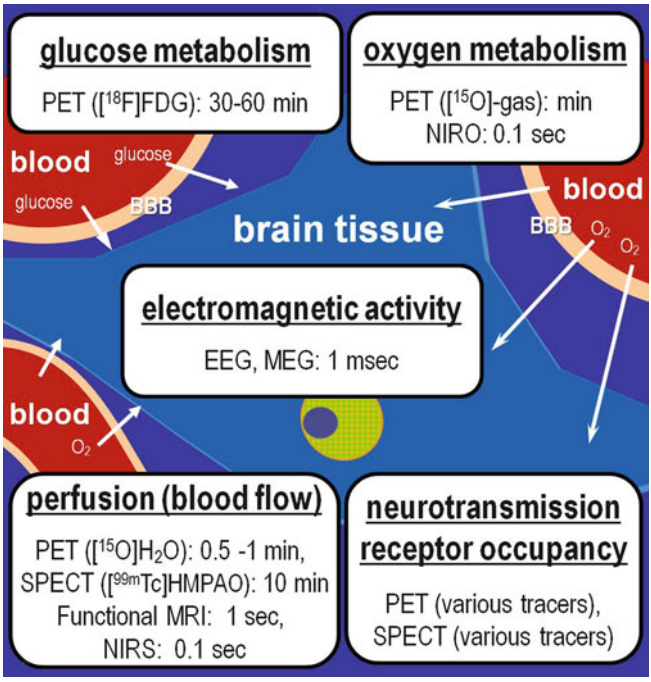

Fig. 15.1 Functional neuroimaging methodologies and biological information retrievable from living human brain studies. The most important energy resource of the human brain is glucose. It is possible to measure and quantify glucose metabolism using positron emission tomography (PET) with [^{18}F]fluorodeoxyglucose ([^{18}F]FDG). The temporal resolution of this method is approximately 30–60 min. Oxygen is necessary for the operation of the tricarboxylic acid cycle (TCA cycle) to synthesize ATP molecules from glucose. The TCA cycle is a series of enzyme-catalyzed chemical reactions that form a key part of aerobic respiration in cells. Oxygen metabolism can be measured using PET with [^{15}O]-gas during inhalation. A relatively new system, near-infrared oximeter (NIRO), is also available for the evaluation of oxygen metabolism. Glucose and oxygen molecules are supplied by the blood flow. Brain regions with increased activity are accompanied by the regional capillary dilation and consecutive increased regional cerebral blood flow (rCBF). Nowadays, rCBF changes can be measured using various methods such as PET with [^{15}O]H_2O (approximate temporal resolution: 0.5–1 min), SPECT (hours), functional MRI (fMRI) (1 s), and near-infrared spectroscopy (NIRS) (0.1–1 s). Interaction of neurotransmitters and receptors can also be measured using PET with various [^{11}C]- and [^{18}F]-labeled ligands and SPECT with various [^{99m}Tc]- and [^{123}I]-labeled ligands

[^{18}F]fluorodeoxyglucose ([^{18}F]FDG) is used to measure the regional metabolic rate of glucose (rCMRglc), while [^{15}O]-labeled H_2O is used to measure regional cerebral blood flow (rCBF) in the brain and in other organs. Assessment of regional pathophysiology by PET provides a clinical index of tissue function, as well as inflammation and malignancy (Fig. 15.1).

In addition, pharmacodynamic/pharmacokinetic information in the tissue of living subjects can be assessed by injecting tiny amounts of specific radiopharmaceuticals in the "nano-" to "pico-" molar scale (Fig. 15.1). For quantification of tissue

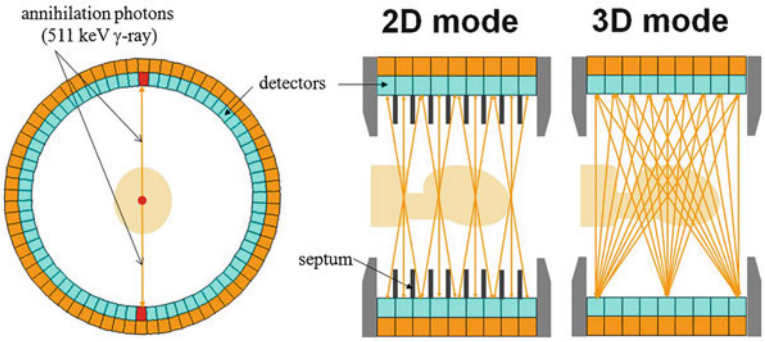

Fig. 15.2 A diagram showing the principle of PET measurement (*left*) and showing the difference between 2D and 3D data acquisition modes

metabolism, knowledge of biochemistry and tracer kinetics is required. Dynamic sequential measurement of tissue radioactivity by PET gives an estimation of tracer delivery and retention in tissues. In the human brain, neurotransmitters can exert their effects even in very small amounts, so it can be difficult to visualize their actions without using highly sensitive techniques such as PET. Using the time course data of radioactivity (time-activity curves) in brain tissue, it is possible to quantify interactions between neurotransmitters and neuroreceptors (see also Chaps. 13 and 22). However, up to now, only studies on dopamine (Wang et al. 2000) and opioid receptors (Boecker et al. 2008) have been reported among the few neurotransmission studies conducted during exercise.

15.2.2 Methodological Aspects of PET Acquisition

There are two scanning modes performed with PET after the completion of the exercise task (see below), namely, "emission" and "transmission" scans. In emission scanning, annihilation photons (gamma rays of 511 keV) emitted from the injected radiopharmaceuticals are detected by the PET detector system; in transmission scanning, external radiation sources such as ^{68}Ge/^{68}Ga emitting 511-keV gamma rays are detected by the PET detector system to map tissue attenuation. These transmission data are used for correcting the emission data affected by tissue attenuation (Fujiwara et al. 1997). In two-dimensional (2D) data acquisition mode (Fig. 15.2), the PET detector rings are separated by inter-ring shields or collimators ("septa") such that gamma-ray signals are detected only by facing detectors in the same and neighboring planes (Fujiwara et al. 1997). In three-dimensional (3D) mode, however, the collimators are removed so that all the possible coincidence events can be collected between detectors. In the 3D mode, measurement sensitivity is improved five- to ten-fold over the conventional 2D mode. This yields better image quality, and a five- to ten-fold reduction of the amount of radioactivity. Due to the increase

in detection angles (lines of responses: LOR), higher load is placed on the data storage and image reconstruction systems. But the calculation time for image reconstruction was considerably shortened from several hours to several minutes by combining the PET with the supercomputer at Tohoku University (Fujiwara et al. 1997). In 3D mode, also the amount of noise will increase, making the image reconstruction procedure more complicated and time-consuming.

In many institutes, the [^{18}F]FDG is synthesized based on the procedure introduced by Hamacher et al. (1986). Subjects have to refrain from eating and drinking for at least 3–4 h before the [^{18}F]FDG injection. When possible, fasting for 5–6 h is ideal because the influx of [^{18}F]FDG molecules into the brain tissue is affected by the plasma glucose level, and an increased level of plasma glucose lowers [^{18}F]FDG uptake into the brain because of competition. The plasma glucose concentration should be measured prior to [^{18}F]FDG injection to determine if the glucose level is within the appropriate range. In exercise studies, subjects should not perform any strenuous exercise for at least 1 day prior to the examinations.

For clinical diagnostic studies using the 2D acquisition mode, usually 190–370 MBq (5–10 mCi) [^{18}F]FDG is administered. As the effective doses in humans using [^{18}F]FDG is estimated to be around 0.02 mSv/MBq (0.8 mSv/mCi) (Brix et al. 2005), the radiation exposure to the patients is estimated to be 3.8–7.4 mSv/study. Using the 3D acquisition mode, 40–80 MBq (1–2 mCi) is sufficient for an exercise study, which is associated with a far lower level of radiation exposure (0.8–1.6 mSv) than the annual accumulated environmental radiation exposure (2.4 mSv). Due to this reduced radiation exposure, we were able to map changes in whole-body glucose metabolism during running in the upright posture (Fujimoto et al. 1996; Tashiro et al. 2001) and to assess skeletal muscle activity in normal healthy volunteers during running (Fujimoto et al. 1996, 2000; Tashiro et al. 2001) or bicycle riding (Gondoh et al. 2009; Masud et al. 2009) (Fig. 15.3). For safety reasons, the 3D acquisition mode is recommended for exercise studies and to minimize radiation exposure, we recommend avoiding scanning the same subject more than twice.

15.2.3 Physiology of Cerebral Blood Flow Control and Glucose Metabolism

The human brain comprises only 2% of the body's mass, but requires up to 20% of the total energy consumption of the human body under resting conditions. This high energy consumption is crucial for the normal functioning of the brain, as an inadequate supply of blood glucose and oxygen to the brain results in injury or death of neurons and glia (Attwell et al. 2010). Based on recent findings, there is evidence that CBF is regulated by neurons and astrocytes. It is recognized that neurotransmitter-mediated signaling, particularly by glutamate, plays a crucial role for CBF regulation (Attwell et al. 2010). Glutamate-mediated signaling leads to the release of nitric oxide (NO) from neurons and of arachidonic acid derivatives from astrocytes (Attwell et al. 2010). It is also recognized that the CBF is controlled by capillaries

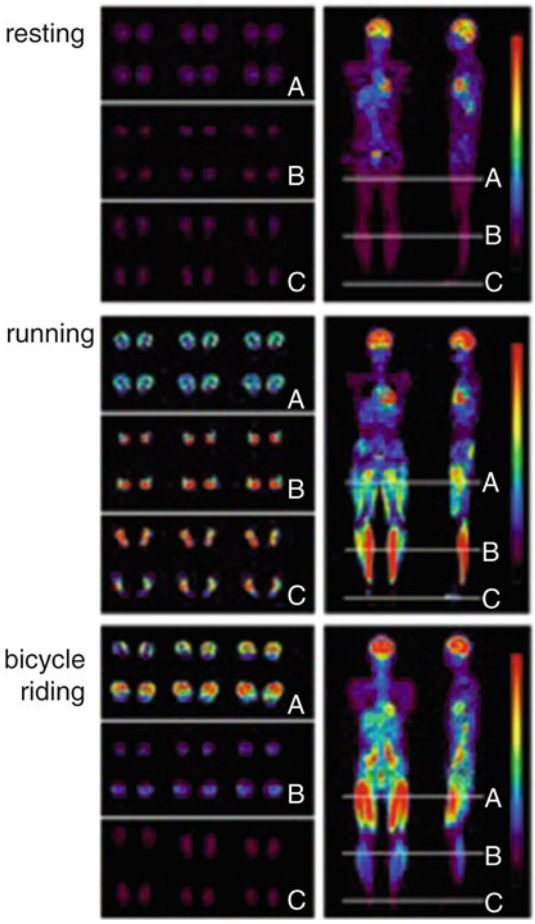

Fig. 15.3 Whole-body [^{18}F] FDG PET images following exercise. Whole-body [^{18}F] FDG PET images recorded following the resting condition (*top*), running condition (*middle*), and bicycle riding condition (*bottom*) in healthy volunteers. In the *left column*, transaxial images of the thighs (A), legs (B), and feet (C) regions are demonstrated. Coronal and sagittal sections of whole-body images are demonstrated in the *right column*. The *white lines* show the levels of transverse scans. Note that in the running condition, the highest [^{18}F] FDG uptake per unit volume was observed in the posterior compartment of the lower legs and sole, while in the bicycle riding condition, the highest [^{18}F]FDG uptake per unit volume was observed in the thigh regions and in the iliopsoas muscles (modified from Tashiro et al. 1999; Gondoh et al. 2009)

and arterioles, as the old dogma that CBF is controlled solely by arterioles has been challenged by the demonstration of contractile cells called "pericytes" that control the diameter of capillaries (Attwell et al. 2010). Under the condition of increased oxygen and glucose demand, capillary dilatation is observed as an increase in rCBF. The rCBF can be measured using [^{15}O]H_2O that circulates throughout the subject's body intermixed with systemic circulation so that the regions with increased perfusion show increased signals detected by PET.

Oxygen and glucose supplied by CBF are crucial for proper functioning and survival of neurons and glias. Oxygen is necessary for the operation of the tricarboxylic acid cycle (TCA cycle) to synthesize adenosine triphosphate (ATP) molecules from glucose. The TCA cycle is a series of enzyme-catalyzed chemical reactions that starts with pyruvate, an end product of glycolysis. Therefore, the amount of glucose cell uptake can be estimated as the amount of energy consumption. [^{18}F]FDG is transported into cells via glucose transporter protein (GLUT) in

proportion to the energy consumption level of tissue, and is then phosphorylated in the presence of hexokinase (or glucokinase). The [^{18}F]FDG molecules are phosphorylated in a manner similar to a glucose molecule. However, the [^{18}F]FDG molecules escape from further metabolism and are eventually trapped in the tissue ("metabolic trapping"), preserving the metabolic pattern for approximately 30–60 min (Gallagher et al. 1978). Thus, in the context of exercise, it is possible to estimate energy consumption in the brain approximately an hour after the completion of physical activity. Historically, the autoradiographic technique using [^{14}C]deoxyglucose ([^{14}C]2-DG) has been a useful imaging method for exercise studies in experimental animals that involves metabolic trapping, i.e., not requiring simultaneous scanning of study subjects during an exercise task (Gallagher et al. 1978). As [^{14}C]2-DG is not applicable to human activation studies because of its too long half-life (5,730 years), Mishina et al. (1999) measured cerebellar glucose uptake before and after walking in neurological patients using the [^{18}F]FDG technique. Although their main purpose was to elucidate the brain mechanism of pathological gait in patients, this was probably the first [^{18}F]FDG PET study in human subjects investigating the relationship between actual walking and regional brain activity (Mishina et al. 1999).

As indicated in Fig. 15.4, the plasma time–activity curve (pTAC) shows that the plasma [^{18}F]FDG concentration is very high in the first 10 min after injection and then gradually decreases. Therefore, it is recommended that exercise tasks are conducted during the first 30 min postinjection. A prolonged exercise task up to 60 min after injection would not produce much difference, as the plasma [^{18}F]FDG concentration is already very low at late time points. With this in mind, [^{18}F]FDG PET is a very suitable technique for studies on exercise physiology, separating the "task phase" (the first 30–40 min) and the "data acquisition phase" (40–90 min or so after injection) (Fig. 15.4). Near-infrared spectroscopy (NIRS) can also allow observation of moving subjects (see also Chaps. 10 and 14); however, NIRS is connected to a data acquisition system by a measurement cap and cables, requiring proximity to the system during task performance. Also, NIRS is prone to movement artifacts. With the [^{18}F]FDG PET technique, as mentioned above, subjects can carry out any task, not only running and bicycle riding (Fig. 15.3) but any other movement, for instance, driving of a car (Jeong et al. 2006) or swimming. Thus, even though the temporal resolution of the [^{18}F]FDG PET technique is limited, it is this unique property enabling the application of this technique to human movement science. Figure 15.5 summarizes the metabolic trapping of [^{18}F]FDG inside the cells as FDG-6-phosphate, where the amount of FDG-6-phosphate in the tissue clearly reflects the level of glucose demand by certain tissues.

As for the cellular and molecular mechanism of the [^{18}F]FDG PET and autoradiography, recent studies have provided some novel findings: Brain glucose/[^{18}F]FDG was thought to be transported and consumed by neurons, but it was recently demonstrated that glucose/[^{18}F]FDG is transported through the blood–brain barrier to be taken up by astrocytes that express large numbers of glucose transporters (GLUT; the GLUT-1 type specifically) on their surface membranes. It has been proposed that neurons receive their energy from these astrocytes in the form of lactate produced by glycolysis and lactate dehydrogenase action (Dalsgaard et al. 2002;

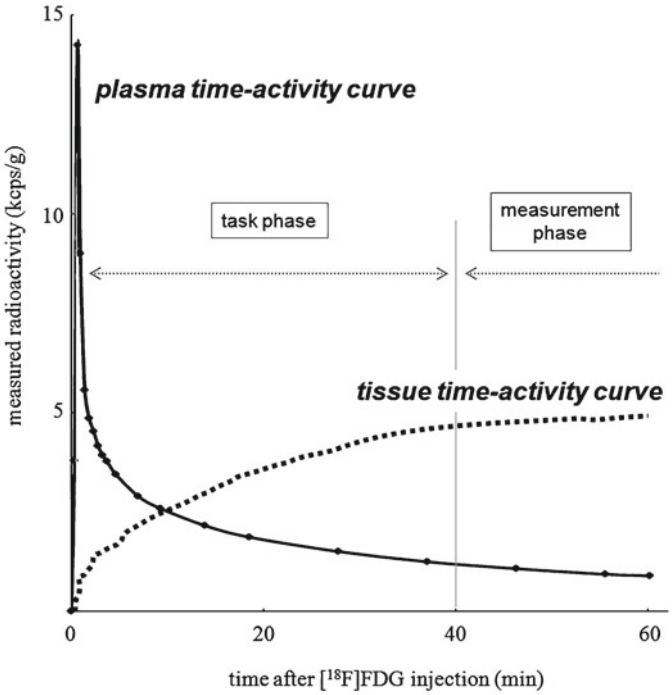

Fig. 15.4 *Curves* demonstrating the changes in radioactivity concentration in the plasma and brain tissue: The time–activity curve in plasma (pTAC: *solid line*) and tissue (tTAC: *dotted line*) following [^{18}F]FDG injection. The plasma concentration of [^{18}F]FDG is very high for the first approximately 10 min after injection and then gradually decreases. Therefore, it is recommended that exercise tasks are completed within the first 30 min or so ("task phase"). [^{18}F]FDG accumulation in the tissue (brain) reaches a plateau level after approximately 40 min following [^{18}F]FDG injection. Usually, PET scanning starts at 50–60 min after [^{18}F]FDG injection (measurement phase), since the prolonged exercise task lasting for longer than 50–60 min after injection does not produce additional [^{18}F]FDG accumulation due to the low plasma [^{18}F]FDG concentration. *kcps* kilo-count per second

Magistretti and Pellerin 1999a; Pellerin et al. 2007). Thus, astrocytes play a critical role in the regulation of brain metabolic responses to activity. One detailed mechanism proposed to describe the role of astrocytes is known as the "astrocyte-neuron lactate shuttle" (ANLS) hypothesis (Dalsgaard et al. 2002; Magistretti and Pellerin 1999a; Pellerin et al. 2007). This is an operational model for the coupling between synaptic activity and glucose utilization that involves activation of aerobic glycolysis in astrocytes and lactate consumption by neurons. It suggests that signals detected during brain activation studies with [^{18}F]FDG PET may predominantly reflect tracer uptake into astrocytes. This is, however, not contradictory to the notion that [^{18}F]FDG uptake reflects regional glucose consumption in the brain and, therefore, does not question the validity of brain activation techniques using [^{18}F]FDG and [^{14}C]2-DG (Dalsgaard et al. 2002; Magistretti and Pellerin 1999a; Pellerin et al. 2007).

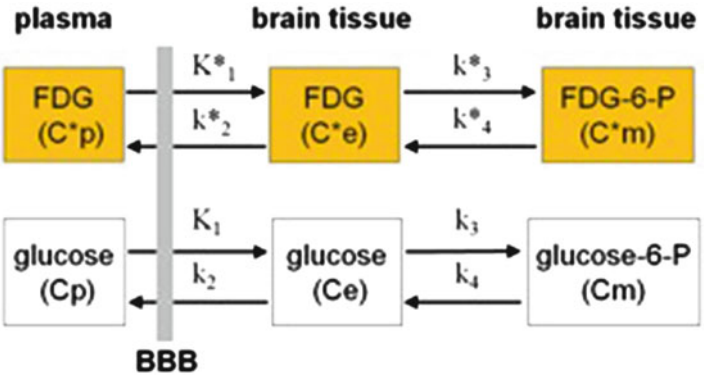

Fig. 15.5 Schematic diagram demonstrating the kinetic model for quantification of regional cerebral metabolic rate of glucose (rCMRglc). This compartment model consists of three compartments for "FDG in plasma," "unmetabolized FDG in the brain," and "metabolized FDG in the brain." Cp, Ce, and Cm denote concentrations of native glucose in plasma and the brain tissue and metabolized glucose (glucose 6-phosphate, glucose-6-P), respectively. C*p, C*e, and C*m denote concentrations of FDG in plasma and the brain tissue and metabolized FDG (FDG 6-phosphate, FDG-6-P), respectively. K_1 to k_4 denote the first-order kinetic rate constants for glucose. K_1^* to k_4^* denote the first-order kinetic rate constants for FDG. *BBB* blood–brain barrier

15.2.4 Methodological Aspects Regarding Evaluations of Cerebral Metabolism

In extension to the tracer modeling described in Chap. 13, we introduce the quantification methods of rCMRglc here, as this is a prerequisite for understanding the [^{18}F]FDG PET data summarized in this chapter. Quantification of rCMRglc is based on the method of Sokoloff et al., who used the equation below (abbreviation: cps = count per second) based on a compartment model consisting of three compartments for "[^{18}F]FDG in plasma," "unmetabolized [^{18}F]FDG in the brain," and "metabolized [^{18}F]FDG in the brain," as shown in Fig. 15.5 (Phelps et al. 1979; Sokoloff et al. 1977).

$$\mathrm{CMRglc} = \frac{\mathrm{Cp}}{\mathrm{LC}}\left[\frac{K_1^* k_3^*}{k_2^* + k_3^*}\right]\left[\frac{\mathrm{C}^*\mathrm{i}(T) - \mathrm{C}^*\mathrm{e}(T)}{\mathrm{C}^*\mathrm{m}(T)}\right]$$

Here, Cp denotes native glucose concentration in plasma, LC denotes the lumped constant for [^{18}F]FDG, K_1^* to k_3^* denote the first-order kinetic rate constants for [^{18}F]FDG, and $[\mathrm{C}^*\mathrm{i}(T) - \mathrm{C}^*\mathrm{e}(T)]/\mathrm{C}^*\mathrm{m}(T)$ is the factor that corrects the ratio between the observed and the population-average metabolic rates (Phelps et al. 1979; Sokoloff et al. 1977). For the calculation of rCMRglc, an LC of 0.52 is often used (Reivich et al. 1977).

Recently, Wakita et al. (2000) established a simplified quantification technique using 1-point blood sampling data of arterial (12 min postinjection) and venous

(40 min postinjection) blood. In addition to the method for quantifying rCMRglc based on the full kinetic model (Sokoloff 1978; Wienhard 2002), simplified graphical analytic methods are also available. These are used in PET scans performed after exercise (lacking the first part of the time–activity curve), as reported by Kemppainen et al. (2005). In their first quantification study, plasma radioactivity tended to be low 25 min after tracer injection and exercise. This finding suggested that the period between the end of exercise and the start of the scan had a minor effect on cerebral tissue tracer counts (Kemppainen et al. 2005), which indicated that the measured K_i reflects the existing condition during exercise.

For exact quantification of absolute glucose consumption rate in clinical studies, the 2D mode is more reliable and recommended. And a catheter should be inserted in the artery of the opposite arm for serial sampling of arterial blood. Some investigators have also used arterialized venous blood data using the opposite antecubital vein. In this case, the forearm should be warmed to open as many arteriovenous shunts as possible. In order to observe "relative" cerebral glucose metabolic changes, however, investigators do not have to carry out serial blood sampling. In addition to the determination of rCMRglc, a rough estimation of [^{18}F]FDG uptake is also sometimes used to identify changes in the global mean glucose metabolism. We previously calculated the modified standardized uptake ratio (SURm), which represents the ratio of the global mean cerebral glucose uptake to the whole-body [^{18}F]FDG uptake, using the following equation especially for 3D mode images that are easily affected by scatters (Tashiro et al. 2008):

$$\text{SURm} = \frac{\text{global mean cerebral } [^{18}\text{F}]\text{FDG uptake per volume (cps / pixel)}}{\text{mean whole body } [^{18}\text{F}]\text{FDG uptake per volume (cps / pixel)}}$$

This SUR was initially introduced by Kubota et al. for clinical evaluation of FDG uptake in cancer cells, as a semiquantitative value that was normalized for body size (body weight or, less often, body surface area) and injected dose only (Kubota et al. 1985). A basic equation is shown below:

$$\text{SUR} = \frac{[^{18}\text{F}]\text{FDG uptake per volume (cps / pixel)} \times \text{body size of subjects (kg)}}{\text{injected dose (MBq)} / \text{calibration factor (cps} \times \text{MBq)}}$$

Nowadays, the SUR is more often called standardized uptake value (SUV) and has been used in many fields of nuclear medicine research.

15.2.5 Methodological Aspects of PET Image Analysis

15.2.5.1 Regions of Interest Analysis

Brain activation is often observed in specific brain regions associated with a specific task; in the case of exercise, activation occurs in various motor regions (e.g., primary motor cortex, premotor cortical regions, basal ganglia, cerebellum), as well as in

sensory regions, and regions controlling the autonomic system. Investigators might have a priori hypotheses regarding a specific neural network, and in such cases, it is possible to examine the regional brain activity directly. It is most exact to first coregister the PET images (i.e., images for exercise and resting conditions) to the MRI T1 image (as a reference image) on an individual basis and then to measure glucose consumption in specific brain regions (Tashiro et al. 2008). There are many software packages available for drawing regions of interest (ROIs). Compared to freehand drawing along with the contour of target brain structures, nowadays, software for automated ROI analysis is available, providing a reliable quantitative estimation of regional cerebral metabolic rate of glucose (rCMRglc) values (Nagano et al. 2000). In automated ROI analysis, standardized ROIs are defined on a mean MRI template image representing the brain anatomy in accordance with the Montreal Neurological Institute (MNI) space. As this method is based on a common stereotactic space, operator-induced errors in defining ROIs individually for each subject can be avoided.

15.2.5.2 Voxel-by-Voxel Analysis Using Statistical Parametric Mapping

Voxel-by-voxel analysis, as provided by the Statistical Parametric Mapping (SPM) software (Wellcome Trust Centre for Neuroimaging, London, UK), is another standard tool for detecting changes in activity levels in certain brain regions. This technique is useful for identifying "neural correlates" of specific tasks and conditions, for instance, in exercise studies between "resting" and "exercise" conditions. Voxel-by-voxel analysis has been useful for detecting correlation of activation levels with factors like age, exercise intensity, blood chemistry, or autonomic nervous function. Prior to statistical analysis, scans of each individual are realigned across different conditions to correct "intrasubject" error due to movement and mispositioning. All brain images are then anatomically normalized by applying mathematical calculations, including linear and nonlinear transformations to minimize "intersubject" anatomical variation (Friston et al. 1991). The methodological details are discussed in Chap. 12. In case that no MRI image is available for normalization, it is possible to normalize the PET scans using a ligand-specific template (such as for [^{18}F]FDG, provided by the SPM website). Next, the brain images should be smoothed in order to increase the signal-to-noise (S/N) ratio of each image. This procedure will increase the statistical power for detection of significant regional differences. Usually, for the smoothing procedure of PET data, a 12–16-mm isotropic Gaussian kernel is used, depending on the spatial resolution of the PET scanner (usually two or three times larger than the resolution).

For statistical analysis, all pixel values are normalized to an arbitrary global mean value of 50 mg/100 ml/min by ANCOVA to exclude the effects of intersubject variability in global cerebral glucose metabolism (i.e., global normalization). When using the calculation image of CMRglc, the global normalization menu does not need to be applied. In our analyses, paired *t*-tests were applied and only clusters were considered surpassing a significance level of $p < 0.001$ and an 8-voxel minimum cluster size. Usually without a priori hypothesis, significance is considered

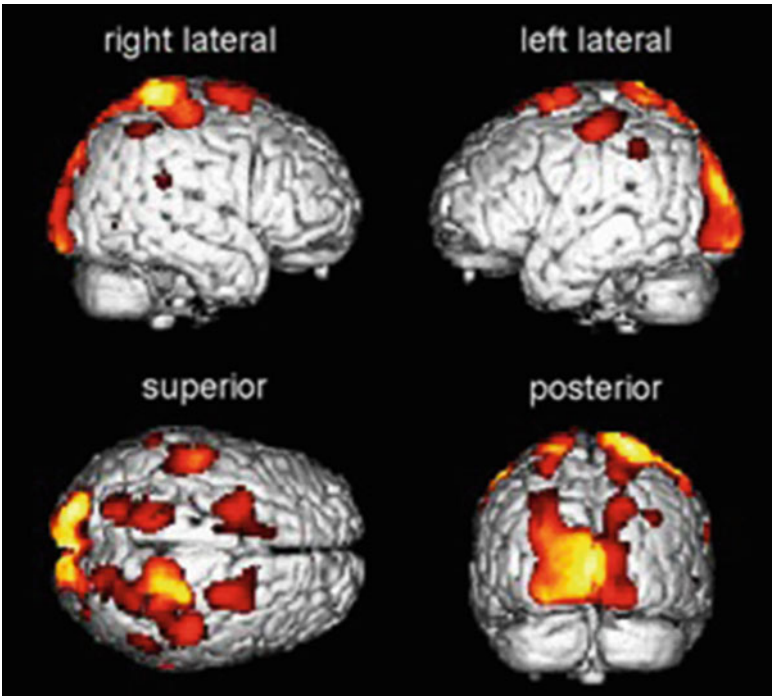

Fig. 15.6 Results of a functional neuroimaging study (modified from Tashiro et al. 2001, 2008) examining running versus rest. Voxel-by-voxel analysis visualizes the regions of *increased* relative [^{18}F]FDG uptake associated with running. The data are superimposed onto the surface MRI images, generated with the statistical parametric mapping (Wellcome Trust Centre for Neuroimaging, London, UK) software package. Activated regions are the bilateral supramarginal gyri (Brodmann's areas or BA 40), superoposterior parietal cortices (BA 5 and 7), primary visual cortices (BA 17), visual association cortices (BA 18 and 19), lateral premotor cortices (BA6), lateral primary sensorimotor cortices (BA 1–4), and the cerebellar vermis as well as the right superomedial sensorimotor cortex, appearing in *yellow* to *red colors* (height threshold at $p < 0.001$, uncorrected for multiple comparisons, with extent threshold of 10 voxel minimum)

when surpassing Bonferroni correction, as implemented in SPM. Uncorrected data are also considered if the analysis results are congruent with a specific a priori hypothesis (Tashiro et al. 2008). Figure 15.6 illustrates the "increased relative uptake" in runners, whereas Fig. 15.7 illustrates the "decreased relative uptake" in exercise. The location of each statistical peak is then identified based on a coplanar stereotaxic atlas of the human brain (Talairach and Tournoux 1988). Recently, this localization procedure is often carried out using the MNI space utility, which first converts the MNI coordinates given by SPM to Talairach coordinates using nonlinear transformation and then identifies each voxel by the anatomical labels presented in the Talairach Daemon database (Lancaster et al. 2000) (see also Chap. 12). Next, statistically significant areas are superimposed on the standard MRI brain template images (Figs. 15.6–15.9).

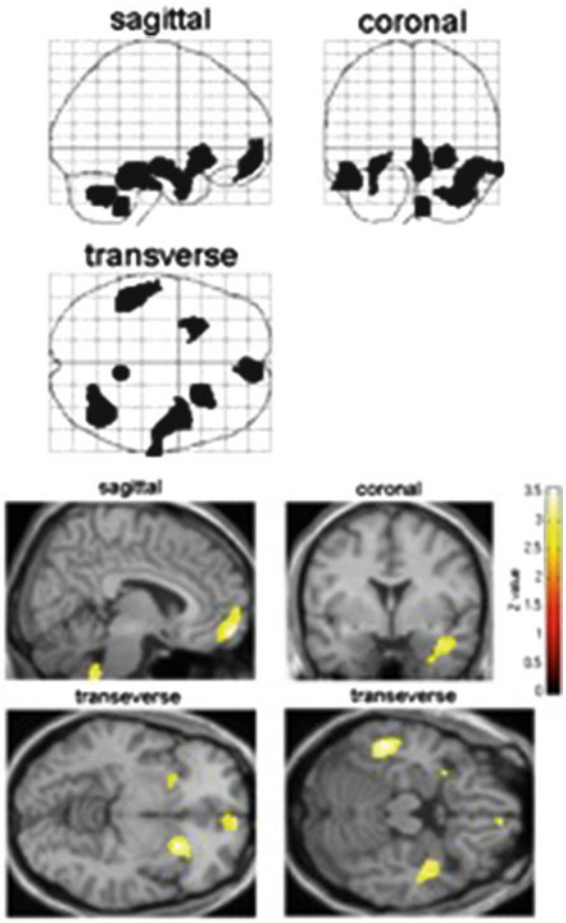

Fig. 15.7 Results of a functional neuroimaging study (modified from Tashiro et al. 2001, 2008) examining running versus rest. Voxel-by-voxel analysis visualizes the regions of *decreased* relative [^{18}F]FDG uptake associated with running. The data are demonstrated in the so-called glass brain (*top*) and superimposed on structural MRI images (*bottom*), both generated with the statistical parametric mapping (Wellcome Trust Centre for Neuroimaging, London, UK) software package. In the glass brain images, the areas with statistically significant changes appear in *black*. In the superimposed images, the areas with statistically significant changes are superimposed onto the 3D MRI images fit to the standard brain space, appearing in *yellow*. These images show lower glucose uptake in the prefrontal and temporal cortices and in the basal ganglia and amygdala (height threshold at $p<0.001$, uncorrected for multiple comparisons with extent threshold of 10 voxel minimum)

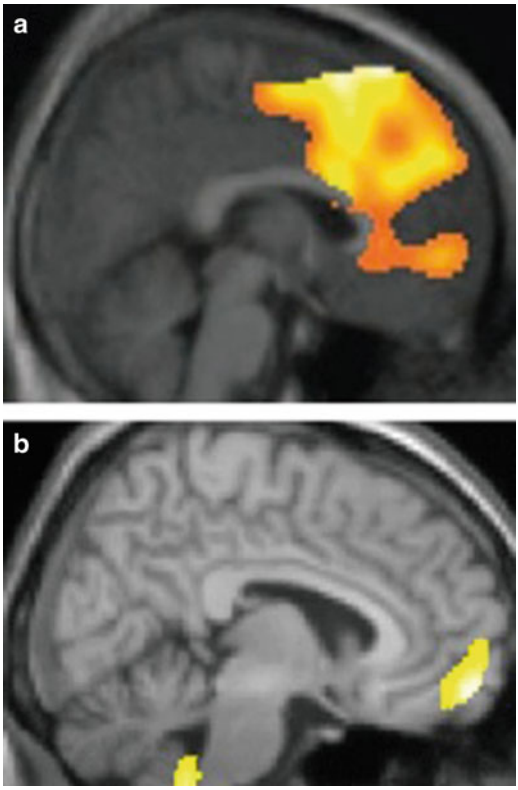

Fig. 15.8 Results of functional neuroimaging studies associated with decreased glucose uptake in medial frontal regions. Voxel-by-voxel analysis visualizes the regions of decreased glucose uptake due to exercise of high intensity (75% of $\dot{V}O_{2\,max}$) compared to low intensity (30% of $\dot{V}O_{2\,max}$) (cluster-level $p<0.001$ corrected for multiple comparisons) (**a**) (modified from Kemppainen et al. 2005). Voxel-by-voxel analysis visualizes the regions of relatively decreased glucose uptake due to running compared to resting (cluster-level $p<0.001$ uncorrected for multiple comparisons) (**b**) (modified from Tashiro et al. 2001)

15.3 Applications of Nuclear Medicine Techniques in Exercise Studies

15.3.1 Initial Applications of Functional Neuroimaging in Exercise

Functional neuroimaging of exercise began with animal experiments. Regional cerebral metabolic changes induced by exercise were measured in experimental animals using autoradiography techniques with [^{14}C]2-DG (Reivich et al. 1974; Schwartzman et al. 1981). [^{14}C]2-DG has been a useful tracer for exercise studies because its metabolic trapping property does not require the simultaneous scanning of subjects during an exercise task (Gallagher et al. 1978). Indeed, Sharp (1976) demonstrated a selective increase in glucose uptake in the cerebellar vermis of swimming rats, whereas free-running rats showed no selective activation in the cerebellar vermis but moderately increased glucose uptake in the entire cerebellum (Vissing et al. 1996).

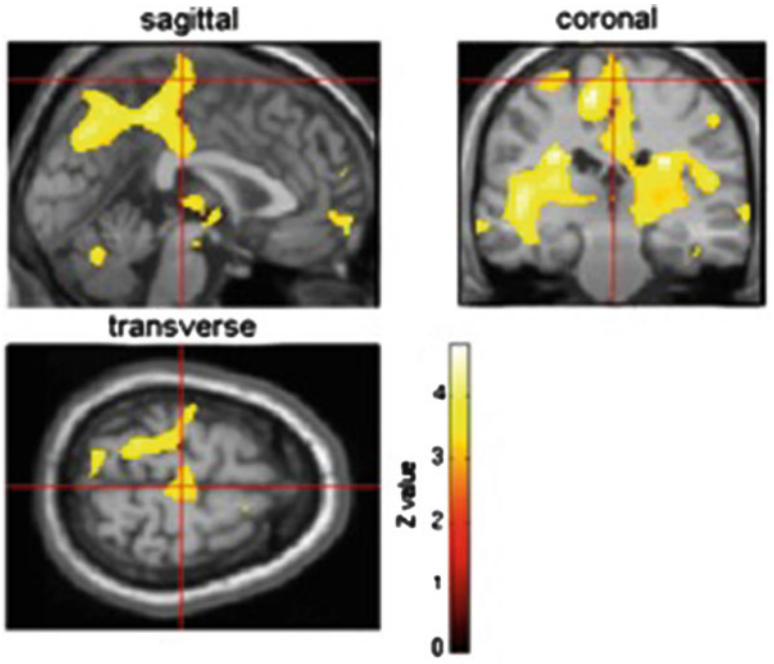

Fig. 15.9 Voxel-by-voxel analysis visualizing brain regions with a statistically significant linear correlation between regional glucose metabolism and the skeletal muscle activity in the lower extremities. The areas with statistically significant correlation appear in *yellow* and are superimposed onto the 3D MRI images fit to the standard brain space. These images show considerably significant correlation with muscular activity in the primary sensorimotor regions, as well as in the temporoparietal association regions, and posterior parietal and premotor regions (height threshold at $p < 0.001$, uncorrected for multiple comparisons; extent threshold of 10 voxel minimum)

The first human functional neuroimaging studies on exercise were conducted by measuring blood flow changes. To the best of our knowledge, the first such study was conducted by Herholz et al. in 1987 (Herholz et al. 1987), where subjects were examined during a bicycle riding task in half-upright posture (about 45°) using the [^{133}Xe] clearance method. In this method, rCBF can be estimated noninvasively by using the clearance curve of injected or inhaled ^{133}Xe into the exhaled air. They demonstrated that the rCBF was significantly higher during exercise than at rest and that the largest rCBF increase was observed in frontal brain regions. This study, however, had many limitations, such as a relatively low spatial resolution, and the subjects' posture in half-upright but not in upright posture. Fink et al. (1995) demonstrated regional activation during and immediately after an ergometer task by PET using [^{15}O]H_2O. The spatial resolution of the PET method was much better (around 4–6 mm) and allowed them to localize activation in the superomedial part of the motor cortex (associated with leg and arm motion), which disappeared after cessation of the motor task, whereas the lateral part of the motor cortex remained

active possibly due to chest wall movement associated with postexercise hyperventilation (Fink et al. 1995).

Based on the fact that muscle fibers and motor neurons form so-called motor units, [^{18}F]FDG uptake in muscles may correlate with activity in corresponding brain regions. Mishina et al. (1999) applied [^{18}F]FDG PET in patients with olivopontine-cerebellar atrophy (OPCA) manifesting with gait disturbances (ataxia): patients exhibited decreased walking-induced activation in the cerebellar vermis as compared with normal subjects. To the best of our knowledge, this was the first human PET study on upright walking/gait. While an elevated [^{18}F]FDG uptake was observed in both healthy controls and OPCA patients during walking in the pyramid, cerebellar regions, and the thalamus, there was relatively reduced activation in the vermis of the OPCA patients. In contrast, relatively higher [^{18}F]FDG uptake was observed in the posterior lobe of the cerebellar hemisphere and in the pons/midbrain, suggesting the presence of compensatory mechanisms in pathological conditions (Mishina et al. 1999).

15.3.2 SPECT Perfusion Studies in Exercise

SPECT with [^{99m}Tc]hexamethyl-propyleneamine oxime ([^{99m}Tc]HMPAO) has been applied for functional neuroimaging of physiological and pathological gait. Due to the slow washout of [^{99m}Tc]HMPAO, subjects can perform exercise shortly before injection. After the experimental task, resting data can be taken: such a double injection method has been used in a series of studies evaluating rCBF changes associated with voluntary walking. Fukuyama et al. (1997) used this technique to demonstrate that supplementary motor area, mesial primary sensorimotor cortex, striatum, cerebellar vermis, and visual cortex are activated during voluntary walking. Subsequently, the pathophysiological mechanisms underlying "paradoxical gait" were studied in patients with Parkinson's disease, which showed compensatory enhanced activation particularly in the right lateral premotor cortex (Hanakawa et al. 1999; Shibasaki et al. 2004). It has to be pointed out that the relatively high radiation dose of [^{99m}Tc]HMPAO SPECT (effective dose: approximately 6.9 mSv) limits its use in healthy subjects.

15.3.3 PET Perfusion Studies in Exercise

Although PET with [^{15}O]H_2O has been used to measure regional brain activation during exercise, it is cumbersome and has some restrictions because of the short half-life of the [^{15}O] nuclide (approximately 110 s) and, hence, rapid washout. This means that subjects must exercise in the supine position during PET measurements (Colebatch et al. 1991; Fink et al. 1995; Friston et al. 1992; Williamson et al. 1997). This is, of course, a rather unnatural condition, restricting the application to limited

Table 15.2 Areas of increased glucose uptake during running observed by PET

Structure	Brodmann area		Talairach coordinates of peak activation			*Z* score of peak activation
			x	*y*	*z*	
Supramarginal gyrus	40	L	−60	−48	46	5.41
		R	54	−54	54	4.64
Superoposterior parietal cortex	5/7	R	22	−46	70	4.93
	7	R	16	−62	60	4.58
		L	−20	−80	46	4.15
Primary visual cortex	17/18	L	−2	−84	12	4.78
	17		0	−90	6	4.69
Visual association cortex	18	L	−4	−94	−4	4.70
		R	16	−96	10	3.91
	19	L	−16	−94	16	4.51
		R	22	−84	42	4.26
Premotor cortex	6	R	28	−2	60	4.29
		L	−24	2	68	4.27
Lateral primary sensorimotor (chest)	1–4	R	35	−22	64	4.01
		L	−28	−22	50	3.26
Superomedial sensorimotor (leg)	1–4	L	−12	−4	74	3.02
Cerebellar vermis			8	−48	−12	4.07
Temporoparietal junction	22/40	R	66	−36	24	3.79
Temporoparietooccipital junction	37/39/19	R	60	−66	−2	3.24

types of movement. Thus, the PET method using [^{15}O]H_2O is not ideally suited for observation of dynamic whole-body exercise tasks. Although this method has been used for measuring the blood flow distribution of individual skeletal muscles during or immediately following exercise (Kalliokoski et al. 2000; Kalliokoski et al. 2005; Laaksonen et al. 2003), it is nowadays used less often for the measurement of CBF changes than other radiation-free methods (see also Chaps. 10–12).

15.3.4 PET Studies of Metabolism in Exercise

To the best of our knowledge, our group was the first to use [^{18}F]FDG PET for exercise studies of healthy human subjects (Tashiro et al. 2001) performing a running task in the upright posture (Figs. 15.6 and 15.7, Tables 15.2 and 15.3). In our study, the SPM analysis demonstrated relative regional increase in the supramarginal gyri (Brodmann's areas or BA 40), superoposterior parietal cortices (BA 5 and 7), primary visual cortices (BA 17), visual association cortices (BA 18 and 19), lateral premotor cortices (BA 6), lateral primary sensorimotor cortices (BA 1–4), bilaterally, as well as in the cerebellar vermis and in the right superomedial sensorimotor cortex (Fig. 15.6, Table 15.2). The SPM analysis also demonstrated relative regional metabolic decrease in basal prefrontal cortices (BA 10/11), basal ganglia, inferior

Table 15.3 Areas of decreased glucose uptake during running observed by PET

Structure	Brodmann area		Talairach coordinates of peak deactivation			*Z* score of peak deactivation
			x	*y*	*z*	
Ventral prefrontal cortex	10/11	R	6	58	−16	3.67
Putamen		R	24	18	−8	3.52
		L	−28	14	−12	3.19
Cerebellar hemisphere		R	40	−60	−34	3.42
Inferior temporal gyrus	20	L	−50	−38	−20	3.38
		R	65	−18	−16	3.12
Anterior temporal gyrus	20/21	R	40	2	−24	3.22
Dorsal medulla			8	−46	−42	3.33

temporal gyri, bilaterally, as well as in the right cerebellar hemisphere (Fig. 15.7, Table 15.3). Activity noted in the left superomedial sensorimotor cortex did not reach statistical significance. We found that glucose consumption in the parieto-occipital region was increased during the task compared with the motor regions. This finding was probably due to the higher energy consumption necessary for integrating multimodal sensory information associated with running (Fig. 15.6).

Subsequently, Kemppainen et al. examined absolute glucose consumption in the human brain of healthy volunteers. In their study, subjects fasted for at least 12 h before the study and any kind of strenuous physical activity was prohibited for at least 1 day before PET examination (Kemppainen et al. 2005). They found, for the first time, using the [^{18}F]FDG PET technique, that the metabolic rate of glucose consumption decreases during strenuous exercise, both globally (32% global decrease) and regionally (27% in the cerebellum, 31% in the superior frontal cortex, 32% in the medial frontal cortex, 33% in the temporal cortex, 26% in the thalamus, and 29% in the dorsal part of the anterior cingulate) (Fig. 15.8). Their results demonstrated that brain glucose uptake decreases during high exercise intensity and also suggested the possibility that substrates other than glucose (most likely lactate, because the lactate concentration during exercise tended to correlate inversely with global brain glucose uptake) are utilized in the human brain in order to compensate the increased energy demand (Kemppainen et al. 2005).

We later replicated their study in a separate cohort and confirmed a decrease of brain glucose uptake during exercise (Masud et al. 2009). Additionally, we conducted a preliminary study to examine the effect of regional changes in brain metabolism induced by ergometer exercise at different loads. Three exercise levels were designed at "light," "moderate," and "heavy" exercise intensities, corresponding to "aerobic," "intermediate," and "anaerobic" metabolic conditions, respectively. Strong regional activation in the motor leg areas was revealed during moderate and heavy exercise, while a strong correlation between exercise intensity and metabolic rate was identified in the primary motor cortex (precentral gyrus) and the cingulate cortex (Khondkar et al. 2008).

We also examined linear correlations between the regional brain activity and regional muscular activity of a lower extremity using the whole-body PET data of our previous study (Tashiro et al. 1999; Tashiro et al. 2001). Significant correlations were observed between the glucose uptake in the leg muscles and in the primary sensorimotor cortex, as well as in temporoparietal association cortex, posterior parietal cortex, and premotor regions (Fig. 15.9). Interestingly, the strongest correlation (Z score = 5.9) was observed in the primary sensorimotor cortex (especially in the leg motor area), while the activation in this region during running merely remained in the threshold level (Fig. 15.6) (Tashiro et al. 1999, 2001). The exquisite correlation between the primary sensorimotor cortex and muscular activities most likely reflects the fact that this region is most tightly functionally connected with the skeletal muscle systems. Hence, this [^{18}F]FDG PET technique can serve as a unique tool to examine the brain–muscle interaction at a whole-body level.

The [^{18}F]FDG PET technique has already been applied to the imaging of other movement tasks conducted apart from PET scanners, such as car driving (Jeong et al. 2006). Significant brain activation was detected during active driving in the primary and secondary visual cortices, primary sensorimotor cortical areas, premotor cortices, parietal association areas, cingulate gyrus, parahippocampal gyrus, thalamus, and cerebellum. Direct comparisons of the active and passive driving conditions revealed a relative activation increase in the cerebellum.

15.3.5 Interpretation of Global and Regional Decreases in [^{18}F] FDG Uptake During Exercise

As demonstrated in Fig. 15.8, decreased glucose uptake was observed in medial frontal regions. Kemppainen et al. (2005) demonstrated a significant reduction in global and regional glucose metabolic rate in cortical regions in association with exercise intensity, especially in the dorsal part of the anterior cingulate cortex. The reason why we observed increased glucose uptake in many brain regions may, thus, be attributed to the fact that we evaluated "relative" changes using the global normalization function of the SPM (Tashiro et al. 2001, 2008). Considering the result of global brain mean values (SUV), it is reasonable to think that net glucose uptake was reduced. One of the possible explanations for this reduction is the use of other energy resources for energy production in the brain; for instance, lactate was utilized in the brain in order to compensate the increased energy demand. Although glucose is the principal substrate for ATP production, substrates other than glucose may serve as an energy source for the brain in certain conditions. Neurons oxidize lactate in the extracellular space transferred via the ANLS (Magistretti and Pellerin 1999b). Kasischke et al. (2004) have recently provided strong evidence in favor of the ANLS for brain energy metabolism (Kasischke et al. 2004) by confirming that the neural activities in the brain are supported by oxidative and nonoxidative metabolic coupling in which oxidative metabolism in neurons is sustained by activation of the nonoxidative metabolism in astrocytes. Lactate may become of value during exercise when blood

lactate level exceeds those of glucose. In humans, it was reported that lactate infusion induces a reduction of glucose consumption and Dalsgaard et al. (2002) implied that lactate is used as energy resource during maximal exercise.

The reduction of metabolism in the prefrontal cortex and in limbic regions is interesting. Previous imaging studies in anxiety disorders have demonstrated increased glucose metabolism in these same regions (Baxter 1990; Perani et al. 1995). We speculated that the frontal and limbic hypometabolism is associated with emotional changes in runners, including the phenomenon called "runner's high," a sensation of well-being and reduced anxiety during running (Boecker et al. 2008). Moreover, Dietrich and Sparling (2004) reported that endurance exercise tended to impair prefrontal-dependent cognitive processing in healthy young male volunteers. Based on this finding and others, Dietrich (2006) proposed a new theory to explain the hypometabolism seen, especially that in the prefrontal region. According to his "transient hypofrontality theory" (THT, see also Chap. 21), prefrontal activity is suppressed indirectly due to the limitation in energy supply to the brain through compensatory rCBF increases in a situation where an enormous amount of energy is needed for endurance exercise (Dietrich 2006).

15.4 Conclusions

Functional neuroimaging with PET in the field of exercise and sports is a relatively new field of research. An advantage of the [^{18}F]FDG PET method is that subjects do not have to be scanned while performing the exercise task. Previous studies demonstrated the feasibility of [^{18}F]FDG PET in monitoring relative changes in the activity of different brain regions induced by exercise, such as running and bicycle riding. We anticipate that this PET technique will become a useful tool in sports and exercise research.

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References

Attwell D, Buchan AM, Charpak S, Lauritzen M, Macvicar BA, Newman EA (2010) Glial and neuronal control of brain blood flow. Nature 468:232–243

Baxter LR (1990) Brain imaging as a tool in establishing a theory of brain pathology in obsessive compulsive disorder. J Clin Psychiatry 51(Suppl):22–25, discussion 26

Boecker H, Sprenger T, Spilker ME, Henriksen G, Koppenhoefer M, Wagner KJ, Valet M, Berthele A, Tolle TR (2008) The runner's high: opioidergic mechanisms in the human brain. Cereb Cortex 18(11):2523–2531

Brix G, Lechel U, Glatting G, Ziegler SI, Munzing W, Muller SP, Beyer T (2005) Radiation exposure of patients undergoing whole-body dual-modality 18F-FDG PET/CT examinations. J Nucl Med 46:608–613

Colebatch JG, Deiber MP, Passingham RE, Friston KJ, Frackowiak RS (1991) Regional cerebral blood flow during voluntary arm and hand movements in human subjects. J Neurophysiol 65:1392–1401

Dalsgaard MK, Ide K, Cai Y, Quistorff B, Secher NH (2002) The intent to exercise influences the cerebral O(2)/carbohydrate uptake ratio in humans. J Physiol 540:681–689

Dietrich A (2006) Transient hypofrontality as a mechanism for the psychological effects of exercise. Psychiatry Res 145:79–83

Dietrich A, Sparling PB (2004) Endurance exercise selectively impairs prefrontal-dependent cognition. Brain Cogn 55:516–524

Fink GR, Adams L, Watson JD, Innes JA, Wuyam B, Kobayashi I, Corfield DR, Murphy K, Jones T, Frackowiak RS et al (1995) Hyperpnoea during and immediately after exercise in man: evidence of motor cortical involvement. J Physiol 489(Pt 3):663–675

Friston KJ, Frith CD, Liddle PF, Frackowiak RS (1991) Comparing functional (PET) images: the assessment of significant change. J Cereb Blood Flow Metab 11:690–699

Friston KJ, Frith CD, Passingham RE, Liddle PF, Frackowiak RS (1992) Motor practice and neurophysiological adaptation in the cerebellum: a positron tomography study. Proc Biol Sci 248:223–228

Fujimoto T, Itoh M, Kumano H, Tashiro M, Ido T (1996) Whole-body metabolic map with positron emission tomography of a man after running. Lancet 348:266

Fujimoto T, Itoh M, Tashiro M, Yamaguchi K, Kubota K, Ohmori H (2000) Glucose uptake by individual skeletal muscles during running using whole-body positron emission tomography. Eur J Appl Physiol 83:297–302

Fujiwara T, Watanuki S, Yamamoto S, Miyake M, Seo S, Itoh M, Ishii K, Orihara H, Fukuda H, Satoh T, Kitamura K, Tanaka K, Takahashi S (1997) Performance evaluation of a large axial field-of-view PET scanner: SET-2400W. Ann Nucl Med 11:307–313

Fukuyama H, Ouchi Y, Matsuzaki S, Nagahama Y, Yamauchi H, Ogawa M, Kimura J, Shibasaki H (1997) Brain functional activity during gait in normal subjects: a SPECT study. Neurosci Lett 228:183–186

Gallagher BM, Fowler JS, Gutterson NI, MacGregor RR, Wan CN, Wolf AP (1978) Metabolic trapping as a principle of radiopharmaceutical design: some factors responsible for the biodistribution of [18F] 2-deoxy-2-fluoro-D-glucose. J Nucl Med 19:1154–1161

Gondoh Y, Tashiro M, Itoh M, Masud MM, Sensui H, Watanuki S, Ishii K, Takekura H, Nagatomi R, Fujimoto T (2009) Evaluation of individual skeletal muscle activity by glucose uptake during pedaling exercise at different workloads using positron emission tomography. J Appl Physiol 107:599–604

Hamacher K, Coenen HH, Stocklin G (1986) Efficient stereospecific synthesis of no-carrier-added 2-[18F]-fluoro-2-deoxy-D-glucose using aminopolyether supported nucleophilic substitution. J Nucl Med 27:235–238

Hanakawa T, Fukuyama H, Katsumi Y, Honda M, Shibasaki H (1999) Enhanced lateral premotor activity during paradoxical gait in Parkinson's disease. Ann Neurol 45:329–336

Herholz K, Buskies W, Rist M, Pawlik G, Hollmann W, Heiss WD (1987) Regional cerebral blood flow in man at rest and during exercise. J Neurol 234:9–13

Jeong M, Tashiro M, Singh LN, Yamaguchi K, Horikawa E, Miyake M, Watanuki S, Iwata R, Fukuda H, Takahashi Y, Itoh M (2006) Functional brain mapping of actual car-driving using [18F]FDG-PET. Ann Nucl Med 20:623–628

Kalliokoski KK, Kemppainen J, Larmola K, Takala TO, Peltoniemi P, Oksanen A, Ruotsalainen U, Cobelli C, Knuuti J, Nuutila P (2000) Muscle blood flow and flow heterogeneity during exercise studied with positron emission tomography in humans. Eur J Appl Physiol 83:395–401

Kalliokoski KK, Knuuti J, Nuutila P (2005) Relationship between muscle blood flow and oxygen uptake during exercise in endurance-trained and untrained men. J Appl Physiol 98:380–383

Kasischke KA, Vishwasrao HD, Fisher PJ, Zipfel WR, Webb WW (2004) Neural activity triggers neuronal oxidative metabolism followed by astrocytic glycolysis. Science 305:99–103

Kemppainen J, Aalto S, Fujimoto T, Kalliokoski KK, Langsjo J, Oikonen V, Rinne J, Nuutila P, Knuuti J (2005) High intensity exercise decreases global brain glucose uptake in humans. J Physiol 568:323–332

Khondkar S, Fujimoto T, Tashiro M, Itoh M (2008) Imaging assessment of local brain metabolic response to changing load during exercise in humans. Curr Med Imaging Rev 4:14–18

Kubota K, Matsuzawa T, Ito M, Ito K, Fujiwara T, Abe Y, Yoshioka S, Fukuda H, Hatazawa J, Iwata R et al (1985) Lung tumor imaging by positron emission tomography using C-11 L-methionine. J Nucl Med 26:37–42

Laaksonen MS, Kalliokoski KK, Kyrolainen H, Kemppainen J, Teras M, Sipila H, Nuutila P, Knuuti J (2003) Skeletal muscle blood flow and flow heterogeneity during dynamic and isometric exercise in humans. Am J Physiol Heart Circ Physiol 284:H979–H986

Lancaster JL, Woldorff MG, Parsons LM, Liotti M, Freitas CS, Rainey L, Kochunov PV, Nickerson D, Mikiten SA, Fox PT (2000) Automated Talairach atlas labels for functional brain mapping. Hum Brain Mapp 10:120–131

Magistretti PJ, Pellerin L (1999a) Astrocytes couple synaptic activity to glucose utilization in the brain. News Physiol Sci 14:177–182

Magistretti PJ, Pellerin L (1999b) Cellular mechanisms of brain energy metabolism and their relevance to functional brain imaging. Philos Trans R Soc Lond B Biol Sci 354:1155–1163

Masud MM, Fujimoto T, Miyake M, Watanuki S, Itoh M, Tashiro M (2009) Redistribution of whole-body energy metabolism by exercise: a positron emission tomography study. Ann Nucl Med 23:81–88

Mishina M, Senda M, Ishii K, Ohyama M, Kitamura S, Katayama Y (1999) Cerebellar activation during ataxic gait in olivopontocerebellar atrophy: a PET study. Acta Neurol Scand 100: 369–376

Nagano AS, Ito K, Kato T, Arahata Y, Kachi T, Hatano K, Kawasumi Y, Nakamura A, Yamada T, Abe Y, Ishigaki T (2000) Extrastriatal mean regional uptake of fluorine-18-FDOPA in the normal aged brain – an approach using MRI-aided spatial normalization. Neuroimage 11:760–766

Pellerin L, Bouzier-Sore AK, Aubert A, Serres S, Merle M, Costalat R, Magistretti PJ (2007) Activity-dependent regulation of energy metabolism by astrocytes: an update. Glia 55: 1251–1262

Perani D, Colombo C, Bressi S, Bonfanti A, Grassi F, Scarone S, Bellodi L, Smeraldi E, Fazio F (1995) [18F]FDG PET study in obsessive-compulsive disorder. A clinical/metabolic correlation study after treatment. Br J Psychiatry 166:244–250

Phelps ME, Huang SC, Hoffman EJ, Selin C, Sokoloff L, Kuhl DE (1979) Tomographic measurement of local cerebral glucose metabolic rate in humans with (F-18)2-fluoro-2-deoxy-D-glucose: validation of method. Ann Neurol 6:371–388

Reivich M, Sokoloff L, Shapiro H, de Rosiers M, Kennedy C (1974) Validation of an autoradiographic method for the determination of the rates of local cerebral glucose utilization. Trans Am Neurol Assoc 99:238–240

Reivich M, Kuhl D, Wolf A, Greenberg J, Phelps M, Ido T, Casella V, Fowler J, Gallagher B, Hoffman E, Alavi A, Sokoloff L (1977) Measurement of local cerebral glucose metabolism in man with 18F-2-fluoro-2-deoxy-d-glucose. Acta Neurol Scand Suppl 64:190–191

Schwartzman RJ, Greenberg J, Revich M, Klose KJ, Alexander GM (1981) Functional metabolic mapping of a conditioned motor task in primates utilizing 2-[14C]deoxyglucose. Exp Neurol 72:153–163

Sharp FR (1976) Relative cerebral glucose uptake of neuronal perikarya and neuropil determined with 2-deoxyglucose in resting and swimming rat. Brain Res 110:127–139

Shibasaki H, Fukuyama H, Hanakawa T (2004) Neural control mechanisms for normal versus parkinsonian gait. Prog Brain Res 143:199–205

Sokoloff L (1978) Mapping cerebral functional activity with radioactive deoxyglucose. Trends Neurosci 1:75–79

Sokoloff L, Reivich M, Kennedy C, Des Rosiers MH, Patlak CS, Pettigrew KD, Sakurada O, Shinohara M (1977) The [14C]deoxyglucose method for the measurement of local cerebral glucose utilization: theory, procedure, and normal values in the conscious and anesthetized albino rat. J Neurochem 28:897–916

Talairach J, Tournoux P (1988) Co-planar stereotaxic atlas of the human brain. Georg Thieme, Stuttgart

Tashiro M, Fujimoto T, Itoh M, Kubota K, Fujiwara T, Miyake M, Watanuki S, Horikawa E, Sasaki H, Ido T (1999) 18F-FDG PET imaging of muscle activity in runners. J Nucl Med 40:70–76

Tashiro M, Itoh M, Fujimoto T, Fujiwara T, Ota H, Kubota K, Higuchi M, Okamura N, Ishii K, Bereczki D, Sasaki H (2001) 18F-FDG PET mapping of regional brain activity in runners. J Sports Med Phys Fitness 41:11–17

Tashiro M, Itoh M, Fujimoto T, Masud MM, Watanuki S, Yanai K (2008) Application of positron emission tomography to neuroimaging in sports sciences. Methods 45:300–306

Vissing J, Andersen M, Diemer NH (1996) Exercise-induced changes in local cerebral glucose utilization in the rat. J Cereb Blood Flow Metab 16:729–736

Wakita K, Imahori Y, Ido T, Fujii R, Horii H, Shimizu M, Nakajima S, Mineura K, Nakamura T, Kanatsuna T (2000) Simplification for measuring input function of FDG PET: investigation of 1-point blood sampling method. J Nucl Med 41:1484–1490

Wang GJ, Volkow ND, Fowler JS, Franceschi D, Logan J, Pappas NR, Wong CT, Netusil N (2000) PET studies of the effects of aerobic exercise on human striatal dopamine release. J Nucl Med 41:1352–1356

Wienhard K (2002) Measurement of glucose consumption using [(18)F]fluorodeoxyglucose. Methods 27:218–225

Williamson JW, Nobrega AC, McColl R, Mathews D, Winchester P, Friberg L, Mitchell JH (1997) Activation of the insular cortex during dynamic exercise in humans. J Physiol 503(Pt 2):277–283

Chapter 16
Physical Exercise and the Resting Brain

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Abstract This chapter provides a summary of the research to date on the effects of exercise on the resting brain. We concentrate on the neuroimaging techniques of cerebral perfusion and brain connectivity to discuss the resting-state brain and how exercise affects the brain. Certain brain regions, such as the hippocampus and the so-called default mode network, are specifically discussed.

16.1 Introduction

By Chap. 16 of this book, you are no doubt convinced that brain imaging is a valuable method to probe the effects of exercise on brain structure and function. Less obvious may be the connection between physical exercise and the "resting" brain. This chapter will focus on the resting brain, on the evidence for the role of a set of structures in the brain known as the default mode network (DMN), and on the effects of exercise on resting cerebral blood flow (CBF) and connectivity. Most of the physiological neuroimaging methods used to investigate the effects of exercise on the brain are detailed earlier in this textbook, so we concentrate in this chapter mostly on the resting brain itself and how exercise affects the resting brain.

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Neuroimaging provides a valuable tool for observing ongoing changes in the brain in response to exercise—its relatively noninvasive nature allows repeated observations of the same subjects, and similar methods can be used in both human and animal studies. It is intuitive that imaging the brain while an individual performs a challenging task would provide insights into how exercise affects the brain and cognition. However, it might not be as intuitive that investigating the brain while it is at rest, when it is doing "nothing," can be predictive of what it does when it is actively doing "something." By the end of this chapter, we hope that you will be convinced that resting CBF and resting-state functional magnetic resonance imaging (fMRI) are valuable tools to assess the effects of exercise on brain function and that in addition to its other effects, exercise affects the resting brain.

16.2 Definition of the Resting State and How It Can Be Assessed

It is perhaps an archaic notion that the brain ever "rests" or is doing nothing, but until the advent of recent imaging techniques, it is arguable that this was a dominant paradigm. A person was given a cognitive task and this turned "on" certain brain regions responsible for that behavior. Modern imaging methodology has advanced the notion that the brain works in dynamically shifting networks and that these networks can be observed even when no task is being performed. In fact, the brain requires a significant amount of metabolic activity even when not actively engaged in a task, and increases in response to an external stimulus or task are relatively small. Most importantly for this discussion is our theory that the functions the brain undertakes at rest are important for its function during all other active processing.

Experimentally, the so-called resting state is operationally defined as lying quietly alert. Thus, imaging of the resting-state brain occurs when the participant is lying in a scanner in an awake and alert, but resting state. Resting brain activity can be measured with the eyes open or closed, or when giving the participant a focus point, such as a cross in the middle of a screen. Measuring neural activity during the resting state can be challenging. Traditional task-based fMRI studies assess changes in neural activity relative to a baseline reference condition. However, there is no baseline condition in a resting-state scan. Rather than looking at differences in activity between two conditions, resting-state data are typically analyzed looking at functional connections between brain regions. A simple definition of a functional connection is two regions that exhibit strong correlations between their time courses (for a more esoteric discussion of functional connectivity, please see Friston 1994 and also Chap. 12). Networks of regions that are functionally connected can be identified without the use of a reference condition using a seeded functional connectivity analysis (Cordes et al. 2000; Greicius et al. 2003; Lowe et al. 1998; Waites et al. 2005) or blind-source separation techniques such as independent component analysis (ICA) (Beckmann and Smith 2004; Damoiseaux et al. 2006; van de Ven

et al. 2004). In a seeded functional connectivity analysis, a region is typically selected as a seed region based on prior comparisons of two states. For instance, the posterior cingulate/precuneus region is a characteristic region of the DMN and is therefore often chosen as a seed region. Every voxel in the brain is then correlated with the time course of the seed voxel to see which regions show a highly correlated time course. In contrast, ICA is a form of blind-source separation analysis, meaning that the analysis is conducted blind to sources of variance in the data (e.g., a known time course from a specific brain region). Instead of asking what brain regions are correlated with a specific time course, the question being asked with ICA is what independent sources of variation (in this case individual networks) contribute to the overall functional signal seen in the brain. Even without using seed regions, this method can reliably identify brain networks that are also seen in more traditional comparisons of brain states and with seeded functional connectivity analyses.

Functional connectivity and ICA predominantly reflect temporal correlations between network regions rather than magnitude of network activity. Quantitative perfusion imaging is a method that is similar to blood oxygen level dependent (BOLD) fMRI in that it indexes neural activity through changes in blood flow (Aguirre et al. 2002; Wang et al. 2003). Unlike fMRI, perfusion imaging generates quantitative maps of cerebral blood flow (CBF), meaning that neural activity can be assessed without using a referent condition (see also Chap. 11). Perfusion imaging has not supplanted traditional fMRI because as a dynamic measure, it has lower signal and poorer time resolution. However, the technique has excellent signal as a steady-state technique that measures average blood flow over several minutes (Aguirre et al. 2002; Wang et al. 2003).

More recently, functional and structural brain networks have been explored using network analysis techniques (Hagmann et al. 2008; Honey et al. 2009; Zhu et al. 2003). Network science is a relatively new field of study that has been used to investigate complex systems, including social networks, the US power grid, gene interactions, and neural networks (Barabasi and Albert 1999; Watts and Strogatz 1998). Network analyses performed on brain imaging data allow for the investigation of many functional connections in the brain simultaneously. They are distinct from other ways of measuring functional connectivity because the structure of the entire network is evaluated rather than connections from a single brain region and because the metrics that arise from them yield information about the organization of functional connections in the brain. In brief, in network analysis, each region is considered to be a "node." This region can be as small as an individual voxel or a region of interest identified on a map like the AAL atlas (Hayasaka and Laurienti 2010). If the time course of two nodes is correlated above a certain threshold, those two nodes are said to be connected. This connection is termed an "edge." This procedure is repeated for all possible node pairs, and the final outcome is a network that contains all functional interactions between distributed voxels in the entire brain. The overall structure or organization of the network is termed its topology. Both global and local measures of the network can be calculated to ascertain network topology. Some common measures used to determine network topology include path length and clustering. Path length is essentially a measure of distance in the network and

represents the smallest number of edges that must be traversed to get from one node to another. A short path length means that two nodes are close functionally, but not necessarily structurally. Clustering measures the "cliquishness" of nodes or how tightly neighboring nodes are connected. Examples of different network topologies would be a completely structured network, like a lattice, which has high clustering (neighboring nodes are highly connected) and long path lengths (it takes many steps to get from one point on the network to another), or a completely random network, which has very low clustering (neighboring nodes are not tightly connected) and short path lengths (it takes only a few steps to get to any point in the network). The network topology most reliably observed in the brain is a small-world network (Bullmore and Sporns 2009; Sporns and Zwi 2004; Watts and Strogatz 1998) in which there is both high local clustering, indicating regional specialization through tightly linked short-range connections, and short path lengths, characteristic of distributed processing that is enabled by long-range connections.

Some common metrics derived from network analysis that will be discussed further in this chapter are degree, global efficiency, and local efficiency (see Bullmore and Sporns 2009 for review). "Degree" is the number of edges connected to each node. Nodes that are highly connected ("high degree") are typically termed hubs. Given their high level of connectivity, damaging a hub can have drastic consequences to the functioning of the whole network (Sporns et al. 2007). "Global Efficiency" is related to path length and measures the closeness of one node to all other nodes and identifies particularly influential nodes in the network (Latora and Marchiori 2001). "Local Efficiency" is related to clustering and measures how interconnected the neighbors of a node are (Latora and Marchiori 2001). Networks can also be analyzed for their "community structure," also termed "modularity" (Meunier et al. 2009; Newman and Girvan 2004). In brief, this type of analysis identifies communities (modules) where nodes within that community are more tightly linked with each other than with nodes in other communities. A module is analogous to a social clique, like "the jocks" or "the geeks." While a member of one group may have some ties to other groups, most of their connections are within their own community.

16.3 Definition of Resting Brain Networks and Functional Relevance of the Default Mode Network

While there are several networks that can be consistently identified in the resting state, (Damoiseaux et al. 2006) the network thought to be most active during rest, the DMN, has garnered the most attention in neuroscience research since Raichle et al. (2001) suggested that it might constitute a true baseline state for the brain. The reason for this hypothesis is the unique characteristic that the oxygen extraction fraction (OEF), or balance between oxygen supply and demand, is essentially uniform across the resting brain. Raichle et al. consistently observed that glucose and

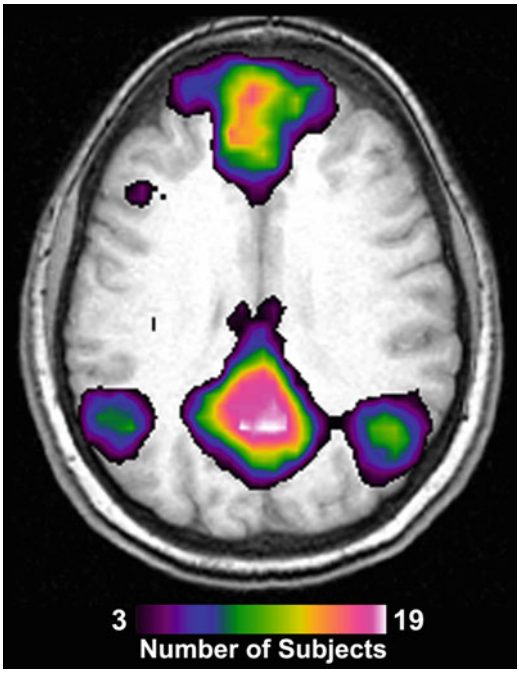

Fig. 16.1 Regions of the default mode network identified through independent component analysis during resting state. This map of unpublished findings from our laboratory illustrates the overlap in the default mode network (DMN) across 19 young, healthy subjects. The hub of the DMN is the posteromedial cortex in the region of the posterior cingulate and precuneus, as is evident through the high degree of overlap between participants. Other regions typically associated with the DMN are evident as well, including medial frontal and bilateral parietal cortices

oxygen consumption are greatest in the DMN at rest and are reduced during a cognitive task. However, oxygen delivery and blood flow are not balanced throughout the brain and are greater in these same regions. Thus, in the resting brain, oxygen consumption and oxygen delivery are elevated in the DMN compared to the rest of the brain, resulting in a homogeneous OEF throughout the brain at rest.

The hallmark of the resting state is the activity of the DMN, a group of brain regions including the posterior cingulate/precuneus, anterior cingulate, and parietal cortices (Fig. 16.1) that are more active during resting state than any other task state (Gusnard et al. 2001). Stated another way, activity in the DMN is typically suppressed during cognitive tasks. The exact function of the DMN is not known, but it has been hypothesized to act as an attentional filter that monitors the external environment, integrates this information into a self-referenced representation of the world, and orients attention accordingly (Buckner et al. 2008; Raichle et al. 2001; Shulman et al. 2007). Failure to suppress the DMN during tasks is linked with lapses

of attention (Weissman et al. 2006), increased error commission (Li et al. 2007), and intrusion of task-unrelated thoughts (McKiernan et al. 2006). It has been therefore inferred that good cognitive functioning when engaging in external tasks requires effective suppression of the DMN. Interestingly, healthy aging is associated with reduced suppression of activity of the DMN during tasks of memory and attentional functioning (Grady et al. 2006; Lustig et al. 2003; Persson et al. 2007). In addition, it has been hypothesized that failure to suppress the DMN is related to common subclinical cognitive deficits in older adults (Damoiseaux et al. 2008; Grady et al. 2006; Lustig et al. 2003; Persson et al. 2007).

Suppression of the DMN during tasks is important, but conceptualizing the network in terms of suppression implies that the DMN is a sort of nuisance network, where its importance to voluntary cognitive functions lies primarily in minimizing its activity during task performance. Following this logic, early stage Alzheimer's disease patients who show early hypometabolism in the precuneus/posterior cingulate (Bradley et al. 2002; Chetelat et al. 2008; Langbaum et al. 2009; Petrie et al. 2009; Schroeter et al. 2009) before cortical hypometabolism can be detected in other brain areas (Minoshima et al. 1994) should have very good cognitive functioning during tasks with little mind wandering or inattention because the DMN is well suppressed. However, this is clearly not the case. Data from current work in our laboratory, however, have led us to the hypothesis that the importance of the DMN lies not in the fact that it is suppressed (although this is important), but rather in what it is doing when it is "on," and that the DMN may actively establish a baseline tone for the brain. Disruption of its activity at rest would therefore have important implications for functioning during almost any state or task. The data that spawned this hypothesis are currently unpublished from our laboratory showing that healthy aging is associated with decreased perfusion in the DMN. In this study, quantitative resting-state MRI perfusion scans were acquired on 29 younger (mean age = 27) and 28 older (mean age = 73) healthy adults with normal or corrected-to-normal sensory functioning and Mini Mental State Examination (MMSE) scores within 2.5 standard deviations of their age- and education-adjusted norms (mean = 28.2, sd = 1.75). A noninvasive arterial spin labeling (ASL) brain perfusion technique (see also Chap. 11) was used to acquire the CBF images. After accounting for well-known global decreases in CBF with age, voxel-wise maps indicated that perfusion in regions associated with the DMN was differentially affected by aging during rest (Fig. 16.2).

As noted above, it has been observed that older adults suppress the DMN less than younger adults. The primary rationale put forward to explain this is that decreased suppression of the DMN during memory and attention tasks in older adults is due to increased activity of the DMN during tasks. Decreased suppression is interpreted as an intrusion of default mode functions during the task, resulting in slower and less accurate performance for older adults (Grady et al. 2006; Lustig et al. 2003; Persson et al. 2007; Stevens et al. 2008). However, the observation of reduced CBF suggests that older adults show less difference in activity between resting and active states not because the network is more "on" during tasks, but because it is less active in the resting referent condition (Fig. 16.3). Therefore, if the

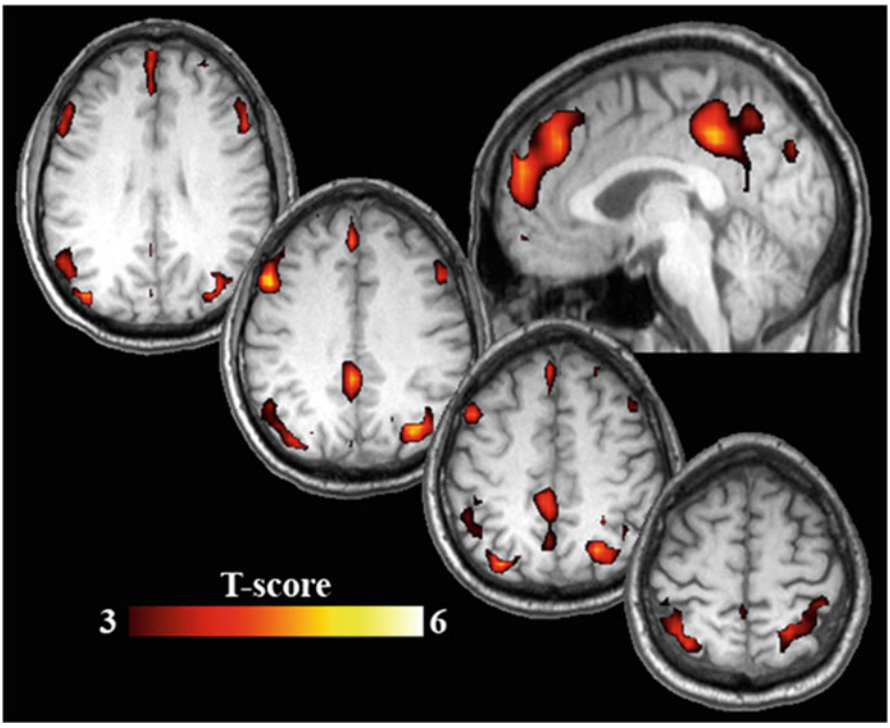

Fig. 16.2 Voxel-wise analysis reveals decreased resting perfusion in default mode regions in older adults. In unpublished data from our laboratory, decreased perfusion was noted across the brain, including the precuneus ($T=5.88$), left ($T=5.69$) and right ($T=5.81$) parietal cortices, and medial anterior cortex ($T=4.74$), regions typically associated with the DMN. Decreased perfusion in left ($T=4.86$) and right ($T=4.75$) dorsolateral prefrontal cortices was also observed. While these regions are not typically thought of as part of the DMN, they have been associated with the DMN in other analyses (Hagmann et al. 2008; Sporns et al. 2007)

DMN is related to cognitive decline in healthy older adults, it is likely not because the network is intruding during tasks. The idea that the DMN acts as an attention filter and is important for integration of self-referential thoughts and emotions is inferentially supported by solid research and is likely true in whole or in part (Buckner et al. 2008; Fransson 2005; Geday and Gjedde 2009; Greicius et al. 2003; Gusnard et al. 2001; Iacoboni et al. 2004; Polli et al. 2005; Raichle et al. 2001; Raichle and Snyder 2007; Shulman et al. 2007; Sonuga-Barke and Castellanos 2007). However, it does not explain why activity of this network at rest might be important to cognitive functioning that occurs when the network is suppressed. Thus, we suggest that the DMN actively establishes a baseline for brain activity that is critical for subsequent cognitive function.

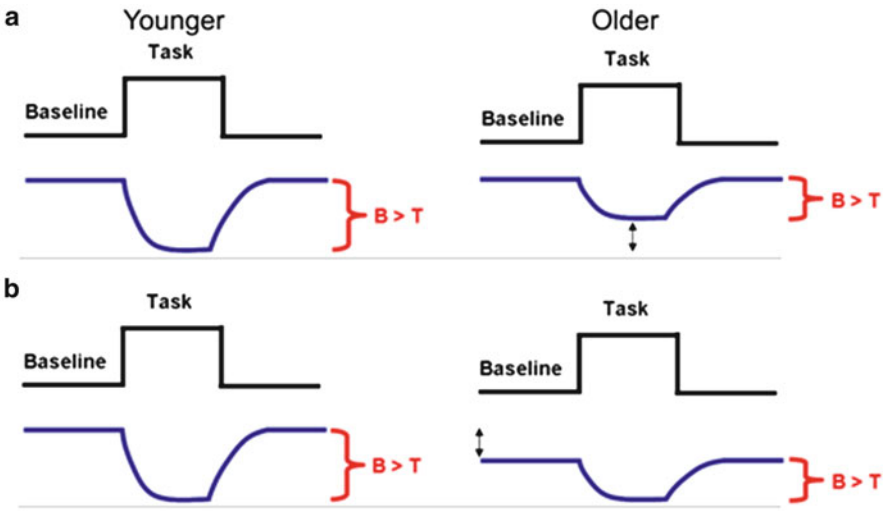

Fig. 16.3 Illustration of the effects of decreased resting perfusion on suppression of the default mode network during a cognitive task. The *black trace* on the *top* shows the onset and offset of the task, as in a basic block design. Hypothetical neural activity of the DMN is illustrated here in the *blue trace* on the *bottom* (which is unitless in this representation). The magnitude of the difference between task and baseline is shown using the *orange bracket* to the *right* of the *blue trace*. (**a**) Illustrates the interpretation of the observation that older adults suppress the DMN less than younger adults during a cognitive task (Grady et al. 2006; Lustig et al. 2003; Persson et al. 2007). Older adults start with the same amount of baseline neural activity but do not turn the DMN down as effectively as younger adults during a task. This results in a smaller difference in activity between baseline and task states seen in fMRI results as a smaller deactivation. (**b**) Here the illustration is modified to reflect the resting perfusion data presented here. The overall difference between task and baseline does not change between panels (**a**) and (**b**). Older adults still show less deactivation. However, in panel (**b**), the age difference in magnitude of suppression is caused by a shift in baseline activity rather than a shift in the final absolute level of neural activity

16.4 Evidence for the Role of the Default Mode Network as a Baseline for the Brain

The DMN, the resting-state network most active during the resting state, has been shown to be important for functioning in many different tasks and disorders (Di Martino et al. 2009; Fellows 2006; Greicius et al. 2004; Li et al. 2007; Raichle and Snyder 2007; Sambataro et al. 2010; Singh and Fawcett 2008; Sonuga-Barke and Castellanos 2007), and there is even evidence that connectivity of the DMN is heritable (Glahn et al. 2010). This is relevant for larger-scale exercise trials that may include genetic analyses to investigate the interplay of genes and environment in determining the effects of exercise on the brain. Finally, as will be discussed later in this chapter, measurements of functional connectivity and CBF taken in exercise intervention studies have shown that the DMN and other measurements resting-state correlate with important metrics like neurogenesis, angiogenesis, and cognitive function.

In addition to the observations about metabolic activity from the neuroimaging literature, the resting state is characterized by a constellation of consistent "idle" rhythms in electro- and magnetoencephalography (EEG and MEG, respectively) studies. These idle rhythms are associated with specific cortices—the mu rhythm in sensorimotor cortex, tau (or third) rhythm in temporal cortex, and alpha rhythm in occipital cortex (Hari and Salmelin 1997). Immediately before an action or engagement with the environment, these rhythms desynchronize (Hari and Salmelin 1997). For instance, in the motor cortex, the desynchronization occurs immediately before movement onset (see Neuper et al. 2006 for review). The actual motor movement is accompanied by widespread desynchronization along with small regions of high-frequency synchronizations. Observations from simultaneous EEG and fMRI suggest that desynchronizations in EEG are associated with task-related activations in fMRI and with the DMN (Beaver et al. 2011; Jann et al. 2009; Musso et al. 2010; Ritter et al. 2009).

How does this support the idea of the DMN actively establishing a baseline state for the brain? If the DMN drives resting rhythms, it would be important for the network to turn off during tasks to allow neurons to respond to incoming stimuli. If it did not turn off, neurons would remain locked in synchronous activity, and activity of the DMN during tasks would be detrimental to performance (Li et al. 2007; McKiernan et al. 2006; Weissman et al. 2006). Its structural and functional network properties make the DMN an ideal candidate to serve as a generator that allows these pools of neurons to synchronize more readily: The DMN is the most active network when resting activity is synchronous and is specifically associated with alpha rhythm activity (Jann et al. 2009), it is suppressed during tasks when the rhythms become desynchronized, and it has been identified as one of the most connected regions of the brain, both structurally and functionally (Hagmann et al. 2008; Honey et al. 2009).

One might wonder why the brain would support a network that has to be shut off in order to engage in externally oriented tasks. The fundamental job of the brain is to extract relevant environmental signals from noise. The ideal system would minimize neural background noise so that the response to an external stimulus would be distinct. A synchronized population of neurons with a tight distribution of activity is preferable for a baseline, as little variance in the baseline distribution would allow the brain to detect small changes in signal, like subtle variations in color. In contrast, a wide distribution of baseline frequencies with high variance either would require high signal-to-noise, such as a high-contrast visual image, or would require more time to accumulate the information necessary to make a decision. The system would be slower and less responsive to small changes in the environment. Figure 16.4 illustrates conceptually how a tight distribution of activity in the referent condition facilitates detection of a simple visual stimulus. If the DMN is playing an active role in maintaining a true baseline state as the driving input for characteristic resting oscillations, the decrease in resting metabolic activity and CBF, as shown in Fig. 16.2, suggests that resting rhythms in older adults should be disrupted. In fact, older adults show a general decrease in the power of all resting rhythms and a concomitant loss of spatial specificity (Klimesch 1996, 1999; Prichep 2007; Rossini et al. 2007). Resting oscillations in younger adults have a tight distribution with spatial and spectral specificity, while older adults have broader spatial distributions that have less power in the dominant frequency. That is, the older brain is more

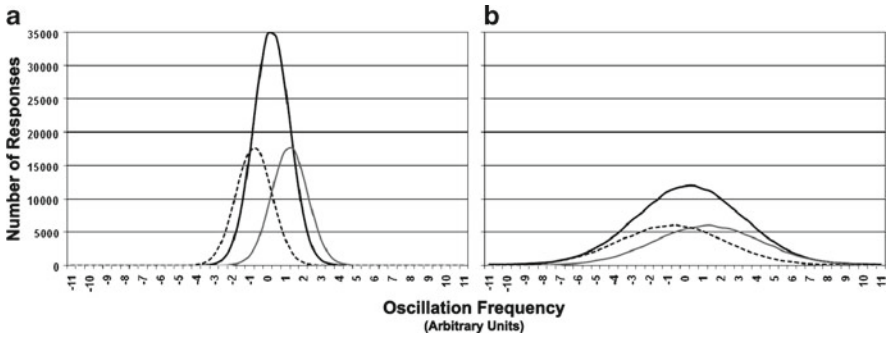

Fig. 16.4 Model of distributions of baseline activity. In this model, oscillation frequency is on the *x*-axis, and the amplitude of each curve represents the number of neurons oscillating at that frequency (*y*-axis). The *black curve* represents activity at rest, and the *dashed* and *gray curves* illustrate activity in response to a stimulus. (**a**) Illustrates a tight resting distribution (*black*) where the neurons are oscillating at a narrow range of frequencies. When a stimulus is presented, half of the neurons in the resting distribution increase their mean firing rate by one standard deviation (*gray*). The other half of the neurons decrease their activity relative to rest by one standard deviation (*dashed*). The changes in their activity create a clear difference from their previous behavior at rest and create two distinct neural population responses. This is a model of healthy DMN function, where there is a tight distribution of neuronal activity at rest. (**b**) Illustrates the outcome of a broader baseline distribution of oscillatory frequencies. These distributions include the same total numbers of neurons as in the *left panel*, but this time distributed across a wider range of frequencies at rest. When a stimulus is presented, half the neurons shift their activity one standard deviation to the right of rest and the other half shift one standard deviation to the left, as in (**a**). However, the broad resting distribution results in broad response curves. While the mean of each response curve is still shifted the same amount as in (**a**), there is now little distinction between the response and resting state. There is also little distinction between the responses of the two pools of neurons. This is a model of how a disturbance in the DMN, for instance, in aging or pathology, might affect function in many different brain states if the DMN were setting a baseline state for the brain

spatially and spectrally homogenous, an idea supported by observed higher coherence between oscillations in different brain regions in older adults (Maurits et al. 2006; Prichep 2007).

To summarize, DMN activity during the resting state is an important marker of healthy brain function. It is important from a physiological perspective and is also associated with cognitive function across a wide range of tasks. It is a well-characterized brain state that is easily replicable across studies and is heritable. For all these reasons, the resting state is relevant for assessing brain function in studies of the effects of exercise on the brain.

16.5 The Effects of Cardiovascular Fitness and Exercise on Connectivity in the DMN

Voss et al. observed that functional connectivity fMRI data collected during passive viewing of visual tasks was associated with cardiovascular fitness (Voss et al. 2010a) and was altered by a 12-month exercise intervention (Voss et al. 2010b). The latter

study included 32 young adult controls (mean age = 24), 35 older adults in a control stretching and toning group (mean age = 65), and 30 older adults in an aerobic exercise intervention (mean age = 67). In this study, both exercise programs, the walking aerobic intervention and control stretching and toning group, met three times a week. All walking sessions began and ended with approximately 5 min of stretching. The aerobic walking condition began with a duration of 10 min that was increased 5 min each week until week 7, when a duration of 40 min was achieved. The flexibility, toning, and balance control group also began each session with warm-up and cool-down stretches, but this was followed by four muscle toning exercises, two balance exercises, one yoga sequence, and one exercise of their choice. In addition to the exercise intervention, participants completed a battery of neuropsychological tasks, and MR images were also acquired, including fMRI data taken while participants passively viewed three different visual tasks.

Voss et al. identified three networks of interest that they chose from previous research: the DMN, a frontal executive network, and a frontoparietal network. These networks were analyzed using a functional connectivity seeding analysis, where a voxel from a known hub in each network was taken as a referent time course, and regions that showed temporal correlation with this voxel were identified as being part of the network. This resulted in a global measure of overall connectivity of the network that represented the correlation across each networks as a whole, along with pair-wise correlations between each region identified in each network.

They found no significant effects of exercise on the overall connectivity for any of the three networks tested, although the DMN trended toward significance ($p = 0.09$). However, regional effects were observed in all three networks. In the DMN after 12 months of exercise, connectivity improved between several brain regions in the walking group. Connections in the DMN improved by walking included local connections in the medial temporal lobe (bilateral medial temporal gyrus—bilateral parahippocampal gyrus), connections between the medial temporal lobe—lateral occipital cortex, and connections between middle temporal gyrus—prefrontal cortex. In the frontal executive network, only a connection between right anterior prefrontal cortex—prefrontal cortex showed increasing connectivity and that was in the walking group. The connection between right insula—right lateral occipital cortex was the only connection that showed increasing connectivity in the fronto-parietal network, this time after 12 months in the stretching and toning group. Results from cognitive testing showed no significant improvements ($p = 0.12$) for the walking group on composite measures of short-term verbal memory and executive performance relative to the stretching and toning control group. Of note, the only significant correlation between functional connectivity and cognitive performance was in the DMN, with an increase in connectivity between bilateral parahippocampal gyrus—bilateral lateral occipital cortex, correlating with improved executive function ($p = 0.003$). There was also a trend for association between the left middle frontal gyrus—bilateral medial temporal gyrus connection from the DMN with executive function ($p = 0.03$).

These analyses support the idea that exercise-induced changes in DMN function during passive tasks are important and predict cognitive function. The next section will address the importance of resting CBF and network analysis of functional relationships in the brain in explaining how exercise interventions affect the brain.

16.6 The Effects of Exercise on Resting Cerebral Blood Flow

There is convincing evidence in humans that cardiovascular exercise affects the hippocampus, a brain area important for higher cognitive functions, particularly declarative memory. In addition, the hippocampus is one of the few brain areas known to support adult neurogenesis (Ming and Song 2011) (see also Chaps. 1 and 2). Healthy aging is associated with atrophy of the hippocampus (Allen et al. 2005; Lemaitre et al. 2005) and decreased blood flow in the hippocampus that is correlated with cognitive performance (Heo et al. 2010). Exercise-induced increases in resting CBF in the hippocampus could promote cognitive health by increasing blood supply necessary for neurogenesis and maintenance of existing tissue and may therefore underlie observed increases in hippocampal volume with exercise and cardiovascular fitness. Also, there is recent evidence that factors in blood may have a direct effect on neurogenesis in regions like the hippocampus (Villeda et al. 2011). In fact, there is support for these theories in the literature: Pereira et al. (2007) studied the effects of exercise on the hippocampus in mice and humans and showed that, using MR cerebral blood volume measurements, exercise differentially targets the dentate gyrus, a hippocampal subregion important for memory and implicated in cognitive aging. Twenty-three 7-week-old mice were provided with running wheels and ran voluntarily for 2 weeks. These were compared with a control group of 23 non-exercising mice who followed the same protocols. MR images were acquired at weeks 0, 2, 4, and 6. After the administration of a gadolinium contrast agent, cerebral blood volume (CBV) was determined during the second week of the experiment: Bromodeoxyuridine (BrdU) was injected for 7 days to mark new cells that developed as a result of the exercise intervention. In addition to the animal work, Pereira et al. performed a human study on 11 young human subjects (mean age = 33 years, range = 21–45 years), who were selected for having below-average fitness and who then completed a 12-week exercise intervention. Four days a week, the participants completed approximately 1 h of exercise at a university fitness center consisting of 5 min of stretching, 40 min of aerobic training, and 10 min of cool-down. Participants were imaged before and after the exercise intervention, and CBV maps were specifically acquired of the hippocampus (not whole brain). The participants also completed the Rey Auditory Verbal Learning Task (RAVLT), a memory task believed to rely on the hippocampus

In the mice, specific areas of the hippocampus were assessed for an increase in CBV, including the entorhinal cortex, dentate gyrus, and the CA1 and CA3 subfields. The dentate gyrus was the only region that showed a significant difference between the exercise groups across time. A maximum increase in CBV was observed in the exercising mice after the exercise intervention between weeks 2 and 4, a delay the authors anticipated if the increased CBV was due to angiogenesis. The exercising mice also exhibited greater BrdU labeling than the non-exercising mice, meaning that they created more new cells than the non-exercisers. Co-labeling with the neuronal marker NeuN revealed that 90% of the BrdU-positive cells were likely neurons. Again, a significant effect was only observed in the dentate gyrus during weeks 2–4.

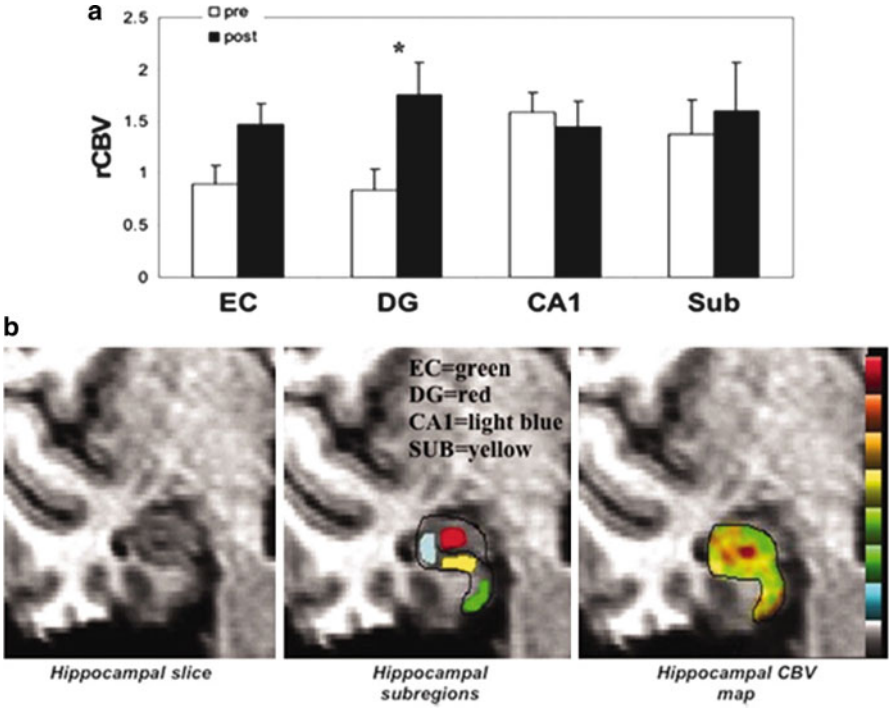

Fig. 16.5 Exercise selectively increases dentate gyrus CBV in humans. (**a**) Exercise selectively affected CBV in the dentate gyrus. The *open bars* show the mean relative CBV (rCBV) values in each hippocampal subregion before exercise, and the filled bars show rCBV after exercise. The dentate gyrus was the only region that showed a significant effect of exercise, as in mice. (**b**) An example of a CBV map from an individual subject. (*Left*) High-resolution anatomical image of the hippocampal formation. (*Center*) Regions of interest within the hippocampus (*green*: entorhinal cortex; *red*: dentate gyrus; *blue*: CA1 subfield; *yellow*: subiculum). (*Right*) Map of CBV within the hippocampal formation, where warmer colors represent higher CBV (Figures reprinted with permission, copyright 2011 National Academy of Sciences, USA; originally published in Pereira AC et al (2007) An in vivo correlate of exercise induced neurogenesis in the adult dentate gyrus. Proc Natl Acad Sci USA 104:5638–5643)

Changes in BrdU labeling correlated with CBV, and when BrdU was included as a covariate in the analysis of CBV over time, the effect of exercise on CBV in the dentate gyrus was abolished. Thus, the increases in CBV in the mouse hippocampal dentate gyrus induced by exercise were interpreted to be due to neurogenesis in this region. In the humans, CBV was reported for the entorhinal cortex, dentate gyrus, and CA1 subfield, and as seen in the mice, the dentate gyrus was the only region that showed increased CBV over time (Fig. 16.5). Aerobic fitness, as assessed by $\dot{V}O_2$max, increased with time, and the increases in CBV correlated with the $\dot{V}O_2$max (Fig. 16.6). Cognitively, the participants improved on only one aspect of the RAVLT-trial-1 learning, which is a word-list recall task. Performance on trial-1 learning correlated with $\dot{V}O_2$max and also with CBV in the dentate gyrus (Fig. 16.6).

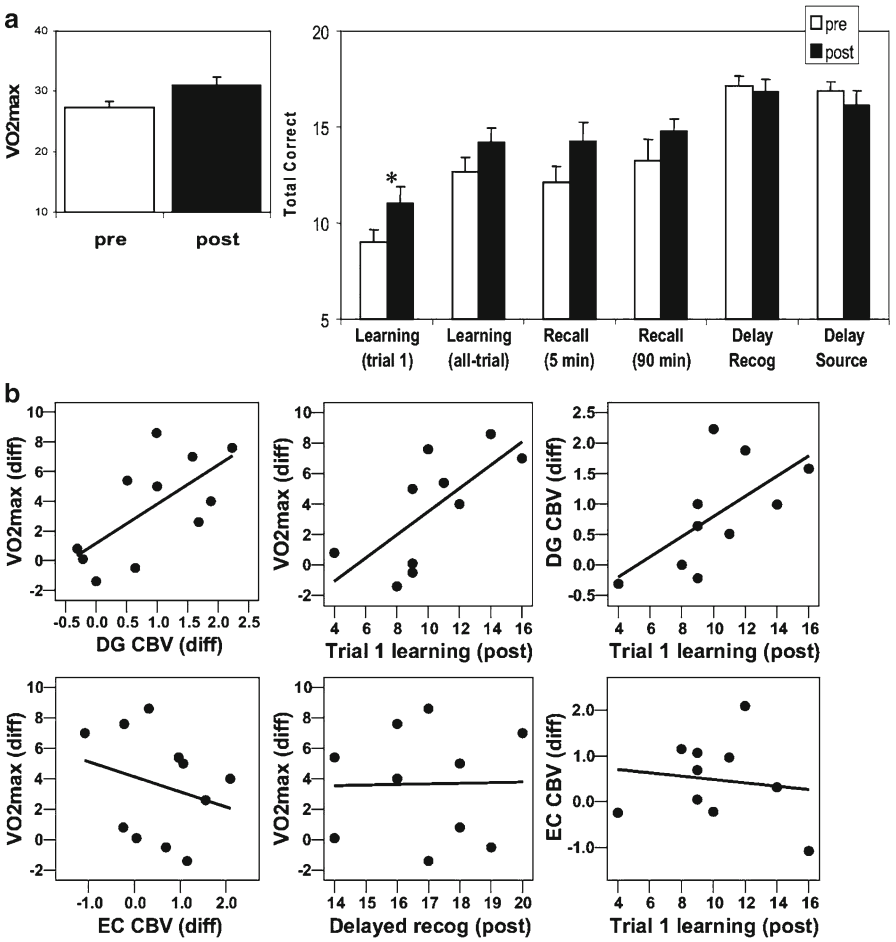

Fig. 16.6 Exercise-induced increases in dentate gyrus CBV in humans correlate with aerobic fitness and cognition. (**a**) (*Left*) Increased $\dot{V}O_2$max postexercise indicates that cardiovascular fitness increased after the exercise intervention. (*Right*) *Bars* show the number of words correctly recalled at different delays. The only significant increase in word recall occurred on first-trial learning of new declarative memories. (**b**) (*Left*) Changes in $\dot{V}O_2$max due to exercise correlated with changes in CBV in the dentate gyrus (DG) but not with other hippocampal subregions such as the entorhinal cortex (EC). (*Center*) Changes in $\dot{V}O_2$max correlated with postexercise trial-1 performance on the RAVLT. (*Right*) Trial-1 performance after the exercise intervention correlated with changes in CBV in the dentate gyrus but not with CBV changes in other hippocampal subregions, such as the EC (Figures reprinted with permission, copyright 2011 National Academy of Sciences, USA; originally published in Pereira AC et al (2007) An in vivo correlate of exercise induced neurogenesis in the adult dentate gyrus. Proc Natl Acad Sci USA 104:5638–5643)

In conclusion, Pereira et al. demonstrated increased CBV in the dentate gyrus of both humans and mice in response to an exercise intervention. In addition, the rodent data demonstrated elevated neurogenesis in response to exercise that was coupled with increased angiogenesis. Moreover, advanced statistical analyses suggested that

the increase in CBV could be attributed to neurogenesis. Human data corresponded well with this, showing increased CBV specifically in dentate gyrus that was correlated with aerobic fitness and cognitive function on a hippocampus-dependent task.

16.7 Beyond Blood Flow: Implications of Increased Cerebral Perfusion on Brain Networks

The impact of increased resting CBF in the hippocampus is, however, likely not as simple as just improving the function of one structure in the brain. A recent analysis from our group of both resting fMRI and resting CBF data after an exercise intervention takes these observations about the effects of exercise on the hippocampus one step further (Burdette et al. 2010). Burdette et al. analyzed a subset of data from the Seniors Health and Activity Research Program Pilot trial (SHARP-P). The SHARP-P trial included 80 adults between the ages of 70 and 85 years who were at risk for cognitive decline, as defined by being in this age group and having self-reported memory loss. Participants were randomized into four different intervention groups: exercise training (ET), cognitive training (CT), exercise + cognitive training, and an educational control group (healthy aging control: HAC; please note this does not imply that these subjects are healthy agers but rather that they participated in the health education control group). The interventions lasted 4 months. Of these participants, six from the ET and five from the HAC group qualified for and agreed to participate in a pilot MR scanning sub-study. The exercise training consisted of two 40-min center-based sessions and two home-based sessions each week, with a target of 150/min a week of walking with the intent to improve cardiovascular fitness. The HAC group participated in light stretching and health education-based lectures covering topics such as medications, foot care, and nutrition. These sessions lasted 60 min each and were conducted weekly for the first 3 months and monthly from that point forward. A region of interest analysis was performed on the post-intervention arterial spin labeling (ASL) perfusion data to test for differences in hippocampal perfusion between the ET and HAC groups. In brief, the ASL technique used in this study is a MRI procedure that noninvasively magnetically tags blood below the brain and images that tagged blood as it perfuses the brain (see also Chap. 11). The ET participants showed significantly greater hippocampal perfusion than HAC participants. This analysis was followed by a voxel-wise analysis within the hippocampal region of interest, which revealed that the increased perfusion extended bilaterally throughout the hippocampus (Fig. 16.7). This novel finding complements previous observations of increased hippocampal volume due to a cardiovascular exercise intervention (Erickson et al. 2011) as well as the above-mentioned findings of Pereira et al. (2007) that hippocampal CBV was increased by exercise in rats and humans.

In addition to regional analysis of the CBF data, Burdette et al. performed a *network analysis* of resting-state fMRI data using the measures of degree, global efficiency, and local efficiency. The techniques used in this paper were described

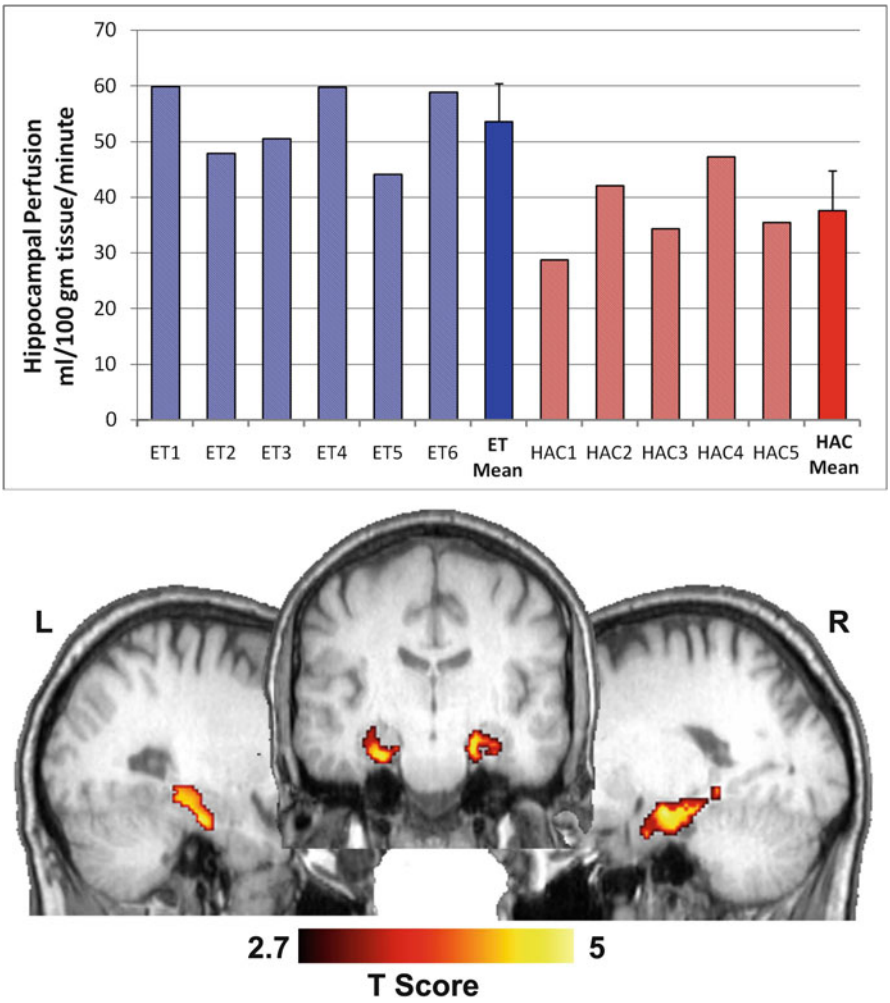

Fig. 16.7 Hippocampal CBF is increased in the exercise training group after the 4-month exercise intervention. The *top panel* shows hippocampal perfusion in each subject. The *lighter colored bars* show CBF for individuals, and the *darker blue* and *red bars* reflect the group means for the ET and HAC groups. The *bottom panel* shows statistical parametric maps of significant differences in CBF in the hippocampus between the ET and HAC groups (Figures originally published in Burdette JH et al (2010) Using network science to evaluate exercise-associated brain changes in older adults. Front Aging Neurosci 2:23. doi:10.3389/fnagi.2010.00023)

above in Sect. 16.2. While there were no global differences between the ET and HAC groups in terms of overall global network properties, regional differences did exist. This is similar to the observation from the Voss study (Voss et al. 2010b) that no overall changes in functional connectivity were observed between the two groups; rather, changes were more specific to pair-wise relationships within the

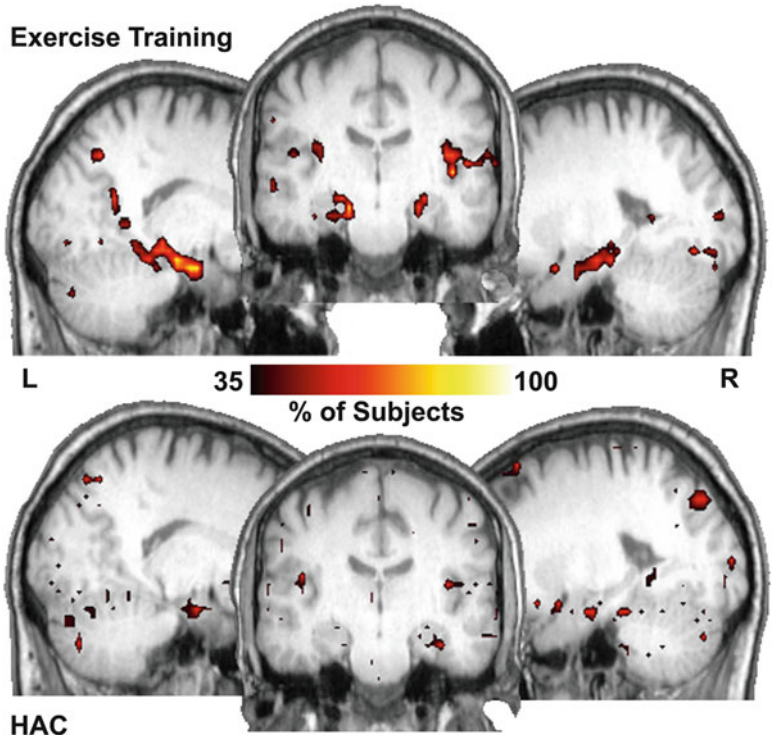

Fig. 16.8 The hippocampus is a significant hub in the exercise training group but not the educational control group. Hub maps illustrate the overlap between subjects of regions that are highly connected. A voxel is shown if it is among the top 15% of voxels in terms of connections and the intensity of color reflects the percentage of subjects for whom that voxel was a hub. In the exercise training group (*top*), the hippocampus is one of the major hubs in the brain. In contrast, the HAC group shows only a small portion of the hippocampus as a common hub (Figures originally published in Burdette JH et al (2010) Using network science to evaluate exercise-associated brain changes in older adults. Front Aging Neurosci 2:23. doi:10.3389/fnagi.2010.00023)

networks. Consistency in hub regions for each group is shown in Fig. 16.8. Interestingly, the hippocampus was shown to consistently be a hub in the ET group, but not in the HAC group. When network properties within the hippocampal ROI were compared, the ET group showed significantly larger degree (mean = 49.5, sd = 17 connections) within the hippocampi than the HAC group (mean = 28.3, sd = 16 connections). These data suggest that the hippocampi in the ET group are more highly connected to other areas of the brain than those in the HAC group and add to the neurogenesis findings of Pereira et al., discussed earlier.

An analysis of community structure was then conducted to explore which brain regions showed enhanced connectivity with the hippocampus in the exercise group. The community structure analysis of the exercise data showed that the major change in hippocampal connectivity is with the anterior cingulate cortex (ACC) (Fig. 16.9). In the exercise group, the ACC and the hippocampi were within the same module, but this

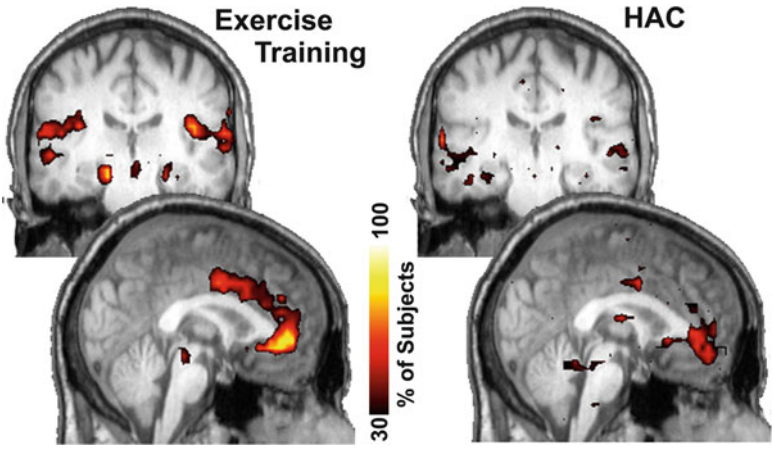

Fig. 16.9 Community structure analysis revealed that the hippocampus and anterior cingulate cortex were highly connected in the exercise training group. Maps of the community structure of the brain, showing regions that are most interconnected, demonstrated that the hippocampus was most notably interconnected with the anterior cingulate gyrus (ACC) in the exercise training group, but there were only minor connections between these regions in the HAC group. Color intensity on these maps reflects the percentage of subjects that have each voxel in this network community (Figures originally published in Burdette JH et al (2010) Using network science to evaluate exercise-associated brain changes in older adults. Front Aging Neurosci 2:23. doi:10.3389/fnagi.2010.00023)

was not the case for the HAC group. This observation was followed up with post hoc evaluation of blood flow and network metrics of the ACC. No increase in perfusion of the ACC was noted in the ET group relative to the HAC group. However, the ET group did show marginally significant increases ($p<0.07$) in ACC degree compared to the HAC group. Finally, a significant correlation was observed between the degree of the ACC and hippocampal perfusion ($p<0.03$). That is, participants with higher hippocampal perfusion showed greater connectivity in the ACC. This is important because it suggests that the functional relevance of increased perfusion in the hippocampus may not be simply better performance of the hippocampus itself but rather a shift in the functional architecture of the brain system. Although results across groups were quite reliable, generalization of these findings is limited given the small sample size and only post-intervention assessment, leaving open important and exciting opportunities to investigate the effects of exercise on brain networks in larger cohorts.

16.8 Summary and Conclusions

Although it has not often been used in exercise studies, the resting state is a metabolically and functionally active brain state that can provide important insights into the effects of exercise on brain function. The hallmark of the resting state is the

DMN, a network of brain regions that includes the posterior cingulate/precuneus, anterior cingulate, and parietal cortices. The DMN has been shown to be important for optimal cognitive performance in an array of different tasks. In fact, Voss et al. (2010b) observed that an exercise intervention strengthened connectivity within the DMN and that these changes in connectivity were associated with improved memory performance. Functional connectivity analyses during the resting state are not limited to the DMN; activity of multiple different networks can be observed during the resting state (Damoiseaux et al. 2006), and as Voss et al. (2010b) observed, exercise can modify connectivity within these networks as well.

In addition to looking at functional connectivity, CBF can be assessed during the resting state. Two studies have observed increased resting cerebral perfusion due to an exercise intervention. In the first of these, Pereira et al. (2007) showed resting CBV to be increased in the dentate gyrus of the hippocampus in both humans and mice after exercising for a few weeks. Importantly, increased CBV in mice was associated with neurogenesis and angiogenesis. In the second study, Burdette et al. (2010) observed increased resting CBF throughout the hippocampus in humans who exercised for 4 months, and this increased blood flow was accompanied by changes in the network architecture of the brain. In addition to this evidence that the resting state is important for overall brain function and is affected by exercise, the resting state is an attractive option for assessing brain function in larger studies because it is easy to implement, well characterized, and heritable. We believe that the number of studies using functional measures of the resting brain to assess the effects of exercise will only increase as the importance and utility of this method are realized.

References

Aguirre GK, Detre JA, Zarahn E, Alsop DC (2002) Experimental design and the relative sensitivity of BOLD and perfusion fMRI. Neuroimage 15:488–500

Allen JS, Bruss J, Brown CK, Damasio H (2005) Normal neuroanatomical variation due to age: the major lobes and a parcellation of the temporal region. Neurobiol Aging 26:1245–1260, discussion 1279–1282

Barabasi AL, Albert R (1999) Emergence of scaling in random networks. Science 286:509–512

Beaver JD, Long CJ, Cole DM, Durcan MJ, Bannon LC, Mishra RG, Matthews PM (2011) The effects of nicotine replacement on cognitive brain activity during smoking withdrawal studied with simultaneous fMRI/EEG. Neuropsychopharmacology 36:1792–1800

Beckmann CF, Smith SM (2004) Probabilistic independent component analysis for functional magnetic resonance imaging. IEEE Trans Med Imaging 23:137–152

Bradley KM, O'Sullivan VT, Soper ND, Nagy Z, King EM, Smith AD, Shepstone BJ (2002) Cerebral perfusion SPET correlated with Braak pathological stage in Alzheimer's disease. Brain 125:1772–1781

Buckner RL, Andrews-Hanna JR, Schacter DL (2008) The brain's default network: anatomy, function, and relevance to disease. Ann N Y Acad Sci 1124:1–38

Bullmore E, Sporns O (2009) Complex brain networks: graph theoretical analysis of structural and functional systems. Nat Rev Neurosci 10:186–198

Burdette JH, Laurienti PJ, Espeland MA, Morgan A, Telesford Q, Vechlekar CD, Hayasaka S, Jennings JM, Katula JA, Kraft RA, Rejeski WJ (2010) Using network science to evaluate exercise-associated brain changes in older adults. Front Aging Neurosci 2:23

Chetelat G, Desgranges B, Landeau B, Mezenge F, Poline JB, de la Sayette V, Viader F, Eustache F, Baron JC (2008) Direct voxel-based comparison between grey matter hypometabolism and atrophy in Alzheimer's disease. Brain 131:60–71

Cordes D, Haughton VM, Arfanakis K, Wendt GJ, Turski PA, Moritz CH, Quigley MA, Meyerand ME (2000) Mapping functionally related regions of brain with functional connectivity MR imaging. AJNR Am J Neuroradiol 21:1636–1644

Damoiseaux JS, Rombouts SA, Barkhof F, Scheltens P, Stam CJ, Smith SM, Beckmann CF (2006) Consistent resting-state networks across healthy subjects. Proc Natl Acad Sci USA 103:13848–13853

Damoiseaux JS, Beckmann CF, Arigita EJ, Barkhof F, Scheltens P, Stam CJ, Smith SM, Rombouts SA (2008) Reduced resting-state brain activity in the "default network" in normal aging. Cereb Cortex 18:1856–1864

Di Martino A, Ross K, Uddin LQ, Sklar AB, Castellanos FX, Milham MP (2009) Functional brain correlates of social and nonsocial processes in autism spectrum disorders: an activation likelihood estimation meta-analysis. Biol Psychiatry 65:63–74

Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, Chaddock L, Kim JS, Heo S, Alves H, White SM, Wojcicki TR, Mailey E, Vieira VJ, Martin SA, Pence BD, Woods JA, McAuley E, Kramer AF (2011) Exercise training increases size of hippocampus and improves memory. Proc Natl Acad Sci USA 108:3017–3022

Fellows LK (2006) Deciding how to decide: ventromedial frontal lobe damage affects information acquisition in multi-attribute decision making. Brain 129:944–952

Fransson P (2005) Spontaneous low-frequency BOLD signal fluctuations: an fMRI investigation of the resting-state default mode of brain function hypothesis. Hum Brain Mapp 26:15–29

Friston KJ (1994) Functional and effective connectivity in neuroimaging: a synthesis. Hum Brain Mapp 2:56–78

Geday J, Gjedde A (2009) Attention, emotion, and deactivation of default activity in inferior medial prefrontal cortex. Brain Cogn 69(2):344–352

Glahn DC, Winkler AM, Kochunov P, Almasy L, Duggirala R, Carless MA, Curran JC, Olvera RL, Laird AR, Smith SM, Beckmann CF, Fox PT, Blangero J (2010) Genetic control over the resting brain. Proc Natl Acad Sci USA 107:1223–1228

Grady CL, Springer MV, Hongwanishkul D, McIntosh AR, Winocur G (2006) Age-related changes in brain activity across the adult lifespan. J Cogn Neurosci 18:227–241

Greicius MD, Krasnow B, Reiss AL, Menon V (2003) Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. Proc Natl Acad Sci USA 100:253–258

Greicius MD, Srivastava G, Reiss AL, Menon V (2004) Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. Proc Natl Acad Sci USA 101:4637–4642

Gusnard DA, Raichle ME, Raichle ME (2001) Searching for a baseline: functional imaging and the resting human brain. Nat Rev Neurosci 2:685–694

Hagmann P, Cammoun L, Gigandet X, Meuli R, Honey CJ, Wedeen VJ, Sporns O (2008) Mapping the structural core of human cerebral cortex. PLoS Biol 6:e159

Hari R, Salmelin R (1997) Human cortical oscillations: a neuromagnetic view through the skull. Trends Neurosci 20:44–49

Hayasaka S, Laurienti PJ (2010) Comparison of characteristics between region-and voxel-based network analyses in resting-state fMRI data. Neuroimage 50:499–508

Heo S, Prakash RS, Voss MW, Erickson KI, Ouyang C, Sutton BP, Kramer AF (2010) Resting hippocampal blood flow, spatial memory and aging. Brain Res 1315:119–127

Honey CJ, Sporns O, Cammoun L, Gigandet X, Thiran JP, Meuli R, Hagmann P (2009) Predicting human resting-state functional connectivity from structural connectivity. Proc Natl Acad Sci USA 106:2035–2040

Iacoboni M, Lieberman MD, Knowlton BJ, Molnar-Szakacs I, Moritz M, Throop CJ, Fiske AP (2004) Watching social interactions produces dorsomedial prefrontal and medial parietal BOLD fMRI signal increases compared to a resting baseline. Neuroimage 21:1167–1173

Jann K, Dierks T, Boesch C, Kottlow M, Strik W, Koenig T (2009) BOLD correlates of EEG alpha phase-locking and the fMRI default mode network. Neuroimage 45:903–916
Klimesch W (1996) Memory processes, brain oscillations and EEG synchronization. Int J Psychophysiol 24:61–100
Klimesch W (1999) EEG alpha and theta oscillations reflect cognitive and memory performance: a review and analysis. Brain Res Rev 29:169–195
Langbaum JB, Chen K, Lee W, Reschke C, Bandy D, Fleisher AS, Alexander GE, Foster NL, Weiner MW, Koeppe RA, Jagust WJ, Reiman EM (2009) Categorical and correlational analyses of baseline fluorodeoxyglucose positron emission tomography images from the Alzheimer's Disease Neuroimaging Initiative (ADNI). Neuroimage 45:1107–1116
Latora V, Marchiori M (2001) Efficient behavior of small-world networks. Phys Rev Lett 87:198701
Lemaitre H, Crivello F, Grassiot B, Alperovitch A, Tzourio C, Mazoyer B (2005) Age- and sex-related effects on the neuroanatomy of healthy elderly. Neuroimage 26:900–911
Li CS, Yan P, Bergquist KL, Sinha R (2007) Greater activation of the "default" brain regions predicts stop signal errors. Neuroimage 38:640–648
Lowe MJ, Mock BJ, Sorenson JA (1998) Functional connectivity in single and multislice echoplanar imaging using resting-state fluctuations. Neuroimage 7:119–132
Lustig C, Snyder AZ, Bhakta M, O'Brien KC, McAvoy M, Raichle ME, Morris JC, Buckner RL (2003) Functional deactivations: change with age and dementia of the Alzheimer type. Proc Natl Acad Sci USA 100:14504–14509
Maurits NM, Scheeringa R, van der Hoeven JH, de Jong R (2006) EEG coherence obtained from an auditory oddball task increases with age. J Clin Neurophysiol 23:395–403
McKiernan KA, D'Angelo BR, Kaufman JN, Binder JR (2006) Interrupting the "stream of consciousness": an fMRI investigation. Neuroimage 29:1185–1191
Meunier D, Achard S, Morcom A, Bullmore E (2009) Age-related changes in modular organization of human brain functional networks. Neuroimage 44:715–723
Ming GL, Song H (2011) Adult neurogenesis in the mammalian brain: significant answers and significant questions. Neuron 70:687–702
Minoshima S, Foster NL, Kuhl DE (1994) Posterior cingulate cortex in Alzheimer's disease. Lancet 344:895
Musso F, Brinkmeyer J, Mobascher A, Warbrick T, Winterer G (2010) Spontaneous brain activity and EEG microstates. A novel EEG/fMRI analysis approach to explore resting-state networks. Neuroimage 52:1149–1161
Neuper C, Wortz M, Pfurtscheller G (2006) ERD/ERS patterns reflecting sensorimotor activation and deactivation. Prog Brain Res 159:211–222
Newman ME, Girvan M (2004) Finding and evaluating community structure in networks. Phys Rev E Stat Nonlin Soft Matter Phys 69:026113
Pereira AC, Huddleston DE, Brickman AM, Sosunov AA, Hen R, McKhann GM, Sloan R, Gage FH, Brown TR, Small SA (2007) An in vivo correlate of exercise-induced neurogenesis in the adult dentate gyrus. Proc Natl Acad Sci USA 104:5638–5643
Persson J, Lustig C, Nelson JK, Reuter-Lorenz PA (2007) Age differences in deactivation: a link to cognitive control? J Cogn Neurosci 19:1021–1032
Petrie EC, Cross DJ, Galasko D, Schellenberg GD, Raskind MA, Peskind ER, Minoshima S (2009) Preclinical evidence of Alzheimer changes: convergent cerebrospinal fluid biomarker and fluorodeoxyglucose positron emission tomography findings. Arch Neurol 66:632–637
Polli FE, Barton JJ, Cain MS, Thakkar KN, Rauch SL, Manoach DS (2005) Rostral and dorsal anterior cingulate cortex make dissociable contributions during antisaccade error commission. Proc Natl Acad Sci USA 102:15700–15705
Prichep LS (2007) Quantitative EEG and electromagnetic brain imaging in aging and in the evolution of dementia. Ann N Y Acad Sci 1097:156–167
Raichle ME, Snyder AZ (2007) A default mode of brain function: a brief history of an evolving idea. Neuroimage 37:1083–1090, discussion 1097–1089

Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL (2001) A default mode of brain function. Proc Natl Acad Sci USA 98:676–682

Ritter P, Moosmann M, Villringer A (2009) Rolandic alpha and beta EEG rhythms' strengths are inversely related to fMRI-BOLD signal in primary somatosensory and motor cortex. Hum Brain Mapp 30(4):1168–1187

Rossini PM, Rossi S, Babiloni C, Polich J (2007) Clinical neurophysiology of aging brain: from normal aging to neurodegeneration. Prog Neurobiol 83:375–400

Sambataro F, Murty VP, Callicott JH, Tan HY, Das S, Weinberger DR, Mattay VS (2010) Age-related alterations in default mode network: impact on working memory performance. Neurobiol Aging 31(5):839–852

Schroeter ML, Stein T, Maslowski N, Neumann J (2009) Neural correlates of Alzheimer's disease and mild cognitive impairment: a systematic and quantitative meta-analysis involving 1351 patients. Neuroimage 47:1196–1206

Shulman GL, Astafiev SV, McAvoy MP, d'Avossa G, Corbetta M (2007) Right TPJ deactivation during visual search: functional significance and support for a filter hypothesis. Cereb Cortex 17:2625–2633

Singh KD, Fawcett IP (2008) Transient and linearly graded deactivation of the human default-mode network by a visual detection task. Neuroimage 41:100–112

Sonuga-Barke EJ, Castellanos FX (2007) Spontaneous attentional fluctuations in impaired states and pathological conditions: a neurobiological hypothesis. Neurosci Biobehav Rev 31:977–986

Sporns O, Zwi JD (2004) The small world of the cerebral cortex. Neuroinformatics 2:145–162

Sporns O, Honey CJ, Kotter R (2007) Identification and classification of hubs in brain networks. PLoS One 2:e1049

Stevens WD, Hasher L, Chiew KS, Grady CL (2008) A neural mechanism underlying memory failure in older adults. J Neurosci 28:12820–12824

van de Ven VG, Formisano E, Prvulovic D, Roeder CH, Linden DE (2004) Functional connectivity as revealed by spatial independent component analysis of fMRI measurements during rest. Hum Brain Mapp 22:165–178

Villeda SA, Luo J, Mosher KI, Zou B, Britschgi M, Bieri G, Stan TM, Fainberg N, Ding Z, Eggel A, Lucin KM, Czirr E, Park JS, Couillard-Despres S, Aigner L, Li G, Peskind ER, Kaye JA, Quinn JF, Galasko DR, Xie XS, Rando TA, Wyss-Coray T (2011) The ageing systemic milieu negatively regulates neurogenesis and cognitive function. Nature 477:90–94

Voss MW, Erickson KI, Prakash RS, Chaddock L, Malkowski E, Alves H, Kim JS, Morris KS, White SM, Wojcicki TR, Hu L, Szabo A, Klamm E, McAuley E, Kramer AF (2010a) Functional connectivity: a source of variance in the association between cardiorespiratory fitness and cognition? Neuropsychologia 48:1394–1406

Voss MW, Prakash RS, Erickson KI, Basak C, Chaddock L, Kim JS, Alves H, Heo S, Szabo AN, White SM, Wojcicki TR, Mailey EL, Gothe N, Olson EA, McAuley E, Kramer AF (2010b) Plasticity of brain networks in a randomized intervention trial of exercise training in older adults. Front Aging Neurosci 2.pii:32

Waites AB, Stanislavsky A, Abbott DF, Jackson GD (2005) Effect of prior cognitive state on resting state networks measured with functional connectivity. Hum Brain Mapp 24:59–68

Wang J, Aguirre GK, Kimberg DY, Roc AC, Li L, Detre JA (2003) Arterial spin labeling perfusion fMRI with very low task frequency. Magn Reson Med 49:796–802

Watts DJ, Strogatz SH (1998) Collective dynamics of 'small-world' networks. Nature 393:440–442

Weissman DH, Roberts KC, Visscher KM, Woldorff MG (2006) The neural bases of momentary lapses in attention. Nat Neurosci 9:971–978

Zhu H, Wang X, Zhu JY (2003) Effect of aging on network structure. Phys Rev E Stat Nonlin Soft Matter Phys 68:056121

Chapter 17
Structural Plasticity Induced by Physical Exercise

Destiny L. Miller, Andrea M. Weinstein, and Kirk I. Erickson

Abstract Nonhuman animal studies have provided a low-level biological basis for examining the effect of exercise on the human brain. Beginning in 2003, magnetic resonance imaging (MRI) technology started to be used to examine how cardiovascular fitness, physical activity, and exercise were related to volumetric assessments of the brain and its subregions. These studies, at first confined to samples of healthy older adults, have provided convincing evidence that physical activity has the capacity to increase brain volume and offset age-related atrophy of both subcortical and cortical areas.

17.1 Introduction

In this chapter, we focus on the studies that have examined the effect of cardiorespiratory fitness, physical activity, and exercise on brain morphology in older adults. However, there has been an emergence of investigators using physical activity to examine variation in brain morphology in populations other than older adults. For example, associations between brain morphology and cardiorespiratory fitness have been examined in younger adults (Peters et al. 2009), in middle-aged multiple sclerosis patients (Prakash et al. 2010), in preadolescent children (Chaddock et al. 2010a, b), and in schizophrenia patients (Pajonk et al. 2010). All of these studies have consistently found that greater amounts of exercise and higher fitness levels are associated with greater brain volumes. In the remaining sections of this chapter, we critically examine the possibility that exercise and fitness could be associated with greater brain volume during a period of life when atrophy is prevalent and the risk for cognitive impairment increases at an exponential rate.

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17.2 The Aging Brain and the Promise of Exercise

Normal aging is associated with deterioration of both cortical and subcortical areas that lead to decline in cognitive processes that are supported by these afflicted areas. The effects of aging are especially pronounced within the domains of memory and executive functions (Hertzog et al. 2009). Executive functions are a set of higher order processes that include cognitive flexibility, planning, goal-oriented behavior, working memory, selecting appropriate and inhibiting inappropriate actions, and high-level abstract reasoning. Corresponding to these losses in executive function, tissue in the frontal, parietal, and medial temporal cortices that support memory and executive functions experiences significant loss throughout the life span. It is estimated that healthy adults lose approximately 15% of their neocortical tissue between ages 30 and 90 (Raz 2000). In addition, healthy adults over the age of 55 experience an approximate 1–2% annual decline in hippocampal volume, a region involved in memory formation (Raz et al. 2004).

Physical activity, or active behavior that can be either aerobic or anaerobic in nature, might be both an effective prevention and treatment for late-life brain atrophy and cognitive decline. Indeed, in contrast to most medications, aerobic exercise interventions are consistently associated with increased cognitive performance in older adults (Kramer and Erickson 2007; Kramer et al. 1999). In the studies reviewed below, aerobic exercise and aerobic fitness have been defined in specific ways, so we will briefly explain how these terms are used in this literature and how they will be subsequently used throughout this chapter. First, aerobic exercise is physical exertion that relies on the cardiovascular system's ability to take in oxygen in order to generate energy. In the studies described below, aerobic exercise is usually used only in the context of an intervention in which sedentary adults are randomly assigned to a group that receives monitored and structured moderate-intensity exercise, usually in the form of regular walking. Anaerobic exercise, on the other hand, does not require an increase in oxygen consumption to produce energy. Instead, anaerobic exercise is usually brief in duration and relies on glucose for energy rather than oxygen. In the studies described below, the term anaerobic exercise has been primarily used within the context of an intervention and refers to the control-group condition that receives stretching and toning exercises that are not significantly aerobic in nature. Finally, the term aerobic exercise is slightly different than aerobic fitness, or cardiovascular fitness, which is the capacity of the cardiovascular system to take in oxygen during physical stress. In general, the term "aerobic exercise" is used to refer to physical activity interventions with an aerobic component, whereas "aerobic fitness" or "cardiovascular fitness" refers to a single measurement in a cross-sectional or observational design. However, intervention studies often examine changes in aerobic fitness levels resulting from an aerobic exercise intervention.

Physiologically, aerobic exercise improves brain health by inducing the proliferation of neurons and enhancing synaptic plasticity. Experimental studies in rodents demonstrate that aerobic exercise increases cell survival and neurogenesis, the growth of new neurons, especially in the dentate gyrus of the hippocampus (van Praag et al. 1999, 2005). Increased cell proliferation requires more extensive vasculature

to support the distribution of nutrients and energy to the newly formed cells. Therefore, exercise has also been associated with widespread angiogenesis, or the creation of new vasculature, in the cortex, cerebellum, striatum, and hippocampus (Cotman et al. 2007; Ding et al. 2006; van Praag et al. 1999). Increased vascularization increases blood flow and nutrient transport to the supported brain areas, resulting in increased brain mass and elevated blood volume (Swain et al. 2003).

If age-related brain atrophy is due to changes in cell morphology and loss of vasculature, then exercise is well suited to rebuild the decaying brain. While it was once thought that the adult brain was incapable of plasticity and adaptability, it is now known that the brain remains relatively plastic throughout the life span. Aerobic exercise is poised to capitalize on this plasticity and beneficially impact the adult brain. For instance, aerobic exercise increases the number of cells in the hippocampus and improves learning and memory, even in adult animals (van Praag et al. 2005).

In one study, 33 young and old mice were divided into sedentary or voluntary wheel-running groups for 2–4 months (van Praag et al. 2005). After the experiment, the animals were sacrificed, and their brains examined for cell proliferation in the hippocampus. Importantly, running induced cell proliferation in the hippocampus of the aged exercising mice such that they matched the young sedentary mice in number of newly formed hippocampal cells. In addition, running increased acquisition and retention on a spatial memory task in both the young and old mice as compared to their sedentary counterparts. This study demonstrated that aerobic exercise *could* change brain morphology and function, even in older animals. In fact, exercise even turned back the clock such that the older mice experienced cell genesis rates similar to those seen in younger sedentary mice. This and other animal studies have demonstrated that aerobic exercise not only improves learning and memory but also enhances the neural circuitry supporting memory processes in areas known to be susceptible to age-related deterioration including cortical and hippocampal regions.

The extensive research from animal studies set the stage for examining whether fitness or aerobic exercise treatments can alter brain morphology in humans. In human studies, structural MRI techniques are used to acquire high-resolution brain images. Specific algorithms then compute volumetric information of particular areas to determine whether the volume of certain brain regions varies as a function of cardiovascular fitness or as a function of an aerobic exercise treatment (see also Chap. 12 for extensive description of the methods).

17.3 Early Imaging Studies

In the past several years, voxel-based morphometry (VBM) has become a widely used technique to investigate fitness effects on brain morphology. Colcombe et al. (2003) used VBM to examine cortical volume as a function of age and fitness in a sample of 55 healthy older adults between the ages of 55 and 79. In this cross-sectional study examining the association between aerobic fitness and gray and white matter volume, the authors predicted that higher fitness levels (a) would be

associated with greater volume and (b) would ameliorate an age-related reduction in volume. Cardiovascular fitness was assessed using an estimated $\dot{V}O_2$ score, the "gold standard" measure of the cardiovascular system's capacity to intake oxygen. Consistent with previous research, the authors found significant age-related brain atrophy in anterior white matter tracts as well as in gray matter in the frontal, parietal, and temporal cortices. Importantly, higher fitness levels offset the age-related deterioration in both gray and white matter. This effect remained significant even after controlling for the variance from several potentially confounding factors such as socioeconomic status, years of education, and sex. This study provided support for the hypothesis that aerobic fitness is effective at attenuating brain atrophy due to the normal aging process.

While the study by Colcombe et al. (2003) provides support for a relationship between fitness and brain volume, the cross-sectional design prohibits causal associations for the impact of improving fitness on brain structure. It is possible that aerobic fitness and brain volume covary with an unmeasured third variable and therefore are not directly related. For example, people who engage in cognitively stimulating activities might also have a greater propensity to exercise, and it could be the cognitive activity rather than the physical activity that caused changes in brain structure. Another possibility is that genetic variations influence brain morphology, and individuals with certain genetic profiles are also more likely to exercise. In these cases, exercise would merely covary with brain plasticity rather than having a causal effect on plasticity. However, introducing an experimental manipulation of exercise in which fitness levels change across time *could* elucidate whether a causal relationship exists between fitness and brain volume.

Colcombe et al. (2003) therefore followed up the cross-sectional study described above with an exercise intervention in order to address this concern. In this study, 59 older adults were randomly assigned to either a moderate-intensity walking group or a stretching and toning control group (Colcombe et al. 2006). Both groups came into the laboratory three times per week for 6 months and were monitored by an exercise physiologist. To obtain brain volume data, participants were scanned before and after the intervention using MR procedures. The only difference between the two groups was that the intervention group received aerobic exercise training through walking, whereas the control group received anaerobic exercise training through stretching and toning. Using VBM, the authors found that the aerobic exercise group showed a significant increase in both gray and white matter volume over the 6-month period. More specifically, whereas the stretching and toning control group demonstrated a small (1–2%) decline in gray and white matter volume over this period, the exercising group demonstrated a significant increase in prefrontal and temporal brain areas as well as the genu of the corpus callosum after the completion of the exercise intervention. This study provides important causal evidence for the impact of aerobic exercise on brain health in older adults. That is, a relatively short 6-month period of moderate-intensity exercise, in the form of walking, was sufficient to increase cortical gray and white matter volume in a sample of healthy older adults experiencing normal age-related brain atrophy.

Early research studies using MRI technology show a clear link between aerobic fitness and brain morphology. More highly fit individuals show less age-related brain atrophy in both gray and white matter, even when controlling for differences in lifestyle factors that may affect health and access to medical care. Furthermore, 6 months of aerobic exercise in the form of moderate-intensity walking is enough to increase volume in the same brain areas that experience atrophy through the course of normal aging. Data from these early neuroimaging studies set the groundwork for further investigation into fitness-related effects on cognition (see Fig. 17.1 for a review or early and current studies linking physical activity and fitness to brain outcomes).

17.4 Population-Based and Moderating Effects on Brain Integrity

There is increasing evidence that a moderate amount of aerobic exercise is beneficial to brain health. However, there may be other lifestyle factors that influence the extent to which fitness affects brain structure. In fact, exercise does not occur in isolation of other lifestyle habits and behaviors such as diet and vitamin supplementation, hormone therapy in postmenopausal women, and intellectual stimulation in the form of education. It is possible that participation in some behaviors (e.g., a healthy diet) accentuates the beneficial effects of exercise while other behaviors (e.g., an unhealthy diet) attenuates the beneficial effects of exercise. There are also genetic factors that could affect whether fitness benefits brain integrity, such as apolipoprotein (ApoE) allele status. Also, it may matter *when* individuals begin exercise regimens, making the fitness and brain volume relationship dependent on the age at which physical activity is initiated. Studies are beginning to explore how these factors might moderate fitness effects on brain health.

The literature exploring how hormone therapy affects cognition in postmenopausal women lacks a clear consensus. Findings from some cross-sectional and small randomized, controlled trials have found that hormone treatment is associated with improved verbal memory performance and decreased risk for developing dementia in older women (Duka et al. 2000; Maki et al. 2001; Miller et al. 2001). However, findings from larger randomized, controlled trials, the most famous of which is the Women's Health Initiative, reported an *increased* risk for developing dementia in postmenopausal women treated with hormone therapy (Rapp et al. 2003; Resnick et al. 2006; Shumaker et al. 2003, 2004). These disparate findings have fueled speculation regarding the causes for these discrepancies. One theory for these mixed findings is that hormone therapy may slow age-related cognitive decline and brain atrophy when used in relatively short durations, but long-term hormone therapy may negatively impact cognitive and brain health (Kang et al. 2004). In addition, interactive effects between hormone treatment and physical activity levels may also account for discrepancies in the hormone therapy literature. If exercise is to be used as a possible treatment for brain decay in older women, then

Study (Year)	Sample Size (Mean Age)	Method	Summary of finding
Colcombe et al. (2003)	55 (66.5)	*Design:* Cross-sectional *Measures:* VBM, Rockport & VO_{2peak}	Age-related loss of white and gray matter in prefrontal, temporal, parietal regions was moderated by higher aerobic fitness levels.
Colcombe et al. (2006)	*59* *Exercisers:* (65.5) *Stretchers:* (66.9) *Younger:* 20 (Not reported)	*Design:* 6-mo randomized exercise intervention. *Measures:* VBM, VO_{2peak}	Increases in white and gray matter volume in frontal and temporal regions after aerobic exercise intervention.
Erickson et al. (2007)	54 (69.6)	*Design:* Cross-sectional *Measures:* VBM, VO_{2peak} & hormone therapy (HRT) use	Higher fitness augmented increased cortical volume related to short-term HRT and offset volume-losses related to long-term HRT.
Gordon et al. (2008)	*Older:* 40 (71.5) *Younger:* 20 (22.5)	*Design:* Cross-sectional *Measures:* VBM, VO_{2peak}, & neuropsychological battery	Higher fitness related to greater gray matter volumes in temporal, parietal, and inferior frontal area. Education predicted white matter volume.
Burns et al. (2008)	*Normal:* 64 (72.7) *Early AD*: 57 (74.3)	*Design:* Cross-sectional *Measures:* Total volume, VO_{2peak}	Higher fitness was related to larger whole brain and white matter volumes; this was not significant in older adults without dementia.
Honea et al. (2009)	*Normal:* 56 (73.3) *Early AD:* 60 (74.3)	*Design:* Cross-sectional *Measures:* VBM, VO_{2peak}, PASE	Higher fitness was related to larger gray and white matter volumes in inferior frontal and medial temporal lobe in early AD. APOE genotype did not moderate the effects.
Erickson et al. (2009)	165 (66.6)	*Design:* Cross-sectional *Measures:* Automated segmentation, VO_{2peak}	Higher aerobic fitness was related to greater hippocampal volume and accounted for 35% of the variance in volume. Volume partially mediated a fitness-memory association.
Bugg and Head (2011)	52 (69.0)	*Design:* Cross-sectional *Measures:* 10-year retrospective physical activity survey	Higher levels of self-reported exercise were associated with larger superior frontal volume. Exercise moderated age-related atrophy of the medial temporal lobe.
Rovio et al. (2010)	*Active:* 32 (52.1) *Sedentary:* 43 (48.8)	*Design:* Cross-sectional *Measures:* VBM, physical activity questionnaire	Higher reported physical activity was associated with greater gray matter volumes, however, the association between mid-life physical activity level and white matter value fell to non-significance after controlling for relevant covariates.

Fig. 17.1 A description of MRI volumetric studies examining brain function in relation to physical activity and fitness

Study (Year)	Sample Size (Mean Age)	Method	Summary of finding
Erickson et al. (2010)	299 (78.0)	*Design:* Longitudinal *Measures:* VBM, physical activity self-report,	Self-report walking at least 72 blocks per week was associated with greater volume of frontal, occipital, entorhinal, and hippocampal regions 9-years later.
Flöel et al. (2010)	75 (60.5)	*Design:* Cross-sectional *Measures:* VBM, physical activity, aerobic fitness	Increased physical activity was associated with increased cerebral gray matter volume in prefrontal and cingulate cortex.
Erickson et al. (2011)	*Walkers*: 60(67.6) *Stretchers*: 60 (65.5)	*Design:* 6-mo. Randomized exercise intervention *Measures:* Automated segmentation, serum concentrations, VO_{2max}	Exercise increased hippocampal volume by 2%, reducing age-related tissue loss. Increased hippocampal volume positively related to greater serum level of BDNF. Caudate nucleus and thalamus volumes remained unaffected by the aerobic exercise intervention.

Fig. 17.1 (continued)

understanding what factors enhance or inhibit the effects of aerobic exercise on brain structure in late life is imperative for successful treatment prescription.

One study explored the relationship between both hormone therapy and fitness on brain volume in postmenopausal women (Erickson et al. 2007). Since the duration of hormone therapy may play a key role in brain health, Erickson et al. (2007) investigated the interaction between cardiovascular fitness and duration of hormone therapy on tissue volume in a group of healthy postmenopausal women. Fifty-four women between the ages of 58 and 80 years old participated in this cross-sectional study. Data from structural MR brain images, cardiovascular fitness (as assessed by $\dot{V}O_2$max), cognitive function, and duration of hormone therapy were collected on each participant. Hormone therapy duration was defined as never (0 years), short (1–10 years), mid (11–15 years), and long (16+ years). The authors used VBM techniques and confirmed previous findings that higher fitness levels were associated with more gray matter volume in parietal, prefrontal, and frontal areas. In contrast, longer hormone therapy use was associated with less gray matter tissue volume in the left and right prefrontal cortex, left parahippocampal gyrus, and left subgenual cortex near the cingulate cortex. These are some of the same brain regions that show the greatest atrophy during the aging process. Fortunately, higher fitness levels offset this decline in tissue volume in the prefrontal and subgenual cortices. Furthermore, higher fit women who had reported a short duration of hormone therapy showed the most tissue sparing when compared to the other three durations. Thus, while fitness had an overall beneficial effect on tissue volume, higher cardiovascular fitness was able to augment the beneficial effects of short-term hormone therapy on tissue volume,

as well as offset the negative effects from longer durations of hormone therapy. Some of the disparate findings regarding the effect of hormone therapy on cognitive function may result from an untested interaction between hormone therapy and aerobic fitness. This illustrates the importance of understanding how common lifestyle factors may enhance or reduce the effects of fitness on brain health.

Other lifestyle factors in addition to hormone therapy may differentially moderate the effect of exercise or fitness on brain structure. For instance, *cognitive reserve*, or functional resilience to neuropathological damage, may be related to brain integrity. The theory of cognitive reserve states that an individual's ability to cope with neuropathological damage relies upon that individual's brain processing ability—conceptualized as brain reserve (Stern 2009). Differences in efficiency, capacity, and flexibility in neural processing result in differences in the ability to withstand damage to the brain's processing system. A more resilient neural system likely leads to better long-term brain health by withstanding neural insults and injuries. In order to estimate cognitive reserve, researchers often use the measure of years of education since it is a proxy for intelligence and is reliably self-reported. People with more education often engage in more cognitively stimulating activities such as reading and attending museums. Education is also related to dementia risk: individuals with lower education have a higher risk for developing dementia, whereas higher education is associated with the maintenance of cognitive function (Stern et al. 1994; Yaffe et al. 2009). Since education is achieved over time, it is possible that educational attainment could act as another lifestyle factor to prevent brain decay. Additionally, education may moderate the effect of exercise or fitness on brain volume.

Gordon et al. (2008) investigated this question by examining the effect of education on brain volume using similar VBM techniques to those described above. The authors examined a group of 40 older adults between the ages of 65 and 81 years old for fitness level, education, and brain volume. The $\dot{V}O_2$ max assessment of cardiovascular fitness was used to estimate fitness levels. Age was associated with tissue loss in areas similar to those discussed in the Colcombe et al. (2003) study: gray matter loss in prefrontal, parietal, and temporal regions and white matter deterioration in anterior medial white matter tracts. Higher fitness levels were associated with greater gray matter volume in medial temporal, anterior parietal, and inferior frontal areas, but no effect was found between fitness and white matter volume. On the other hand, higher education was associated with more anterior white matter volume, especially in the corpus callosum and inferior frontal cortex. This was the first study to show that fitness and education had dissociable and complementary effects on brain morphology. Modifying lifestyle factors, such as education, throughout the life span may be the key to preventing or treating age-related brain atrophy.

In addition to examining the factors that accentuate or attenuate the effect of fitness on brain integrity, some studies have begun to examine the extent to which these effects extend to populations experiencing more precipitous rates of brain atrophy. Most of the fitness and exercise literature to date has focused on healthy older adults and has shown that exercise can attenuate and even reverse age-related brain atrophy in both gray and white matter. Individuals with cognitive impairment such as Alzheimer's disease (AD) show brain atrophy in regions similar to those

affected in normal aging, but at an accelerated rate compared to age-matched controls without dementia. For example, the hippocampus, a region critically involved in memory formation, deteriorates to a greater extent in AD patients than in healthy controls (Desikan et al. 2008; Mueller et al. 2010). This begs an important clinical question: Could fitness or exercise offset AD-related brain atrophy in the same way that it offsets age-related brain atrophy in the course of normal aging?

Several large-scale epidemiological studies have explored the relationship between physical activity and incidence of AD and consistently report that greater amounts of physical activity are associated with a reduced risk for developing dementia several years later (Podewils et al. 2005; Yaffe et al. 2009). These epidemiological studies are consistent with a growing animal literature that suggests that exercise is effective at reducing the buildup of amyloid deposits and neurofibrillary tangles, two of the putative causes of AD (Nichol et al. 2008). Overall, these data suggest that fitness and exercise in humans might spare or prevent brain tissue loss in patients with AD.

Cross-sectional studies have begun to explore this avenue with early-stage AD patients (Burns et al. 2008). Using T1-weighted datasets, cardiovascular fitness levels as measured by $\dot{V}O_2$max, and neuropsychological function in 57 early-stage AD patients, Burns et al. (2008) predicted that higher fitness levels would be associated with greater brain volume in AD patients. Consistent with their hypotheses, in AD patients, higher fitness levels were associated with greater whole brain volume and white matter volume, even after controlling for the variance associated with age, sex, dementia severity, self-reported physical activity levels, and physical frailty. This study suggests that aerobic fitness may have an important moderating effect on AD-related brain atrophy, similar to fitness effects in healthy older adults. Furthermore, this study demonstrates that measuring cardiovascular fitness in patients experiencing cognitive decline is feasible, suggesting that aerobic exercise interventions could be conducted to examine whether monitored regimens of exercise could augment cognitive and brain health in AD patients.

In explorations of AD, it has become increasingly prudent to explore whether interventions are equally effective for all users or if some users benefit more or less than others. Specific genetic risk factors may position some AD patients to benefit less from exercise than those patients who do not exhibit these same genetic markers. For example, the ApoE gene is known to be a risk factor gene for late-onset AD with those carrying the ApoE ε4 allele at higher risk than those carrying an ε2 or ε3 variant. Along these lines, Honea et al. (2009) examined whether the association between fitness and brain integrity among AD populations would be moderated by the ApoE polymorphism. Honea et al. (2009) used $\dot{V}O_2$peak as the main predictor of cardiorespiratory fitness, in addition to self-reported physical activity levels, while VBM was used to calculate regional white and gray matter volumes. Consistent with previous findings (Burns et al. 2008), higher aerobic fitness levels were related to greater white matter volume in the bilateral inferior parietal cortex and greater gray matter volume in the medial temporal lobe including the hippocampus in early AD patients, but not in healthy controls. These results suggest that higher fitness levels may ameliorate some brain atrophy experienced by AD patients. Interestingly, presence

of the ApoE ε4 allele failed to modify the relationship between fitness and brain volume in either healthy adults or AD patients, suggesting that individuals at genetic risk for AD benefitted as much as their peers carrying the ApoE ε3 allele. Thus, in a group of adults already experiencing dementia, cardiorespiratory fitness was associated with greater brain volume independent of the ApoE risk allele.

The association between fitness and exercise on brain integrity is rather robust as demonstrated by relatively consistent patterns in sample sizes in the range of 50–70 participants. However, these effects may depend on other lifestyle factors such as hormone therapy or intellectual stimulation. Unfortunately, studies exploring the moderating effect of diet have yet to be conducted, but it seems plausible to predict that a diet high in saturated fats might eliminate or reduce the benefits gained from exercise while a healthy diet high in antioxidants might accentuate the benefits of exercise. In addition, we have described above the studies that demonstrate that physical activity might preserve brain health in those experiencing cognitive decline (e.g., AD). Though age-related cognitive decline and brain atrophy are exacerbated in early stages of AD, higher fitness has a beneficial impact on brain volume.

17.5 Recent Imaging Studies

Recent imaging studies have tested three main hypotheses: (1) whether exercise and fitness could explain variation in hippocampal volume, (2) whether fitness-related brain volume would be associated with a reduced risk of developing cognitive impairment, and (3) whether changes in brain volume could be linked to changes in circulating biomarkers or cognitive function.

The hippocampus atrophies in late adulthood (Raz et al. 2004) and is considered to be an early marker and predictor of conversion to AD. Because of the clinical significance of this structure, it is important to examine whether higher fitness levels would be associated with greater hippocampal volume. To test this hypothesis, 165 healthy older adults (mean age = 66.5 years) without dementia, depression, or a history of stroke or vascular damage participated in an MR session to acquire high-resolution brain images. Cardiovascular fitness levels were measured by $\dot{V}O_2$peak, and memory was tested by a computerized test of spatial memory. Instead of using VBM to calculate volume, left and right hippocampal volumes were obtained using a semiautomated segmentation algorithm. Consistent with their hypothesis, Erickson et al. (2009) found that higher fitness levels were associated with larger hippocampal volumes, but did not offset an age-related decline in volume. Further, when age, sex, and years of education were included in the model along with fitness levels, 35% of the variance in hippocampal volume was explained (Fig. 17.2). Higher fitness levels and larger hippocampal volumes were also related to better spatial memory performance, and, in mediation analyses, hippocampal volumes partially mediated the association between fitness and memory performance. Taken together, these data suggest that among healthy older adults, higher aerobic fitness levels are associated with greater hippocampal volumes, even after adjusting for common confounding factors. The triple association between fitness, spatial memory

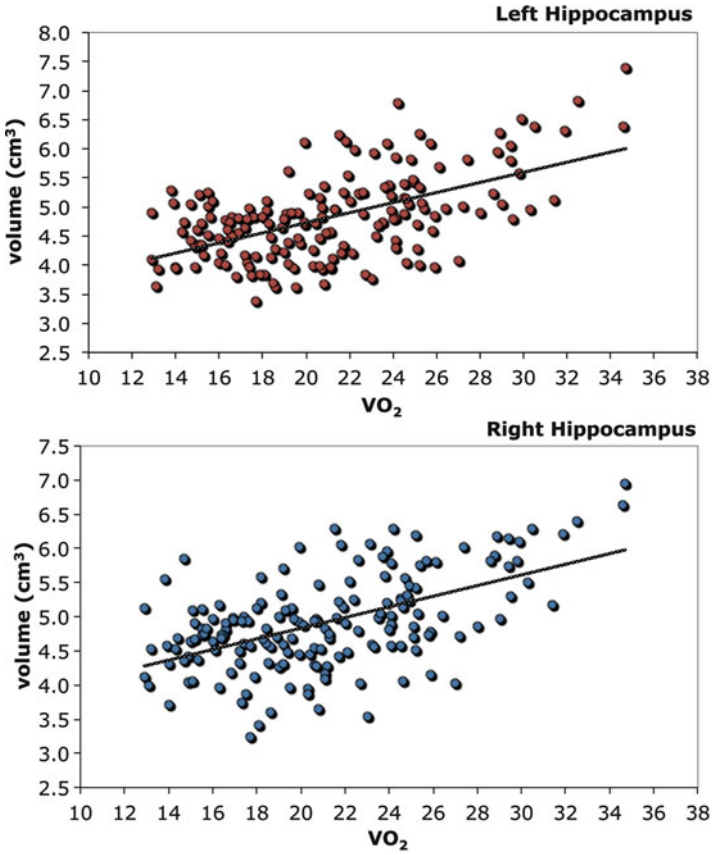

Fig. 17.2 Higher levels of fitness ($\dot{V}O_2$peak) are associated with larger hippocampal volumes (cm^3) bilaterally. These relationships remained significant after controlling for the variance associated with age, sex, and years of education (Adapted from Erickson et al. 2009)

performance, and hippocampal volume suggests that larger hippocampal volume may be one way that higher fitness levels improve memory function.

Cross-sectional evidence (Colcombe et al. 2003; Erickson et al. 2009) suggests that higher fitness levels are associated with greater volume in some regions of the brain (e.g., prefrontal cortex, hippocampus) and are not strongly associated with the volume of other areas (e.g., visual cortex; Colcombe et al. 2003). However, as described above, cross-sectional studies are limited in drawing causal inferences. Methodologies that incorporate assessments at multiple time points allow researchers to investigate whether brain volume varies as a function of changes in fitness. While randomized controlled intervention trials are the "gold standard" for this type of inference, a variety of study designs can help illuminate the causal associations between fitness and brain health.

For example, using a retrospective design, Bugg and Head (2011) examined the association between physical activity earlier in life and regional brain volume measured later in life. Their physical activity metric was average monthly METs, or metabolic

equivalent of tasks, for the 10 years prior to the MRI assessment of brain volume. Calculating METs via self-report of physical activities allows for a quantifiable estimate of energy expenditure. Participants retrospectively reported their engagement in physical exercises for the prior 10 years in a phone interview and regional brain volumes were obtained approximately 2 years before physical activity data were acquired. Those reporting less than 2.44 METs were considered the "low-active" group compared to those above the median split. Consistent with the hypothesis that more physical activity is associated with greater volume, they found that higher monthly physical activity during midlife was associated with larger superior frontal cortices. However, more importantly, they found that physical activity moderated an age-related decline in medial temporal lobe volume. That is, less active older adults had less tissue in the medial temporal lobe compared to their more active older adult peers.

These results suggest that physical activity can offset age-related brain atrophy in the medial temporal lobe. A moderating effect of physical activity on age-related atrophy of the hippocampus was not found, however, in a different study (Erickson et al. 2009). There could be several reasons for this discrepancy: (1) differences in the unit being measured, that is, self-reported physical activity versus cardiorespiratory fitness as the predictor variable; (2) sample size differences between the two studies; (3) differences in the algorithms used to calculate regional volumes; and (4) differences in the experimental designs (retrospective vs. cross-sectional). However, despite these differences, using estimates of midlife physical activity to explore later changes in brain structure allows insight into a possible age-dependent pattern. Perhaps the fitness-related effect on the hippocampus and other regions occurs only after a certain age. This highlights the need for longitudinal studies to determine the age at which low or high fitness may have preservative effects on brain integrity.

These prior studies beg the next question: at what age is exercise most important for preserving brain health throughout the life span? That is, must physical activity be initiated in young adulthood, maintained throughout life, initiated within 10 years of retirement, or could older adults benefit from exercise if they initiate it for the first time in late life? While these questions are still open to debate, some studies (Bugg and Head 2011; Rovio et al. 2010) begin to provide some clarity by exploring the associations between physical activity during midlife on brain integrity later in life.

In one study, Rovio et al. (2010) examined whether midlife physical activity was related to structural brain integrity later in life in adults that were healthy, mildly cognitively impaired (MCI),[1] or diagnosed with dementia using DSM IV criteria. Assessments of physical activity were completed during midlife (average age at assessment = 51 years) and included several self-reports of physical activity and more objective measures of overall physical health including blood pressure, body mass index (BMI), and blood cholesterol levels. Later in life, when adults were approximately 72 years old, participants provided brain structure data via high-resolution MRI. VBM methods were used to calculate regional volume from the structural data.

[1] Mild cognitive impairment is a condition where individuals experience notable cognitive deficits but do not meet the clinical criteria for dementia and do not generally experience significant difficulties in their daily lives.

Consistent with their hypotheses, Rovio et al. (2010) found that whole brain gray matter volumes were larger among those who reported being more active at midlife. This effect continued to hold even after adjusting for individual variation in health factors (e.g., BMI, blood pressure, ApoE ε4 status). While more physical activity at midlife was associated with larger white matter volume, this association failed to hold after adjusting for covariates. Rovio et al. (2010) also found that more active older adults had larger middle frontal gyrus volumes than their less active peers, even after adjustments for nuisance variables (i.e., sex, age, total intracranial volumes).

Using a similar design, Erickson et al. (2010) examined the effect of walking on brain integrity 9 years after the assessment of physical activity. Nearly 300 healthy adults were asked how many blocks they walked on average per week. Nine years later, VBM-based assessments of brain volume were calculated from high-resolution structural MRI. An additional 4 years later, 13 years after the self-report of average number of blocks walked per week, a clinical adjudication was conducted to determine whether participants had cognitive impairment. Consistent with the hypothesis that greater amounts of physical activity would predict greater brain volume over a long-term span, they found that participants who reported walking a greater number of blocks had larger frontal, temporal, and occipital lobes, as well as the hippocampus and entorhinal cortex, 9 years later. This effect held even after accounting for possible confounding factors, such as gender, age, education, mobility, and overall health. Further, after splitting participants into quartiles, Erickson et al. (2010) found that gray matter volume was greatest among those walking at least 72 blocks per week. Groups walking less than 72 blocks per week did not differ from one another, suggesting a threshold for the amount of activity needed to observe long-term effects of physical activity on brain volume. Highly active older adults that surpass some activity level, in this case 72 blocks per week, may not experience the same extent of brain tissue loss that their lesser active peers experience at lower activity levels. Although the number of city blocks constituting one mile or kilometer differs by the length of the city block, in this study, it was estimated that approximately ten city blocks constitute 1 mile. Hence, 72 blocks per week is equivalent to nearly 7 miles or 11 km of walking per week. Finally, this study found that at the 13-year follow-up, approximately one third of the sample had developed MCI and/or dementia, but greater amounts of walking reduced the risk of developing cognitive impairment twofold. These results brought together measures of physical activity, brain volume, and the risk for cognitive impairment and suggest that physical activity reduces risk of dementia by reducing brain atrophy.

Although longitudinal studies have provided compelling data arguing that physical activity earlier in life is related to more brain tissue later in life, these study designs make it difficult to determine causality between increased physical activity and increased gray matter volume. For example, individuals who partake in more physical activity earlier in life might also be more educated and have healthier diets, confounds that make it difficult to determine which factor is associated with increased brain volume. In order to more firmly establish causality between these constructs, a randomized controlled trial is necessary. Along these lines, a recent

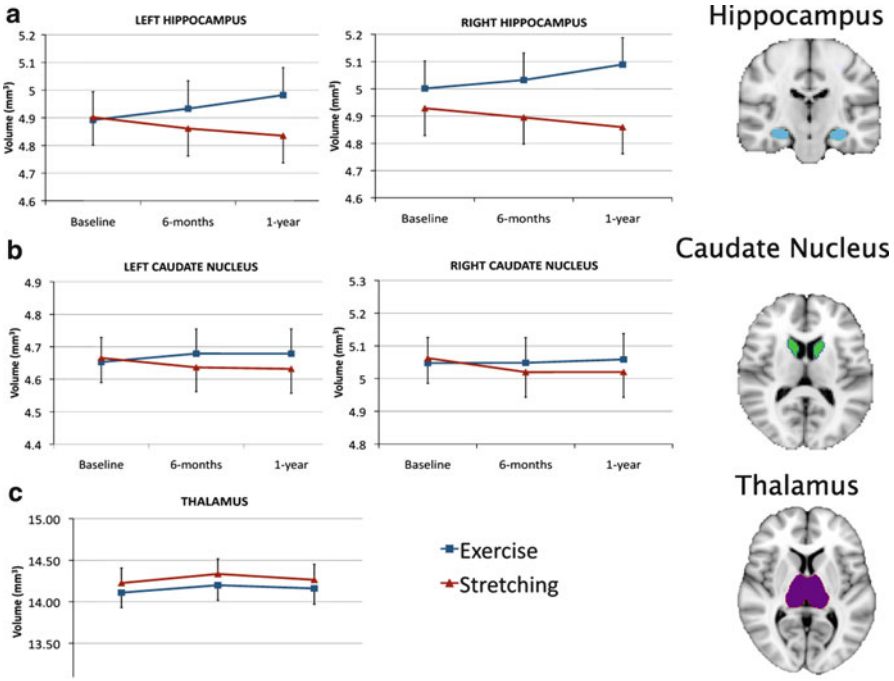

Fig. 17.3 Fitness-related intervention effects on subcortical volumes over time. The time X group interaction was significant for left and right regions for the hippocampus. The attenuation of tissue decline observed in the caudate nucleus was not significant; no changes were significant for the thalamus (Adapted from Erickson et al. 2011)

large-scale aerobic exercise intervention suggests that some age-related tissue loss is modifiable. A total of 120 non-demented adults over the age of 65 were randomized into either a stretching and toning control group or a walking group for 12 months (Erickson et al. 2011). MR scans were completed at baseline, 6, and 12 months. Volume of the hippocampus, caudate nucleus, and thalamus was calculated using a semiautomated segmentation algorithm. Within the course of 1 year, walkers showed a 2% increase in volume in the hippocampus compared to their stretching and toning peers that lost approximately 1.4% of their hippocampal volumes. Thus, aerobic exercise is effective at increasing hippocampal volume, even in older adults. These effects, however, were relatively specific such that caudate nucleus and thalamus volumes were unaffected by aerobic exercise (see Fig. 17.3).

To explore whether aerobic exercise increases volume in areas where cell proliferation is most consistently found (i.e., the dentate gyrus), Erickson et al. (2011) divided the segmented hippocampus into anterior and posterior sections. After segmentation, they found that aerobic exercise increased anterior hippocampal volume (including dentate gyrus and CA1 subfields) but had a minimal effect on the posterior section of the hippocampus. In contrast, stretchers and toners showed a decline in anterior volumes but no change in the posterior hippocampus. Further, increased

hippocampal volume was related to greater improvements in spatial memory performance, suggesting that these changes in volume translate to memory function.

Recent evidence described above begins to explain the relationship between physical activity and fitness with brain volume in late life and the possibility that physical activity could prevent atrophy (Erickson et al. 2010; Rovio et al. 2010; Bugg and Head 2011) and even be an effective treatment to reverse atrophy that has already taken place (Colcombe et al. 2006; Erickson et al. 2011). Some of these investigators have also begun to examine the molecular pathways by which these effects occur. Animal research suggests that neurotrophic factors play an essential role in angiogenesis, synaptogenesis, and neurogenesis. Brain-derived neurotrophic factor (BDNF) is one of the most studied molecules involved in neurogenesis and synaptogenesis and is found in both the brain and the periphery, so it can be easily studied in humans before, during, or after an exercise treatment by examining blood concentrations.

Although some studies have found that physical fitness levels were unrelated to BDNF, Erickson et al. (2011) examined whether changes in fitness levels over a 1-year randomized intervention was related to changes in serum BDNF concentrations and whether serum BDNF would be related to increased hippocampal volume. They found that change in serum BDNF was related to increased hippocampal volume over the 1-year intervention period; however, this effect was also regionally specific such that BDNF levels were not associated with larger caudate nucleus or thalamus volumes. Thus, it is possible that regular and sustained aerobic exercise increases BDNF, which in turn increases the volume of the hippocampus.

Other factors, such as granulocyte colony-stimulating factor (G-CSF), have been examined less frequently in relation to exercise or physical activity. However, G-CSF is critical in learning and memory formation, suggesting an involvement in synaptogenesis and dendritic branching (Schneider et al. 2005). Flöel et al. (2010) examined G-CSF levels in relation to physical activity and structural brain integrity to determine whether physical activity was associated with increased G-CSF and whether G-CSF was related to brain volume. They found that higher levels of self-reported physical activity were related to higher levels of G-CSF, larger volumes of several gray matter regional volumes including the prefrontal cortex, cingulate cortex, occipital–temporal regions, and the cerebellum even after adjustments for confounding factors. They also found that higher self-reported levels of physical activity were associated with better memory performance. These data suggest that G-CSF may be involved in the process of increasing or retaining brain volumes, highlighting a possible additional mechanism for how exercise improves brain health.

17.6 Summary

Normal aging is associated with atrophy of cortical and subcortical areas. In this review, we provide convincing evidence that (1) even modest intensity aerobic exercise, such as walking, can improve brain health over relatively short periods; (2) effects of exercise and fitness need to be interpreted within the context of other lifestyle

factors and genetic profiles that moderate the benefits of exercise on brain integrity; (3) exercise can benefit brain integrity even in populations experiencing more rapid atrophy; and (4) exercise can prevent and treat brain atrophy and these effects might be partially mediated by neurotrophic factors.

Early imaging studies demonstrated associations between fitness and brain integrity. That is, higher fit older adults experienced less atrophy than their lesser fit peers (e.g., Colcombe et al. 2003), even after controlling for demographic characteristics. Then, later experimental studies showed that 6 months of walking could increase gray and white matter volume (Colcombe et al. 2006).

A host of other factors have been explored in relation to effects of physical activity and fitness on brain integrity. For example, higher fitness levels augmented the beneficial effects of shorter durations of hormone replacement therapy while offsetting some of the detrimental effects of long-term hormone replacement therapy. The beneficial effects of physical activity and fitness also seem robust across several populations, including individuals experiencing cognitive decline.

The most interesting and compelling evidence for fitness and physical activity effects on brain integrity comes from recent studies. Cross-sectional evidence shows that fitness levels explain 35% of the variance in hippocampal volume in older adults (Erickson et al. 2009). Also, higher self-reported rates of physical activity have been associated with larger cortical and subcortical volumes later in life using both retrospective and prospective reporting (Bugg and Head 2011; Rovio et al. 2010). Even activities as simple as walking are related to larger gray matter brain volumes later in life (Erickson et al. 2010). Aerobic-based physical activity interventions have also successfully increased volumes and prevented the typical atrophy observed in older adults' brains (e.g., Erickson et al. 2011).

There are several major take-home messages from this research. First, older adults that have been inactive throughout most of their lives can benefit from adopting an exercise program in late life. Thus, it is never too late to become more active. On the other hand, those with higher fitness levels earlier in life also have less decline in regional brain volumes, suggesting it may be even more beneficial to adopt an active lifestyle earlier rather than later. Second, the older adult brain remains modifiably well into late adulthood, and even modest amounts of exercise are capable of taking advantage of this characteristic.

Although we have learned a lot about how brain morphology is altered in relation to physical activity, fitness, and exercise, we have much yet to learn. The extent to which these effects extend to other populations with neurologic or psychiatric conditions, the underlying mechanisms and pathways, and the intensity of the exercise that is needed to observe these effects are just a handful of the many questions that investigators are now asking.

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References

Bugg JM, Head D (2011) Exercise moderates age-related atrophy of the medial temporal lobe. Neurobiol Aging 32(3):506–514

Burns JM, Cronk BB, Anderson HS, Donnelly JE, Thomas GP, Harsha A et al (2008) Cardiorespiratory fitness and brain atrophy in early Alzheimer disease. Neurology 71(3):210–216

Chaddock L, Erickson KI, Prakash RS, Kim JS, Voss MW, Vanpatter M et al (2010a) A neuroimaging investigation of the association between aerobic fitness, hippocampal volume, and memory performance in preadolescent children. Brain Res 1358:172–183

Chaddock L, Erickson KI, Prakash RS, VanPatter M, Voss MW, Pontifex MB et al (2010b) Basal ganglia volume is associated with aerobic fitness in preadolescent children. Dev Neurosci 32(3):249–256

Colcombe SJ, Erickson KI, Raz N, Webb AG, Cohen NJ, McAuley E et al (2003) Aerobic fitness reduces brain tissue loss in aging humans. J Gerontol A Biol Sci Med Sci 58(2):176–180

Colcombe SJ, Erickson KI, Scalf PE, Kim JS, Prakash R, McAuley E et al (2006) Aerobic exercise training increases brain volume in aging humans. J Gerontol A Biol Sci Med Sci 61(11): 1166–1170

Cotman CW, Berchtold NC, Christie LA (2007) Exercise builds brain health: key roles of growth factor cascades and inflammation. Trends Neurosci 30(9):464–472

Desikan RS, Fischl B, Cabral HJ, Kemper TL, Guttmann CR, Blacker D et al (2008) MRI measures of temporoparietal regions show differential rates of atrophy during prodromal AD. Neurology 71(11):819–825

Ding YH, Li J, Zhou Y, Rafols JA, Clark JC, Ding Y (2006) Cerebral angiogenesis and expression of angiogenic factors in aging rats after exercise. Curr Neurovasc Res 3(1):15–23

Duka T, Tasker R, McGowan JF (2000) The effects of 3-week estrogen hormone replacement on cognition in elderly healthy females. Psychopharmacology (Berl) 149(2):129–139

Erickson KI, Colcombe SJ, Elavsky S, McAuley E, Korol DL, Scalf PE et al (2007) Interactive effects of fitness and hormone treatment on brain health in postmenopausal women. Neurobiol Aging 28(2):179–185

Erickson KI, Prakash RS, Voss MW, Chaddock L, Hu L, Morris KS et al (2009) Aerobic fitness is associated with hippocampal volume in elderly humans. Hippocampus 19(10):1030–1039

Erickson KI, Raji CA, Lopez OL, Becker JT, Rosano C, Newman AB et al (2010) Physical activity predicts gray matter volume in late adulthood: the Cardiovascular Health Study. Neurology 75(16):1415–1422

Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, Chaddock L et al (2011) Exercise training increases size of hippocampus and improves memory. Proc Natl Acad Sci USA 108(7): 3017–3022

Flöel A, Ruscheweyh R, Kruger K, Willemer C, Winter B, Volker K, et al (2010) Physical activity and memory functions: are neurotrophins and cerebral gray matter volume the missing link? Neuroimage 49(3):2756–2763

Gordon BA, Rykhlevskaia EI, Brumback CR, Lee Y, Elavsky S, Konopack JF, et al (2008) Neuroanatomical correlates of aging, cardiopulmonary fitness level, and education. Psychophysiology 45(5):825–838

Hertzog C, Kramer AF, Wilson RS, Lindenberger U (2009) Enrichment effects on adult cognitive development: can the functional capacity of older adults be preserved and enhanced? Psychol Sci Public Interest 9:1–65

Honea RA, Thomas GP, Harsha A, Anderson HS, Donnelly JE, Brooks WM et al (2009) Cardiorespiratory fitness and preserved medial temporal lobe volume in Alzheimer disease. Alzheimer Dis Assoc Disord 23(3):188–197

Kang JH, Weuve J, Grodstein F (2004) Postmenopausal hormone therapy and risk of cognitive decline in community-dwelling aging women. Neurology 63(1):101–107

Kramer AF, Erickson KI (2007) Effects of physical activity on cognition, well-being, and brain: human interventions. Alzheimers Dement 3(2 Suppl):S45–S51

Kramer AF, Hahn S, Cohen NJ, Banich MT, McAuley E, Harrison CR et al (1999) Ageing, fitness and neurocognitive function. Nature 400(6743):418–419

Maki PM, Zonderman AB, Resnick SM (2001) Enhanced verbal memory in nondemented elderly women receiving hormone-replacement therapy. Am J Psychiatry 158(2):227–233

Miller MM, Monjan AA, Buckholtz NS (2001) Estrogen replacement therapy for the potential treatment or prevention of Alzheimer's disease. Ann N Y Acad Sci 949:223–234

Mueller SG, Schuff N, Yaffe K, Madison C, Miller B, Weiner MW (2010) Hippocampal atrophy patterns in mild cognitive impairment and Alzheimer's disease. Hum Brain Mapp 31(9): 1339–1347

Nichol KE, Poon WW, Parachikova AI, Cribbs DH, Glabe CG, Cotman CW (2008) Exercise alters the immune profile in Tg2576 Alzheimer mice toward a response coincident with improved cognitive performance and decreased amyloid. J Neuroinflammation 5:13

Pajonk FG, Wobrock T, Gruber O, Scherk H, Berner D, Kaizl I et al (2010) Hippocampal plasticity in response to exercise in schizophrenia. Arch Gen Psychiatry 67(2):133–143

Peters J, Dauvermann M, Mette C, Platen P, Franke J, Hinrichs T et al (2009) Voxel-based morphometry reveals an association between aerobic capacity and grey matter density in the right anterior insula. Neuroscience 163(4):1102–1108

Podewils LJ, Guallar E, Kuller LH, Fried LP, Lopez OL, Carlson M et al (2005) Physical activity, APOE genotype, and dementia risk: findings from the Cardiovascular Health Cognition Study. Am J Epidemiol 161(7):639–651

Prakash RS, Snook EM, Motl RW, Kramer AF (2010) Aerobic fitness is associated with gray matter volume and white matter integrity in multiple sclerosis. Brain Res 1341:41–51

Rapp SR, Espeland MA, Shumaker SA, Henderson VW, Brunner RL, Manson JE et al (2003) Effect of estrogen plus progestin on global cognitive function in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. JAMA 289(20): 2663–2672

Raz N (2000) Aging of the brain and its impact on cognitive performance: integration of structural and functional findings. In: Craik FIM, Salthouse TA (eds) The handbook of aging and cognition, vol 2. Lawrence Erlbaum Associates, Mahweh, NJ, pp 1–90

Raz N, Rodrigue KM, Head D, Kennedy KM, Acker JD (2004) Differential aging of the medial temporal lobe: a study of a five-year change. Neurology 62(3):433–438

Resnick SM, Coker LH, Maki PM, Rapp SR, Espeland MA, Shumaker SA (2006) The Women's Health Initiative Study of Cognitive Aging (WHISCA): a randomized clinical trial of the effects of hormone therapy on age-related cognitive decline. Clin Trials 1:440–450

Rovio S, Spulber G, Nieminen LJ, Niskanen E, Winblad B, Tuomilehto J et al (2010) The effect of midlife physical activity on structural brain changes in the elderly. Neurobiol Aging 31(11): 1927–1936

Schneider A, Kuhn HG, Schabitz WR (2005) A role for G-CSF (granulocyte-colony stimulating factor) in the central nervous system. Cell Cycle 4(12):1753–1757

Shumaker SA, Legault C, Rapp SR, Thal L, Wallace RB, Ockene JK et al (2003) Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. JAMA 289(20):2651–2662

Shumaker SA, Legault C, Kuller L, Rapp SR, Thal L, Lane DS et al (2004) Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. JAMA 291(24):2947–2958

Stern Y (2009) Cognitive reserve. Neuropsychologia 47(10):2015–2028

Stern Y, Gurland B, Tatemichi TK, Tang MX, Wilder D, Mayeux R (1994) Influence of education and occupation on the incidence of Alzheimer's disease. JAMA 271(13):1004–1010

Swain RA, Harris AB, Wiener EC, Dutka MV, Morris HD, Theien BE et al (2003) Prolonged exercise induces angiogenesis and increases cerebral blood volume in primary motor cortex of the rat. Neuroscience 117(4):1037–1046

van Praag H, Christie BR, Sejnowski TJ, Gage FH (1999) Running enhances neurogenesis, learning, and long-term potentiation in mice. Proc Natl Acad Sci USA 96(23):13427–13431

van Praag H, Shubert T, Zhao C, Gage FH (2005) Exercise enhances learning and hippocampal neurogenesis in aged mice. J Neurosci 25(38):8680–8685

Yaffe K, Fiocco AJ, Lindquist K, Vittinghoff E, Simonsick EM, Newman AB et al (2009) Predictors of maintaining cognitive function in older adults: the Health ABC study. Neurology 72(23):2029–2035

Part IV
Effects of Exercise on Cognitive Processing

Chapter 18
The Relation of ERP Indices of Exercise to Brain Health and Cognition

Charles H. Hillman, Keita Kamijo, and Matthew B. Pontifex

Abstract This chapter describes a program of research aimed at the relation of physical activity to brain health and cognition, with implications for scholastic achievement among youth. We describe a body of neurophysiological research that indicates that both chronic and acute physical activity relate to enhanced cognitive function, albeit over a different temporal duration. Such findings have important implications for public health in school age children, as physical activity stands to increase brain health and cognitive function during childhood and across the life span.

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18.1 Introduction

There is a growing public health burden of inactivity in industrialized nations. In recent years, children have become increasingly sedentary, leading to concomitant increases in the prevalence of being overweight and unfit (DHHS and DOE 2000). Despite the knowledge that physical activity has broad benefits for public health, including increased physical fitness, maintenance of healthy body weight, and a reduced risk of disease (Strong et al. 2005), greater than one third of children do not meet the national guidelines of moderate to vigorous activity on a daily basis (CDC 2008). During adulthood, even fewer individuals meet national guidelines for physical activity (Haskell et al. 2007). At issue, physical inactivity during early childhood has implications for physical activity behaviors across the life span, and has been related to the prevalence of several chronic diseases (e.g., cardiovascular disease and type-2 diabetes) during adolescence and adulthood. In fact, recent estimates have suggested that younger generations in the United States may lead shorter and less healthy lives than their parents, marking the first time in U.S. history that a trend such as this has occurred (Fontaine et al. 2003; Olshansky et al. 2005). These estimates are based on the rise in overweight and obesity status and the fall of physical activity behaviors among children.

However, absent from these public health concerns is the relation of physical inactivity on brain health and cognition. Not too far into our history, our early ancestors engaged in a much more rigorously active lifestyle, suggesting that our evolutionary past may have been shaped by an active lifestyle for much of human existence (Bortz II 1985; Fialkowski 1986). Specifically, it has been conjectured that human evolution (including brain) was shaped during our formative years as hunters (Bortz II 1985). Such a lifestyle required strenuous physical activity through the prolonged, persistent pursuit of prey under considerable heat stress (Fialkowski 1986). As a function of this lifestyle, there is speculation that human beings became specialized for (among other behaviors) endurance physical activity (Carrier 1984), with additional supposition that rapid increases in brain volume occurred to meet the demands of physically active hunting behaviors under heat stress (Fialkowski 1986). Accordingly, brain and body evolved in concert to support the demands of considerable movement.

In many regards, it is unfortunate that contemporary human beings have, for the most part, removed the need for strenuous physical activity from daily life. Vaynman and Gomez-Pinilla (2006, p. 700) state "Ironically, in a world that recognizes the benefits of exercise, physical inactivity characterizes most industrialized societies of our modern age. This is likely due to the benefits reaped by technological advances, which have obviated many of the necessities for physical labor." This statement suggests that human beings may be maladapted to the sedentary lifestyle of today (Booth and Lees 2006; Vaynman and Gomez-Pinilla 2006), with evidence indicating not only poorer physical health but also poorer cognitive health, as suggested by an increasing scientific focus on the relation of physical activity to brain and cognition (see Hillman et al. 2008 for review).

Thus, the purpose of this chapter is to describe a subset of the available data on the relation of physical activity to brain health and cognition across the human life span. In particular, a programmatic approach to this area of research has used measures, which tap the neuroelectric system to provide a greater understanding of cognitive functioning, beyond what may be understood through overt behavioral measures. Electroencephalography (EEG) is considered the oldest measure for assessing functional brain activation. Despite many new advances in neuroimaging, EEG remains a useful tool in understanding covert cognitive operations. The work described in this chapter focuses on the use of EEG to understand the relation of physical activity to brain health and cognition, with a particular focus on the event-related potential (ERP) approach. The overall purpose of this research model is to better understand factors that relate to cognitive health and effective functioning across the human life span. However, before turning to the review, we first describe the concept of cognitive control and briefly review ERPs to provide the necessary background for the literature reviewed. We then review the extant findings of exercise, brain health, and cognition, with a particular focus on ERP indices of cognitive control.

18.2 Cognitive Control

The term cognitive control (also referred to as "executive control") describes an overarching set of higher-order, cognitive operations, which are involved in the regulation of goal-directed interactions within the environment (Botvinick et al. 2001; Meyer and Kieras 1997; Norman and Shallice 1986). These processes allow for the optimization of behavior through the selection, scheduling, coordination, and maintenance of computational processes underlying aspects of perception, memory, and action (Botvinick et al. 2001; Meyer and Kieras 1997; Miyake et al. 2000; Norman and Shallice 1986). The core cognitive processes which are collectively termed "cognitive control" include inhibition, working memory, and cognitive flexibility (Diamond 2006). Although these processes are distinct and distinguishable, it is important to note that they share common neural structures and are functionally interrelated (Miyake et al. 2000). Inhibitory control often requires one to deliberately override a dominant response in order to perform a less potent but correct response, suppress task-irrelevant information in the stimulus environment, or stop an ongoing response (Barkley 1997; Davidson et al. 2006). This ability to inhibit attention to task-irrelevant or distracting stimuli is thought to be central to the ability to sustain attention and allow control over one's actions. That is, it allows one to make decisions based on choice, rather than impulse. Working memory refers to the ability to hold information in one's mind and manipulate it and is heavily involved in each of the other cognitive control processes as it also relates to the ability to represent internal goals and standards for the comparison of those goals against current performance in order to regulate behavior (Bunge and Crone 2009). Lastly, cognitive

flexibility relates to the ability to hold multiple goals, response mappings, and internal representations within the mind and adaptively switch perspectives and attentional foci to meet environmental demands (Diamond 2006). It is these processes, which have demonstrated protracted development during maturation, and early decay during aging, which are among some of the most affected by physical activity behaviors.

18.3 Event-Related Brain Potentials

Beyond the assessment of overt actions, ERPs provide a means of gaining insight into the relationship between physical activity/fitness and cognitive control through the examination of a subset of neurophysiological processes that occur between stimulus encoding and response production. Accordingly, these measures allow for a more precise understanding of the relation of exercise-induced changes on cognition. ERPs refer to a class of neuroelectric activity that occurs in response to, or in preparation for, a stimulus or response (Coles et al. 1990). This neuroelectric activity is reflective of the synchronous activity of large populations of neurons (Hugdahl 1995), and can reflect obligatory responses (exogenous) or higher-order cognitive processing that often require active participation from the individual (endogenous; Hugdahl 1995). The stimulus-locked ERP is characterized by a succession of positive (P) and negative (N) components, which are constructed according to their direction and the relative time that they occur (Hruby and Marsalek 2003). Earlier components (N1, P2) of the stimulus-locked potential relate to aspects of selective attention, while later components (N2, P3) relate to various aspects of endogenous cognitive function (e.g., response inhibition, attentional resource allocation; see Fig. 18.1).

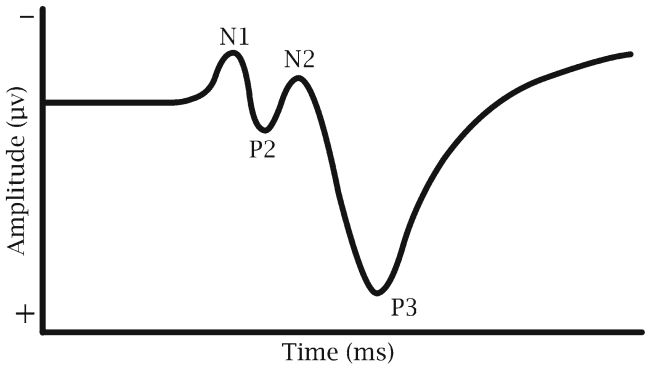

Fig. 18.1 Characterization of a stimulus-locked event-related potential denoting the N1, P2, N2, and P3 components

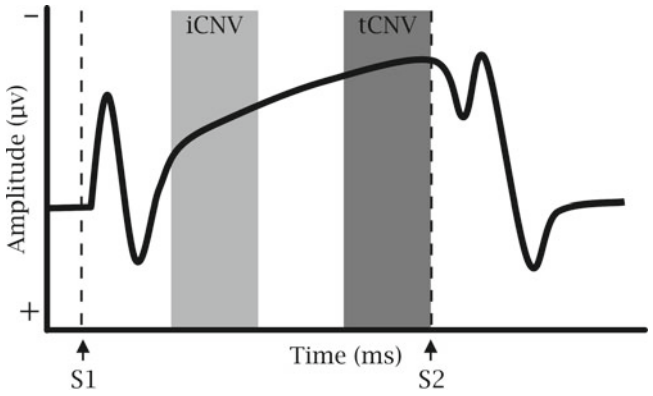

Fig. 18.2 Characterization of a stimulus-locked event-related potential denoting the initial CNV (iCNV) and the terminal CNV (tCNV) and their relationship with warning (S1) and imperative (S2) stimuli

Among ERP components, the P3 (also known as the P300 or P3b) has garnered considerable attention in the literature in regard to the relation of physical activity/fitness to neurocognition. Originally discovered in 1965 by Sutton, Braren, Zubin, and John, the P3 is a positive-going deflection occurring approximately 300–800 ms after stimulus presentation, with a topographic maximum at electrode sites over the parietal cortex (Polich and Kok 1995). This endogenous component reflects neuronal activity associated with the revision of the mental representation of the previous event (Donchin 1981), such that the P3 is sensitive to the allocation of attentional resources during stimulus engagement (Polich 2007). Based on a recent theoretical account of the P3 by Polich (2007), the amplitude is believed to be proportional to the amount of resources allocated toward the suppression of extraneous neuronal activity in order to facilitate attentional processing, such that larger P3 amplitude would reflect greater inhibition of superfluous activity. P3 latency is generally considered to reflect stimulus detection and evaluation time (Ilan and Polich 1999; Magliero et al. 1984), which is independent of response selection and behavioral action (Verleger 1997). Further, P3 latency appears to be negatively correlated with mental function, with shorter latencies related to superior cognitive performance (Emmerson et al. 1989; Howard and Polich 1985; Johnson et al. 1985; Polich and Martin 1992; Polich et al. 1983). Although the precise neural origins of the P3 are still unknown, the generation of the P3 appears to result from the interaction between frontal and temporal/parietal networks with additional contributions stemming from a number of subcortical structures (Ebmeier et al. 1995; Kirino et al. 2000; Polich 2003).

A second ERP component of interest with regard to physical activity/fitness related changes in cognition is the contingent negative variation (CNV; see Fig. 18.2), a negative-going slow cortical potential elicited during the interval between warning (S1) and imperative (S2) stimuli. The term CNV more broadly refers to at least two different ERP components: the initial CNV (iCNV; also called O-wave)

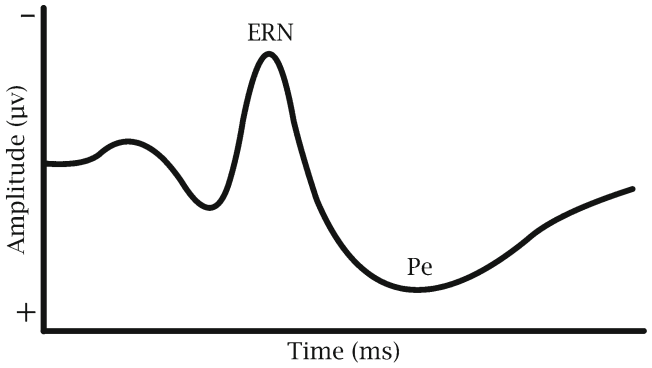

Fig. 18.3 Characterization of a response-locked event-related potential denoting the error-related negativity (ERN) and error positivity (Pe)

and the terminal CNV (tCNV; also called E-wave; Loveless and Sanford 1974; Weerts and Lang 1973). The iCNV has been associated with stimulus orientation with a frontal topographic maximum, while the tCNV is thought to relate to stimulus anticipation and/or response preparation and demonstrates a central topographic maximum (Brunia and van Boxtel 2001; Loveless and Sanford 1974; van Boxtel and Brunia 1994; Weerts and Lang 1973). Further, recent evidence suggests that a more frontal topographic distribution of the CNV is associated with cognitive preparatory processes rather than response preparation (Falkenstein et al. 2003; Leynes et al. 1998; Lorist et al. 2000; Wild-Wall et al. 2007). The CNV has multiple neural generators including the anterior cingulate cortex (ACC), supplementary motor area, prefrontal cortex, and primary motor cortex (Cui et al. 2000; Gómez et al. 2003; Hamano et al. 1997).

Lastly, a separate class of ERPs is time-locked to an individual's response (see Fig. 18.3). One such component of this "response-locked" ERP is the error-related negativity (ERN; also known as the Ne), which is described as a negative-going deflection occurring approximately 50–150 ms after errors of commission with a topographic maximum over fronto-central recording sites (Falkenstein et al. 1991; Gehring et al. 1993). The ERN is believed to reflect the activation of action monitoring processes in response to erroneous behaviors to initiate the upregulation of top-down compensatory processes to correct an individual's responses during subsequent environmental interaction (Falkenstein et al. 1991; Gehring and Knight 2000; Gehring et al. 1993). The ERN has been found to occur regardless of an individual's awareness of error commission (Nieuwenhuis et al. 2001). The neural tissue underlying the generation of the ERN has been localized through hemodynamic (Carter et al. 1998), magneto-encephalographic (Miltner et al. 2003), and high-density dipole modeling (Dehaene et al. 1994; van Veen and Carter 2002) studies to the dorsal portion of the ACC. Accordingly, through the measurement of these (and other) ERP components, information concerning the specific aspects of cognition that are influenced by exercise behaviors may be better understood.

18.4 The Relation of Chronic Physical Activity Participation, Aerobic Fitness, and ERPs

Since Kramer et al. (1999) first reported that increases in aerobic fitness selectively improved performance on tasks requiring greater amounts of cognitive control, there has been growing interest in the selective effects of exercise on cognitive control over the past decade. A meta-analysis (Colcombe and Kramer 2003) supported the notion that although regular physical activity provides general benefits across multiple aspects of cognition, the improvements are selectively and disproportionately greater for processes requiring extensive amounts of cognitive control. However, it should be noted that researchers have not reached consensus on the relationship of chronic physical activity to cognition (see Smith et al. 2010 for review). Regardless, several ERP studies have focused on the general versus selective nature of the relationship between chronic physical activity and cognitive function across the life span. Specifically, these studies are classified into five categories based on types of cognitive task and cognitive processes examined: stimulus discrimination, inhibition, working memory, action monitoring, and cognitive flexibility.

18.4.1 Stimulus Discrimination

Early ERP studies examined the relation of physical activity and aerobic fitness to cognitive function using an oddball task (Dustman et al. 1990; Polich and Lardon 1997). The oddball task requires participants to respond to rare target stimuli (i.e., oddballs) among a train of frequent nontarget stimuli (e.g., 20% target and 80% nontarget). The oddball task requires relatively minimal cognitive control compared to other tasks as will hereafter be described. These pioneering studies indicated that chronic physical activity and aerobic fitness are positively associated with increased attentional resources during stimulus engagement (larger P3 amplitude) in young adults (Polich and Lardon 1997) and faster cognitive processing speed (i.e., shorter P3 latency) in older adults (Dustman et al. 1990). Thus, early findings provided evidence that chronic physical activity and aerobic fitness are positively related to stimulus discrimination processes in adult populations.

A more recent ERP study (Pontifex et al. 2009b) observed that greater aerobic fitness was associated with larger P3 amplitude during an oddball task in both young and older adults, replicating the earlier findings of Polich and Lardon (1997). However, Pontifex et al. 2009b) also manipulated perceptual discrimination difficulty of the oddball task, and indicated that greater aerobic fitness was associated with increased P3 amplitude irrespective of age for the easier task condition, whereas the positive relationship between fitness and P3 amplitude was only observed in young adults for the more difficult task condition. These findings suggested that fitness may not be sufficient to overcome age-related cognitive deficits when task difficulty is too great (Pontifex et al. 2009b). Thus, it would appear that the positive relation of aerobic

fitness to cognitive function is mediated by age and task difficulty. The general relationship between fitness and cognitive function has been also observed in preadolescent children, as higher-fit children exhibited larger P3 amplitude and shorter P3 latency during the oddball task compared to their lower-fit counterparts (Hillman et al. 2005). Collectively, these ERP studies using variants of the oddball task suggest that chronic participation in physical activity and greater aerobic fitness are associated with superior stimulus discrimination across the life span.

18.4.2 Inhibition

Several ERP studies have used modifications of the Eriksen flanker task (Eriksen and Eriksen 1974) to investigate the relation of chronic physical activity and aerobic fitness to inhibitory aspects of cognitive control. This task requires participants to respond to a centrally presented target stimulus amid an array of flanking stimuli, which are task irrelevant. A typical flanker task consists of congruent trials, in which the target letter is flanked by the same letters (e.g., HHHHH or SSSSS), and incongruent trials, in which the target letter is flanked by opposing letters that are mapped to a different response (e.g., SSHSS or HHSHH). Incongruent trials require greater amounts of inhibitory control to gate out interference generated by the flanker stimuli due to the activation of the incorrect response mapping. Hillman et al. (2004) compared the P3 component of young adults with high, moderate, and low physically active older adults during a flanker task. Results indicated that high and moderate active older adults exhibited larger P3 amplitude compared to young adults only for the incongruent condition, while no such differences were observed for low active older adults. Given that larger P3 amplitude, reflecting greater allocation of attentional resources, was observed for both high and moderately active adults, the data suggest that a particular threshold of physical activity may be necessary to accrue neurocognitive benefits. Alternatively, young adults exhibited shorter P3 latency relative to the older adults, replicating the robust finding that cognitive processing speed slows during cognitive aging. However, when physical activity was considered among the older adults, greater physical activity levels were associated with shorter P3 latencies, suggesting a linear relationship between activity level and cognitive processing speed. Thus, these findings suggest that physical activity may be positively related to cognitive function during tasks requiring variable amounts of inhibitory control in older adults.

More recently, Hillman et al. (2009a) extended these findings in older adults to preadolescent children. Specifically, 9–10 year old higher aerobically fit children exhibited larger P3 amplitude and greater response accuracy compared to their lower aerobically fit counterparts during a flanker task, while no such fitness-related differences were observed for P3 latency. Accordingly, these data may indicate that during preadolescent development, fitness may provide a benefit to attention directed toward the stimulus environment during tasks requiring variable amounts of inhibitory control, but that processing speed is not influenced in the same manner.

It is worth noting that other authors have reported no relation of fitness to P3 indices of cognition in adolescent children during a flanker task (Stroth et al. 2009). However, deeper inspection into the study design yields several possible explanations for this contradiction. First, Stroth et al. (2009) used a median split to bifurcate their sample into higher and lower aerobically fit groups. That is, moderate-fit participants might have been included in both groups, which may blur differences in fitness-related inhibitory function between groups. Second, Stroth et al. (2009) used a modified flanker/Go-NoGo task instead of a more traditional flanker task that has been incorporated into prior ERP studies (Hillman et al. 2004, 2009a; Pontifex et al. 2011). Specifically, the flanker/Go-NoGo task consisted of eight types of letter arrays (congruent: BBBBB, DDDDD, UUUUU, and VVVVV; incongruent: DDBDD, BBDBB, VVUVV, and UUVUU). Participants were asked to respond to centrally presented "B" and "U" letters, and to withhold their response to centrally presented "D" and "V" letters. As such, the hybrid flanker/Go-NoGo task necessitates greater working memory demands to maintain multiple rule sets, and flexibly allocate and inhibit these rule sets, compared to standard flanker tasks. As described above, the relation of fitness to cognitive function may be mediated by task difficulty (Pontifex et al. 2009b). Thus, the flanker/Go-NoGo task might have been too difficult for adolescent children to detect subtle differences in inhibitory function between groups (Stroth et al. 2009). Lastly, the P3 component was measured at electrode sites overlying the lateral portions of the central scalp region (Stroth et al. 2009). It is well established that P3 amplitude has a topographic maximal amplitude over the midline-parietal region (Polich 2007), and most ERP studies have indicated the positive relation of physical activity to the P3 component along midline electrode sites (e.g., Hillman et al. 2004; Kamijo and Takeda 2009; Polich and Lardon 1997). Thus, these methodological differences may have accounted for the contradictory findings between Stroth et al. (2009) and other ERP studies using the flanker task (Hillman et al. 2004, 2009a).

Finally, other inhibitory control tasks have been used to assess the relation of chronic physical activity to this aspect of cognition. Kamijo and Takeda (2009) observed a positive relation of physical activity to inhibitory control using a spatial priming task (Tipper et al. 1990) in young adults. In this task, a target letter ("O") and a distractor letter ("X") were presented at two of four possible locations simultaneously. Participants were required to respond to the target location and to ignore the distractor location. When the target in the current trial appeared at the distractor location in the previous trial, RTs become longer compared to other trials (Tipper et al. 1990). This effect, which has been termed "negative priming", is considered to reflect inhibitory control to prevent interference from distractors on working memory. In other words, a larger negative priming effect may reflect superior inhibitory control (Kamijo and Takeda 2009). The results indicated that physically active young adults exhibited larger negative priming effects on RT and P3 latency compared to their sedentary peers, suggesting that regular physical activity is associated with inhibitory control processes during young adulthood. Taken together, the majority of ERP studies that have used inhibition tasks to assess the relation of chronic physical activity and/or aerobic fitness to cognition have observed a

positive relation of these variables to inhibitory control across the life span. Despite differences in tasks and age, the majority of studies report similar P3 findings, suggesting a robust relationship between chronic engagement of exercise and this aspect of cognition.

18.4.3 Working Memory

In addition to the body of research described above that has used stimulus discrimination tasks to examine the allocation of attentional resources, recent research in our laboratory supports a positive relation of physical activity to working memory using a Sternberg task in young adults (Kamijo et al. 2010). The Sternberg task requires participants to encode a memory set (S1) containing an array of letters (e.g., XFJTP) and respond whether a single probe (S2; e.g., ??T??) appeared in the encoded array (S1). In this task, greater working memory demands are required to encode and maintain relevant information for larger set sizes. Further, the Sternberg task allows for the measurement of task preparation processes between S1 and S2 with the CNV. Kamijo et al. (2010) conducted the Sternberg task under differential instructions to respond as accurately as possible or as quickly as possible to manipulate cognitive control demands, because greater allocation of resources is needed during task preparation processes requiring a speeded response (Falkenstein et al. 2003). Kamijo et al. (2010) reported significantly smaller frontal tCNV amplitude for higher aerobically fit compared to lower aerobically fit participants during the speed instruction, while no such relationship was observed during the accuracy instruction. From these findings it was proposed that higher aerobically fit individuals might maintain a more constant level of cognitive control irrespective of the task instructions, resulting in more efficient cognitive preparation (i.e., smaller frontal tCNV) during the speed condition compared to lower aerobically fit individuals (Kamijo et al. 2010). Thus, the CNV findings support a positive relation of chronic physical activity to working memory. Given that preliminary evidence suggests that preadolescent children may derive similar benefits to working memory as a result of increased aerobic fitness (Kamijo et al. 2011), it would appear that chronic physical activity may be positively associated with working memory irrespective of age.

18.4.4 Action Monitoring

Action monitoring is another important aspect of cognitive control. That is, to orchestrate goal-directed behaviors, individuals must monitor and correct response errors during environmental interaction for the maintenance and adaptation of successful task performance. Several studies have employed the ERN to examine the relation of chronic physical activity and aerobic fitness to action monitoring.

Initially, two studies indicated that greater amounts of chronic physical activity participation (Themanson et al. 2006) and aerobic fitness (Themanson and Hillman 2006) were associated with smaller ERN amplitude and larger post-error response slowing in young and older adults under speeded task instructions. This relationship has subsequently been observed in preadolescent children, with higher aerobically fit children exhibiting smaller ERN amplitude and greater post-error response accuracy compared to lower aerobically fit children (Hillman et al. 2009a; Pontifex et al. 2011). Based on the conflict monitoring theory (Botvinick et al. 2001; Carter and van Veen 2007), the ACC, which is a neural generator of the ERN (Carter et al. 1998; Dehaene et al. 1994; Miltner et al. 2003; van Veen and Carter 2002), monitors response conflict and signals the dorsolateral prefrontal cortex to upregulate cognitive control in support of subsequent environmental interaction. As such, longer RT and greater accuracy on trials following errors are believed to reflect the upregulation of cognitive control via the adoption of a more conservative response set. Thus, smaller ERN amplitude for higher physically active and aerobically fit individuals may reflect a reduction in conflict or a lower threshold in which to begin the cascade of processes required for the upregulation of cognitive control (Hillman et al. 2009a; Pontifex et al. 2011; Themanson and Hillman 2006; Themanson et al. 2006).

Although it would appear that this interpretation is convenient on the surface, a functional magnetic resonance imaging (fMRI) study is consonant with the reduced ERN findings in higher aerobically fit individuals. Colcombe et al. (2004) investigated the relationship between aerobic fitness and brain activity using fMRI using both a cross-sectional assessment and a randomized clinical trial. They showed that higher-fit and aerobically trained older adults exhibited less activation in the ACC, along with greater activation of task-related prefrontal and parietal brain regions during a flanker task. In addition, higher-fit/aerobically trained participants performed better on the flanker task compared to the lower-fit/nonaerobic control older adults (Colcombe et al. 2004). These results imply that higher aerobically fit, relative to lower aerobically fit, individuals may interact within the stimulus environment using a strategy that is either less dependent on action monitoring or requiring less activation (i.e., reduced ACC activation) to upregulate cognitive control (i.e., increased prefrontal activation) for subsequent behavioral adaptation. Based on these data, it is plausible that the decreased ERN amplitude, which has been localized to the dorsal ACC, may reflect the same differences in cognitive strategy between higher-active/higher-fit individuals and their less active/fit counterparts (Hillman et al. 2009a; Pontifex et al. 2011; Themanson and Hillman 2006; Themanson et al. 2006). Collectively, greater levels of physical activity and higher amounts of aerobic fitness may be associated with increased cognitive control, resulting in a lower threshold for detection and signaling of conflict (decreased ERN) and greater response slowing to preserve response accuracy on subsequent trials. Thus, these ERN studies suggest that physical activity has a positive relation with the efficiency of the action monitoring system across the life span and support the positive relation of physical activity and aerobic fitness to cognitive control.

18.4.5 Cognitive Flexibility

It is well established that ERN amplitude is increased when instructions stress response accuracy over response speed, which is thought to reflect the increased salience of the error (Gehring et al. 1993) or increased attentional focus due to the emphasis placed upon correct action (Yeung et al. 2004). That is, it would appear that the instruction to respond as accurately as possible requires greater regulation of cognitive control relative to the speed instruction during action monitoring processes. Themanson et al. (2008) examined the relationship between aerobic fitness and ERN in young adults with manipulation of task instructions (i.e., accuracy vs. speed instructions). Results showed that greater aerobic fitness was associated with larger ERN amplitude and greater post-error accuracy under the accuracy instruction, whereas no such association was observed under the speed instruction (Themanson et al. 2008). Interestingly, fitness was positively associated with greater modulation of ERN amplitude and post-error accuracy across the task instruction conditions (i.e., accuracy—speed condition; Themanson et al. 2008). These results suggest that greater aerobic fitness may be associated with increased cognitive flexibility of action monitoring during tasks requiring variable cognitive demands.

Pontifex et al. (2011) extended the findings of aerobic fitness to cognitive flexibility in preadolescent children through manipulation of stimulus–response compatibility using a modified flanker task. Specifically, in the compatible stimulus–response condition, participants were required to press a button consonant with the direction of the centrally presented target arrow, whereas in the incompatible stimulus–response condition, participants pressed a button that opposed the direction of the central target arrow. Prior research indicates that the incompatible, relative to the compatible, condition requires greater flexibility in the modulation of cognitive control (Friedman et al. 2009). Pontifex et al. (2011) found that higher aerobically fit children could preserve response accuracy across the compatibility conditions, whereas lower aerobically fit children exhibited decreased response accuracy for the incompatible compared to compatible condition. In addition, higher aerobically fit children exhibited larger P3 amplitude for the incompatible compared to the compatible condition, while no such a difference was observed for lower aerobically fit children, who exhibited overall smaller P3 responses (Pontifex et al. 2011).

Furthermore, higher aerobically fit children exhibited greater modulation of ERN amplitude based on the compatibility conditions, in a manner similar to prior research in adults (Themanson et al. 2008). Specifically, higher aerobically fit children had smaller ERN amplitude compared to lower aerobically fit children, suggesting a decrease in response conflict during environmental interaction. However, when manipulation of stimulus–response compatibility was considered, the fitness–ERN relationship was observed for the compatible, but not the incompatible, condition. That is, higher aerobically fit children had reduced ERN amplitude in the compatible condition relative to their lower aerobically fit peers, replicating prior findings in children (Hillman et al. 2009a) and adults (Themanson et al. 2006). However, during the incompatible condition, which requires greater amounts of

cognitive control, higher aerobically fit children had a significantly greater ERN potential that did not differ from lower aerobically fit participants, but differed significantly from the ERN response that they exhibited during the compatible condition. This pattern of results suggests that higher aerobically fit children have a greater capacity to flexibly modulate action monitoring processes based on cognitive control demands to optimize behavioral interactions within the task environment. The modulation of ERN across conditions with greater amounts of fitness is also consistent with the above-mentioned P3 amplitude findings (Pontifex et al. 2011). These findings imply that higher aerobically fit children may recruit more attentional resources during stimulus engagement and upregulate action monitoring processes to preserve response accuracy for the task condition requiring greater amounts of cognitive control (i.e., incompatible condition). Alternatively, lower aerobically fit children might not be able to modulate stimulus engagement and action monitoring processes based on cognitive control requirements, which may result in lower response accuracy for the incompatible condition. Taken together, these ERP studies (Pontifex et al. 2011; Themanson et al. 2008) suggest that fitness is positively associated with a greater capability to flexibly modulate cognitive control during stimulus engagement and action monitoring processes in adults and children.

Other research has pursued more traditional means of examining cognitive flexibility as a function of physical activity and fitness. That is, cognitive flexibility requirements have often been manipulated using task-switching paradigms, which require individuals to attend to stimuli in their environment, inhibit response tendencies, hold multiple rule sets in the contents of their working memory, and flexibily execute responses based on the various rule sets. A typical task-switching paradigm consists of homogeneous and heterogeneous task conditions. The homogeneous condition includes a single rule set (i.e., AAAAAA… or BBBBBB…) and requires individuals to make a response based on the stimuli presented. The heterogeneous condition consists of two or more tasks (i.e., multiple rule sets), and requires the individual to flexibly switch between task rules across individual trials (e.g., ABABAB… or AABBAA…). The heterogeneous condition results in longer RT and decreased accuracy compared to the homogeneous condition. The RT difference between homogeneous and heterogeneous conditions has been labeled the "global switch costs" (Bojko et al. 2004; Rogers and Monsell 1995), which is believed to reflect the demands of maintaining two or more rule sets active in working memory (Kray and Lindenberger 2000; Rogers and Monsell 1995).

Hillman et al. (2006) examined the relation of physical activity to working memory and mental flexibility using a task-switching paradigm in both young and older physically active and sedentary adults. Their results indicated that chronically active individuals had shorter P3 latency compared to sedentary individuals for the heterogeneous condition, but not for the homogeneous condition, across age groups. In other words, the relationship between chronic physical activity and cognitive processing speed was only observed for the task condition requiring greater working memory demands and mental flexibility. This finding suggests that physical activity is positively associated with the cognitive control of working memory during mental flexibility tasks. Further,

Kamijo and Takeda (2010) indicated that chronic physically active young adults had smaller global switch costs compared to sedentary young adults. In addition, sedentary participants exhibited smaller P3 amplitude for the heterogeneous condition relative to the homogeneous condition, whereas such a difference in P3 amplitude was not observed for active individuals (Kamijo and Takeda 2010). Based on these findings, active individuals may be able to maintain attentional resources toward a stimulus during task conditions requiring variable working memory demands (i.e., the maintenance of working memory during the heterogeneous condition), which in turn may underlie the production of a smaller global switch cost.

Finally, it should be noted that other researchers have not observed the positive relation of aerobic fitness to cognitive performance using a task-switching paradigm (Scisco et al. 2008). One possible explanation for this discrepancy relates to differences in task difficulty among these ERP studies. That is, Hillman et al. (2006) used two tasks involving single digit numbers (digits 1–9, excluding 5), in which participants were asked to discern whether the number was greater or lesser than 5 (low/high task), or whether the number was odd or even (odd/even task). Alternatively, Scisco et al. (2008) used four tasks involving double digit numbers (digits 11–99), in which participants were required to judge whether numbers were greater or lesser than 50, whether the numbers were odd or even, whether the sum of two digits was greater or lesser than 10, or whether the sum of the two digits was odd or even. Obviously, task-switching paradigms including four tasks (Scisco et al. 2008) are more difficult compared to those involving only two tasks (Hillman et al. 2006), and as such there may be limits to working memory capacity and the ability to inhibit specific rule sets in favor of executing others, beyond which physical activity cannot influence cognitive performance.

Kamijo and Takeda (2010) analyzed the greater/lesser than task and odd/even tasks separately during the above-mentioned task-switching paradigm with two tasks, because task difficulty differed between the two tasks, as the greater/lesser than task exhibited shorter RT and greater accuracy (i.e., easier) compared to the odd/even task. Further, they found a selective relation of chronic physical activity to RT and P3 amplitude as a function of cognitive control demands only for the greater/lesser than task (Kamijo and Takeda 2010). From these findings, and coupled with the well-established findings that the P3 component is sensitive for task difficulty (McCarthy and Donchin 1981; Polich 1987; Pontifex et al. 2009a, b), it is plausible that task difficulty may interact with the relationship between chronic physical activity and neurocognitive performance during tasks requiring mental flexibility. Accordingly, the null relationship between aerobic fitness and cognitive performance in Scisco et al. (2008) may be due to the difficulty of their task-switching paradigm. Thus, the relation of chronic physical activity to task difficulty should be explored further to better elucidate the cognitive health benefits to mental flexibility.

18.4.6 Summary

Previous ERP studies reviewed herein used various types of cognitive tasks to explore the general and selective relationship between chronic physical activity and

cognitive function based on the manipulation of cognitive control requirements. Overall, it would appear that greater participation in physical activity and higher amounts of aerobic fitness are associated with overall superior cognitive function. However, this overall positive relation appears selectively and disproportionately larger for tasks or task components requiring greater amounts of cognitive control. Lastly, although the dataset comprising the relation of physical activity/aerobic fitness to cognitive control is not extensive, the ERP studies reviewed herein have been, for the most part, consonant in suggesting a positive relation with the various aspects of cognitive control irrespective of age.

18.5 The Acute Effects of Single Bouts of Physical Activity on ERPs

Given the apparent link between chronic physical activity and cognition discussed above, a growing body of research has been focused on elucidating how a single acute bout of physical activity may serve to modulate cognitive processes. However, an important distinction must be made with regard to acute exercise investigations, which separate the time during which cognition is assessed. That is, to better understand the influence of a single acute bout of physical activity on cognition one must separate those investigations, which have assessed cognition *during* physical activity from those that have assessed cognition *following* physical activity participation.

18.5.1 Neuroelectric Changes in Cognition Following a Single Acute Bout of Physical Activity

Within the small body of research that has investigated the transient after-effects of a single acute bout of physical activity in adults, findings suggest a beneficial influence on a variety of cognitive functions (Brisswalter et al. 2002; Lambourne and Tomporowski 2010; Tomporowski 2003b), with a disproportionately larger benefit for tasks or task components requiring greater cognitive control demands (Hillman et al. 2003, 2009b; Pontifex et al. 2009a). These findings are consonant with previous research into the effects of acute exercise on cognition in children, with improvements in cognition observed for both simple and choice RT tasks (Ellemberg and St-Louis-Deschênes 2010), aspects of concentration (Caterino and Polack 1999; Mahar et al. 2006; McNaughten and Gabbard 1993), mathematics (Gabbard, and Barton 1979), brief tests of academic achievement (Hillman et al. 2009b), and inhibitory control (Hillman et al. 2009b) following participation in single acute bouts of structured physical activities lasting at least 20 min. However, to date, only a handful of previous investigations have examined the aftereffects of a single acute bout of aerobic exercise on neuroelectric indices of cognition.

18.5.2 Stimulus Discrimination

At first glance, investigations that have assessed the influence of single acute bouts of exercise on stimulus discrimination processes using oddball tasks appear to demonstrate conflicting findings. However, a clearer picture emerges when these findings are considered relative to the intensity of the aerobic exercise bout. Specifically, Kamijo et al. (2004) examined the extent to which the relative intensity of a single acute bout of exercise might differentially influence the P3 component in a sample of college-aged young adults performing a Go task (similar to an oddball task). Findings from this investigation revealed an increase in P3 amplitude only following an acute bout of moderate intensity aerobic exercise, while very light and very high intensity acute exercise did not modulate P3 amplitude (Kamijo et al. 2004). Similarly, Nakamura and colleagues (1999) observed increased P3 amplitude in response to an auditory oddball task following a 30 min acute bout of moderately intense exercise relative to baseline. However, investigations that have assessed the influence of high intensity and maximal intensity aerobic exercise on stimulus discrimination have largely observed no acute exercise-induced modulations of P3 amplitude (Duzova et al. 2005; Yagi et al. 1999), save for one noted exception (Magnié et al. 2000). That is, Magnié et al. (2000) examined a sample of college-aged young adults at rest and following a maximal graded exercise test on a cycle ergometer in response to an auditory oddball task. Findings from this investigation revealed larger P3 amplitude and shorter P3 latency following a single acute bout of maximal exercise, in contrast to the findings of Duzova et al. 2005. It is unclear why these investigations demonstrated conflicting findings; however, given the limited body of research to date, future research will further elucidate the relationship of acute exercise intensity and stimulus discrimination. Despite the lack of consensus for high intensity exercise, the extant literature on single acute bouts of physical activity and stimulus discrimination indicates that moderate intensity exercise is beneficial to neuroelectric indices reflecting the allocation of attentional resources in the service of stimulus discrimination.

18.5.3 Inhibition

Of any cognitive process, inhibition has been the most studied in the acute exercise literature (e.g., Hillman et al. 2003, 2009b; Kamijo et al. 2004, 2007, 2009) and relates to the ability to act on the basis of choice rather than impulse (Davidson et al. 2006). The first investigation of the influence of acute exercise on neuroelectric indices of inhibition was conducted by Hillman et al. (2003), who assessed inhibitory control using a modified flanker task at rest and following a 30 min bout of aerobic exercise at an intensity of 80–85% of maximum heart rate in a sample of 20 college-aged young adults. Findings revealed that following exercise, participants exhibited an increased allocation of attentional resources as indexed by larger P3

amplitude. Further, reduced interference was found for the task condition requiring greater amounts of cognitive control, as indexed by nonsignificant differences in P3 latency across the neutral and incongruent trials following exercise. This effect was not observed during rest, as the incongruent condition elicited longer P3 latency relative to the neutral condition. Accordingly, these findings were the first to demonstrate that single bouts of aerobic exercise had acute and transient effects on neuroelectric processes underlying inhibitory control through an increase in the allocation of neuroelectric resources and alterations in cognitive processing and stimulus classification speed (Hillman et al. 2003).

Building from this investigation Kamijo et al. (2007) assessed the extent to which the relative intensity of an acute aerobic exercise bout modulated these neuroelectric processes underlying inhibitory control. Specifically, Kamijo et al. (2007) examined neuroelectric changes in response to a modified flanker task in a sample of 12 college-aged young adults during a resting baseline session, and following light (at an rating of perceived exertion [RPE] of 11), moderate (at an RPE of 13), and hard (at an RPE of 15) cycling. Although no behavioral differences were observed, findings from this investigation revealed increased P3 amplitude following light and moderate aerobic exercise with no changes following hard exercise relative to the resting baseline condition (Kamijo et al. 2007). Further, replicating Hillman et al. (2003), Kamijo et al. (2007) observed selectively shorter P3 latencies for incongruent trials across light, moderate, and hard exercise conditions.

Additional support for the beneficial effects of acute exercise on neurocognitive processes has been garnered from other research employing a different inhibitory control task. Specifically, Kamijo et al. (2004) examined the influence of a single bout of aerobic exercise on the P3 component in college-aged young adults in response to a NoGo task following very light, moderate, and very hard exercise intensities. Findings revealed that larger P3 amplitude was observed for the NoGo condition, which requires aspects of response inhibition, following an acute bout of moderate intensity aerobic exercise, an effect that was not observed following very light or very hard intensity exercise. Accordingly, these findings (Hillman et al. 2003; Kamijo et al. 2004, 2007) indicate that in college-aged young adults, an increase in the allocation of attentional resources (i.e., larger P3 amplitude) occurs following single bouts of light to moderate intensity aerobic exercise, while facilitations of cognitive processing and stimulus classification speed occur following aerobic exercise of any intensity.

To date only two investigations have assessed neuroelectric indices of cognition in response to inhibitory control tasks in participant populations other than college-aged young adults. Kamijo et al. (2009) assessed the influence of acute aerobic exercise on cognition in a sample of 12 older adults relative to 12 college-aged young adults. Participants completed the modified flanker task at rest and again following 20 min of light exercise at an intensity of 55% of heart rate max, and moderate exercise at an intensity of 74% of heart rate max. Findings from this investigation replicated findings from Hillman et al. (2003) and Kamijo et al. (2007) with increased P3 amplitude following moderately intense exercise in young adults, while no such effect was observed for older adults. Interestingly,

regardless of age and exercise intensity shorter P3 latency was observed following exercise relative to rest. Accordingly, these findings suggest that mechanisms underlying the effects of acute exercise on the allocation of attentional resources may be age-dependent, while cognitive processing speed is enhanced by short duration exercise regardless of age.

Although the majority of research on acute exercise and cognition has focused on adult populations, a more recent focus has been on pediatric populations. Reviews of early behavioral studies testing this relationship suggest that school age children also may derive cognitive benefits from physical activity participation (Sibley and Etnier 2003; Tomporowski 2003a). Accordingly, Hillman et al. (2009b) assessed the extent to which improvements in cognition following a single acute bout of moderate intensity aerobic exercise effect both basic (i.e., laboratory tests) and applied (i.e., scholastic performance) aspects of cognition in preadolescent children. Findings from this investigation revealed that following a single 20 min bout of moderately intense treadmill walking, relative to seated rest, children exhibited improved response accuracy to a modified flanker task, had selectively larger P3 amplitudes only for incongruent trials, and performed better on the reading subtest of the Wide Range Achievement Test—3rd edition (Hillman et al. 2009b). Collectively, these findings indicate a positive effect of single acute bouts of aerobic exercise on inhibitory aspects of cognitive control, which appear to relate to facilitations in attentional resource allocation in an age- and exercise-dependent manner, while cognitive processing and stimulus classification speed appears to more generally be influenced. Lastly, although evidence is sparse, preliminary results suggest that single acute bouts of exercise may serve to benefit scholastic performance, and thus may be an important consideration for educational practices.

18.5.4 Action Monitoring

Although the majority of previous investigations on acute exercise and neuroelectric indices of cognitive control have focused on the stimulus-locked P3 component, only a single study has investigated the effect of acute exercise on response-locked action monitoring processes as indexed by the ERN component. Themanson and Hillman (2006) examined action monitoring processes in response to a flanker task in a sample of college-aged young adults. Findings revealed no relationship between 30 min of moderate intensity aerobic exercise and neuroelectric indices of action monitoring (Themanson and Hillman 2006). Thus, these findings suggest that acute exercise-induced changes in neuroelectric processes underlying cognitive control are selective to the allocation of attentional resources and appear to be unrelated to action monitoring processes. It is important to note, however, that this investigation only assessed college-aged young adults who collectively were performing the flanker task at an accuracy level above 90%, which allowed for a relatively small number of error trials in which to observe modulation of the ERN. Thus, further research is necessary to better understand the effects of single acute bouts of exercise on action monitoring

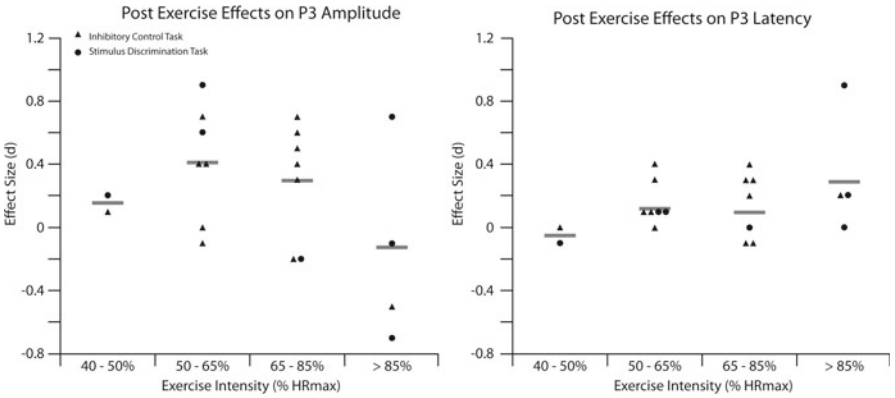

Fig. 18.4 Characterization of the influence of relative exercise intensity on P3 amplitude (*left*) and latency (*right*) following participation in a single bout of short duration aerobic physical activity. Points indicate individual effect sizes by cognitive task; bars indicate mean effect size for each exercise intensity range

processes under conditions allowing a greater number of errors to achieve a more robust index of the neuroelectric indices underlying action monitoring.

18.5.5 Summary

Collectively, findings from these investigations have suggested that a 20–30 min bout of aerobic exercise generally serves to increase the allocation of attentional resources (as indexed by larger amplitude of the P3 component), and facilitates cognitive processing and stimulus classification speed (as indexed by shorter latency of the P3 component) across a number of cognitive tasks. Further, as illustrated in Fig. 18.4, these exercise-induced enhancements in cognition appear to relate to the relative exercise intensity (in a curvilinear fashion). Based on visual inspection of the studies described herein (see Fig. 18.4), the greatest enhancements in the amplitude of the P3 component appear following exercise at an intensity between 50 and 65% of maximal heart rate; however, clear exceptions to this rule exist (see Hillman et al. 2003). Although it should be noted that this optimal intensity may be task dependent with more cognitively demanding workloads requiring more strenuous exercise intensity. Alternatively, enhancements in the latency of the P3 component appear to relate linearly to the intensity of the exercise bout.

18.5.6 Neuroelectric Changes in Cognition During a Single Acute Bout of Physical Activity

Although the research discussed previously has highlighted the beneficial effects of both chronic and acute physical activity participation on neuroelectric and behavioral

indices of performance, it is important to note that a growing body of research suggests that transient decrements in cognition may occur during acute physical activity participation. Specifically, during moderately intense aerobic exercise, behavioral assessments have observed an impairment in perception (Paas and Adam 1991) and cognitive control (Dietrich and Sparling 2004). Alternatively, other researchers have observed a facilitation in performance on tasks of decision making (Arcelin et al. 1998; Davranche and Audiffren 2004; Paas and Adam 1991) and response conflict (Davranche and McMorris 2009). The application of neuroimaging techniques may provide additional insight into these conflicting results; however to date, relatively few investigations have assessed changes in the cognitive processes underlying these behavioral changes in performance during acute exercise. This, in part, may be due to the additional noise (artifact) that is associated with the gross motor movement inherent in physical activity behaviors. Recent technological advancements using "dry" electrodes and careful methodological techniques (see Pontifex and Hillman 2008 for further discussion), however, will allow future researchers greater access to apply these neuroimaging methods to assess changes in cognition during exercise. Thus far, only two investigations have assessed changes in neuroelectric indices of cognition during short duration aerobic exercise. Although both of these investigations have assessed the P3 component, they each assessed a different aspect of cognition.

18.5.7 Stimulus Discrimination

Yagi et al. (1999) assessed how stimulus discrimination processes may be modulated during 10 min of aerobic exercise at a workload equivalent of 65–75% of age-predicted maximum heart rate in a sample of 24 college-aged young adults. To reduce the potential influence of the gross motor movement of exercise, participants exercise on a recumbent cycle ergometer while completing auditory (1,000 Hz nontarget tone and 2,000 Hz target tone) and visual (white "X" nontarget stimulus, white "O" target stimulus) oddball tasks. Findings from this investigation revealed that during exercise, participants exhibited smaller P3 amplitude and shorter P3 latency for both the auditory and visual oddball tasks, relative to pre-exercise measures (Yagi et al. 1999). Although some methodological confounds exist with regard to potential practice effects, these findings suggest that the capacity to allocate attentional resources may be reduced during aerobic exercise, but the processing of environmental information may be facilitated.

18.5.8 Inhibition

Pontifex and Hillman (2007) assessed the influence of moderately intense aerobic exercise on inhibitory control using a modified flanker task (Eriksen and Eriksen

1974) in a sample of 41 college-aged young adults. Participants completed counterbalanced conditions of rest and 6.5 min of steady-state exercise on a cycle ergometer at 60% of their maximum heart rate. Findings from this investigation revealed an increase in P3 amplitude over bilateral frontal electrode sites as well as a global increase in P3 latency during exercise relative to rest. Further, Pontifex and Hillman (2007) assessed the influence of aerobic exercise on earlier ERP components. Specifically, the N1, P2, and N2 components were assessed, which relate to aspects of visual discrimination (Luck 1995; Vogel and Luck 2000), selective attention (Talsma and Kok 2001), and response inhibition (Ridderinkhof et al. 2002), respectively. During exercise, Pontifex and Hillman (2007) observed a parietal reduction in N1 amplitude, increased fronto-central P2 amplitude, and global reductions in N2 amplitude, relative to seated rest. Accordingly, these findings suggest that during aerobic exercise participants experienced a decreased ability to visually discriminate stimuli (N1 amplitude), which requires an increase in selective attention (P2 amplitude), and results in reductions in response conflict (N2 amplitude). These earlier neural inefficiencies thus necessitate a greater allocation of attentional resources toward stimulus engagement (P3 amplitude) and further relate to delays in stimulus evaluation and classification speed (P3 latency). As an extension of these deficits in stimulus acquisition and cognitive processing, participants exhibited behavioral deficits during exercise in response to the incongruent trials, which place greater demands on inhibitory control. Together, these data suggest that the neural inefficiencies that occur during exercise may only manifest as behavioral deficits when the cognitive load is high, with lower cognitive loads seemingly unaffected when measured via overt indices of task performance.

18.5.9 Summary

Given the small and disparate body of literature to date, which has examined modulations in neuroelectric indices of cognition that occur during exercise, it is difficult to make broad generalizations. However, these findings do provide preliminary evidence to suggest that the neural networks underlying aspects of cognition may be differentially influenced during physical activity participation. Thus, future investigations assessing this relationship must be particularly cognizant of the nature of the task to be utilized.

18.6 Future Directions

With few exceptions (Dustman et al. 1990; Polich and Lardon 1997), the vast majority of research on the relation of both chronic and acute exercise to neuroelectric indices of cognition has occurred during the last decade. As such, this field is in its infancy, and there are a number of directions that warrant future consideration.

For instance, considerable investigation has pursued stimulus discrimination and inhibitory aspects of cognition, with only a sparse few studies examining other types of cognition. Memory processes are especially poorly understood at this time. Despite several strong early attempts to better understand the relation of exercise to memory, a programmatic approach to this area is needed. Similar arguments can be made for aspects of attention and cognitive control as well. As this area continues to build, the examination of the different ERP components is necessary to better determine which aspects of cognition are selectively influenced by exercise.

Of equal importance, all prior ERP research examining chronic exercise has employed cross-sectional designs. Although the cross-sectional evidence reported herein has, for the most part, been consonant in its findings, future research must employ more rigorous study designs to more definitively determine the causal effects of chronic exercise on neuroelectric indices of cognition. Recent research in the Neurocognitive Kinesiology Laboratory at the University of Illinois has pursued this question in preadolescent children. The Fitness Improves Thinking in Kids (FITKids) trial began in 2007 and remains ongoing at the time of this chapter. However, preliminary data from the first 120+ participants suggest that daily participation in moderate to vigorous physical activity relates to larger P3 amplitude and shorter P3 latency across a number of cognitive tasks that tap attention, inhibition, and stimulus discrimination. Clearly, other randomized control trials are needed to expound the exercise and cognition database to provide a clear and more definitive understanding of the benefits of exercise to brain health and cognition.

Relative to the acute, transient effects of exercise on cognition, more research is, quite simply, necessary. A review of the available literature on this topic has evidenced conflicting results, but also a number of methodological shortcomings, which limit our understanding not only of the transient effects of acute exercise on cognition, but also of the basis for the conflicting findings. Further, future research needs to programmatically examine exercise mode, intensity, and duration to determine the nature of the "dose–response" relationship between single bouts of exercise and cognition. Along these same lines, programmatic study of the enduring effects of exercise on cognition is needed. Based on a cursory examination of the duration of the effects observed stemming from a single acute bout of exercise, it appears that alterations in cognitive function last approximately one hour from the cessation of the acute exercise bout (Hillman et al. 2003, 2009b). More definitive exploration of the nature and timing of these cognitive changes are sorely needed, as they may have a direct application to cognitive performance in schools and the workplace.

Finally, future exercise-ERP research should begin to bridge basic laboratory science with "real-world" settings in which exercise and cognitive performance occur. That is, ERPs reflect externally valid cognitive operations, and simply understanding the nature of the relationship between exercise and ERPs falls short of understanding how exercise may influence cognition during daily life. Determining the relationship between exercise, ERPs, and cognition in daily life may serve to better inform scientists on the selective aspects of cognition that are affected by exercise and increase the cognitive health and effective functioning of individuals as they progress through the lifespan.

18.7 Conclusions

In summary, the body of research described herein details the relation of chronic and acute exercise participation on neuroelectric indices of brain health and cognition. A growing body of research amassed over the last decade has suggested that chronic participation in physical activity and higher amounts of aerobic fitness are related to better cognitive performance across a variety of cognitive tasks, with disproportionately larger benefits observed for tasks necessitating greater amounts of cognitive control. Similarly, single bouts of acute exercise also positively affect cognition and its neuroelectric underpinnings, with superior performance noted during the time following the cessation of exercise. However, a very small body of research suggests that similar benefits are not accrued for attentional tasks during the exercise bout. Accordingly, future research is warranted to not only detail the aspects of exercise and cognition that lead to positive health outcomes, but also the limitations of this relationship. Regardless, ERPs have provided a unique tool for understanding the select aspects of cognition, which occur between stimulus engagement and response production that are altered by exercise. The overall goal of this body of research is to maximize brain health and cognition, leading to increased effective functioning of individuals during their daily lives.

References

Arcelin R, Delignieres D, Brisswalter J (1998) Selective effects of physical exercise on choice reaction processes. Percept Mot Skills 87:175–185

Barkley RA (1997) Behavioral inhibition, sustained attention, and executive functions. Psychol Bull 121:65–94

Bojko A, Kramer AF, Peterson MS (2004) Age equivalence in switch costs for prosaccade and antisaccade tasks. Psychol Aging 19:226–234

Booth FW, Lees SJ (2006) Physically active subjects should be the control group. Med Sci Sports Exerc 38:405–406

Bortz WM II (1985) Physical exercise as an evolutionary force. J Hum Evol 14:145–155

Botvinick MM, Braver TS, Barch DM, Carter CS, Cohen JD (2001) Conflict monitoring and cognitive control. Psychol Rev 108:624–652

Brisswalter J, Collardeau M, Arcelin R (2002) Effects of acute physical exercise on cognitive performance. Sports Med 32:555–566

Brunia CH, van Boxtel GJ (2001) Wait and see. Int J Psychophysiol 43:59–75

Bunge SA, Crone EA (2009) Neural correlates of the development of cognitive control. In: Rumsey JM, Ernst M (eds) Neuroimaging in developmental clinical neuroscience. Cambridge University Press, New York, NY

Carrier DR (1984) The energetic paradox of human running and hominid evolution. Curr Anthropol 25:483–495

Carter CS, Braver TS, Barch DM, Botvinick MM, Noll D, Cohen JD (1998) Anterior cingulated cortex, error detection, and the online monitoring of performance. Science 280:747–749

Carter CS, van Veen V (2007) Anterior cingulate cortex and conflict detection: an update of theory and data. Cogn Affect Behav Neurosci 7:367–379

Caterino MC, Polack ED (1999) Effects of two types of activity on the performance of second-, third-, and fourth-grade students on a test of concentration. Percept Mot Skills 89:245–248

Center for Disease Control and Prevention (2008) Prevalence of self-reported physically active adults – United States, 2007. MMWR Morb Mortal Wkly Rep 57:1297–1300
Colcombe SJ, Kramer AF (2003) Fitness effects on the cognitive function of older adults: a meta-analytic study. Psychol Sci 14:125–130
Colcombe SJ, Kramer AF, Erickson KI, Scalf P, McAuley E, Cohen NJ, Webb A, Jerome GJ, Marquez DX, Elavsky S (2004) Cardiovascular fitness, cortical plasticity, and aging. Proc Natl Acad Sci USA 101:3316–3321
Coles MGH, Gratton G, Fabiani M (1990) Event-related potentials. In: Cacioppo JT, Tassinary LG (eds) Principles of psychophysiology: physical, social, and inferential elements. Cambridge University Press, New York, NY, pp 413–455
Cui RQ, Egkher A, Huter D, Lang W, Lindinger G, Deecke L (2000) High resolution spatiotemporal analysis of the contingent negative variation in simple or complex motor tasks and a non-motor task. Clin Neurophysiol 111:1847–1859
Davidson MC, Amso D, Anderson LC, Diamond A (2006) Development of cognitive control and executive functions from 4 to 13 years: evidence from manipulations of memory, inhibition, and task switching. Neuropsychologia 44:2037–2078
Davranche K, Audiffren M (2004) Facilitating effects of exercise on information processing. J Sports Sci 22:419–428
Davranche K, McMorris T (2009) Specific effects of acute moderate exercise on cognitive control. Brain Cogn 69:565–570
Dehaene S, Posner MI, Tucker DM (1994) Localization of a neural system for error detection and compensation. Psychol Sci 5:303–305
Department of Health and Human Services [DHHS] and Department of Education [DOE] (2000) Promoting better health for young people through physical activity and sports. A Report to the President from the Secretary of Health and Human Services and the Secretary of Education. Centers for Disease Control, Silver Spring, MD
Diamond A (2006) The early development of executive functions. In: Bialystok E, Craik FIM (eds) Lifespan cognition: mechanism of change. Oxford University Press, New York, NY, pp 70–95
Dietrich A, Sparling PB (2004) Endurance exercise selectively impairs prefrontal-dependent cognition. Brain Cogn 55:516–524
Donchin E (1981) Surprise!…Surprise? Psychophysiology 18:493–513
Dustman RE, Emmerson RY, Ruhling RO, Shearer DE, Steinhaus LA, Johnson SC, Bonekat HW, Shigeoka JW (1990) Age and fitness effects on EEG, ERPs, visual sensitivity, and cognition. Neurobiol Aging 11:193–200
Duzova H, Özi ik HI, Polat A, Emre MH, Gullu E (2005) Correlations between event-related potential components and nitric oxide in maximal anaerobic exercise among sportsmen trained at various levels. Int J Neurosci 115:1353–1373
Ebmeier KP, Steele JD, MacKenzie DM, O'Carroll RE, Kydd RR et al (1995) Cognitive brain potentials and regional cerebral blood flow equivalents during two- and three-sound auditory "oddball tasks". Clin Neurophysiol 95:434–443
Ellemberg D, St-Louis-Deschênes M (2010) The effect of acute physical exercise on cognitive function during development. Psychol Sport Exerc 11:122–126
Emmerson RY, Dustman RE, Shearer DE, Turner CW (1989) P3 latency and symbol digit performance correlations in aging. Exp Aging Res 15:151–159
Eriksen CW, Eriksen BA (1974) Effects of noise letters upon the identification of a target letter in a non-search task. Percept Psychophys 16:143–149
Falkenstein M, Hohnsbein J, Hoormann J, Blanke L (1991) Effects of crossmodal divided attention on late ERP components: II. Error processing in choice reaction tasks. Clin Neurophysiol 78:447–455
Falkenstein M, Hoormann J, Hohnsbein J, Kleinsorge T (2003) Short-term mobilization of processing resources is revealed in the event-related potential. Psychophysiology 40:914–923
Fialkowski KR (1986) A mechanism for the origin of the human brain: a hypothesis. Curr Anthropol 27:288–290
Fontaine KR, Redden DT, Wang C, Westfall AO, Allison DB (2003) Years of life lost due to obesity. J Am Med Assoc 289:187–193

Friedman D, Nessler D, Cycowicz YM, Horton C (2009) Development of and change in cognitive control: a comparison of children, young adults, and older adults. Cogn Affect Behav Neurosci 9:91–102
Gabbard C, Barton J (1979) Effects of physical activity on mathematical computation among young children. J Psychol 103:287–288
Gehring WJ, Goss B, Coles MGH, Meyer DE, Donchin E (1993) A neural system for error detection and compensation. Psychol Sci 4:385–390
Gehring WJ, Knight RT (2000) Prefrontal-cingulate interactions in action monitoring. Nat Neurosci 3:516–520
Gómez CM, Marco J, Grau C (2003) Preparatory visuo-motor cortical network of the contingent negative variation estimated by current density. Neuroimage 20:216–224
Hamano T, Luders HO, Ikeda A, Collura TF, Comair YG, Shibasaki H (1997) The cortical generators of the contingent negative variation in humans: a study with subdural electrodes. Electroencephalogr Clin Neurophysiol 104:257–268
Haskell WL, Lee IM, Pate RR, Powell KE, Blair SN, Franklin BA, Macera CA, Heath GW, Thompson PD, Bauman A (2007) Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. Med Sci Sports Exerc 39:1423–1434
Hillman CH, Belopolsky AV, Snook EM, Kramer AF, McAuley E (2004) Physical activity and executive control: implications for increased cognitive health during older adulthood. Res Q Exerc Sport 75:176–185
Hillman CH, Buck SM, Themanson JT, Pontifex MB, Castelli DM (2009a) Aerobic fitness and cognitive development: event-related brain potential and task performance indices of executive control in preadolescent children. Dev Psychol 45:114–129
Hillman CH, Castelli DM, Buck SM (2005) Aerobic fitness and neurocognitive function in healthy preadolescent children. Med Sci Sports Exerc 37:1967–1974
Hillman CH, Erickson KI, Kramer AF (2008) Be smart, exercise your heart: exercise effects on brain and cognition. Nat Rev Neurosci 9:58–65
Hillman CH, Kramer AF, Belopolsky AV, Smith DP (2006) A cross-sectional examination of age and physical activity on performance and event-related brain potentials in a task switching paradigm. Int J Psychophysiol 59:30–39
Hillman CH, Pontifex MB, Raine LB, Castelli DM, Hall EE, Kramer AF (2009b) The Effect of acute treadmill walking on cognitive control and academic achievement in preadolescent children. Neuroscience 159:1044–1054
Hillman CH, Snook EM, Jerome GJ (2003) Acute cardiovascular exercise and executive control function. Int J Psychophysiol 48:307–314
Howard L, Polich J (1985) P300 latency and memory span development. Dev Psychol 21:283–289
Hruby T, Marsalek P (2003) Event-related potentials – the P3 wave. Acta Neurobiol Exp 63:55–63
Hugdahl K (1995) Psychophysiology: the mind-body perspective. Harvard University Press, Cambridge, MA
Ilan AB, Polich J (1999) P300 and response time from a manual stroop task. Clin Neurophysiol 110:367–373
Johnson R Jr, Pfefferbaum A, Kopell BS (1985) P300 and long-term memory: latency predicts recognition performance. Psychophysiology 22:497–507
Kamijo K, Hayashi Y, Sakai T, Yahiro T, Tanaka K, Nishihira Y (2009) Acute effects of aerobic exercise on cognitive function in older adults. J Gerontol 64:356–363
Kamijo K, Nishihira Y, Hatta A, Kaneda T, Wasaka T, Kida T, Kuroiwa K (2004) Differential influences of exercise intensity on information processing in the central nervous system. Eur J Appl Physiol 92:305–311
Kamijo K, Nishihira Y, Higashiura T, Kuroiwa K (2007) The interactive effect of exercise intensity and task difficulty on human cognitive processing. Int J Psychophysiol 65:114–121
Kamijo K, O'Leary KC, Pontifex MB, Themanson JR, Hillman CH (2010) The relation of aerobic fitness to neuroelectric indices of cognitive and motor task preparation. Psychophysiology 47:814–821

Kamijo K, Pontifex MB, O'Leary KC, Scudder MR, Wu CT, Castelli DM, Hillman CH (2011) The effects of an afterschool physical activity program on working memory in preadolescent children. Dev Sci 14:1046–1058

Kamijo K, Takeda Y (2009) General physical activity levels influence positive and negative priming effects in young adults. Clin Neurophysiol 120:511–519

Kamijo K, Takeda Y (2010) Regular physical activity improves executive function during task switching in young adults. Int J Psychophysiol 75:304–311

Kirino E, Belger A, Goldman-Rakic P, McCarthy G (2000) Prefrontal activation evoked by infrequent target and novel stimuli in a visual target detection task: an event-related functional magnetic resonance imaging study. J Neurosci 20:6612–6618

Kramer AF, Hahn S, Cohen NJ, Banich MT, McAuley E, Harrison CR, Chason J, Vakil E, Bardell L, Bolleau RA, Colcombe A (1999) Ageing, fitness and neurocognitive function. Nature 400:416–419

Kray J, Lindenberger U (2000) Adult age differences in task switching. Psychol Aging 15:126–147

Lambourne K, Tomporowski P (2010) The effect of exercise-induced arousal on cognitive task performance: a meta-regression analysis. Brain Res 1341:12–24

Leynes PA, Allen JD, Marsh RL (1998) Topographic differences in CNV amplitude reflect different preparatory processes. Int J Psychophysiol 31:33–44

Lorist MM, Klein M, Nieuwenhuis S, De Jong R, Mulder G, Meijman TF (2000) Mental fatigue and task control: planning and preparation. Psychophysiology 37:614–625

Loveless NE, Sanford AJ (1974) Slow potential correlates of preparatory set. Biol Psychol 1:303–314

Luck SJ (1995) Multiple mechanisms of visual-spatial attention: recent evidence from human electrophysiology. Behav Brain Res 71:113–123

Magliero A, Bashore TR, Coles MGH, Donchin E (1984) On the dependence of P300 latency on stimulus evaluation processes. Psychophysiology 21:171–186

Magnié MN, Bermon S, Martin F, Madany-Lounis M, Suisse G, Muhammad W, Dolisi C (2000) P300, N400, aerobic fitness and maximal aerobic exercise. Psychophysiology 37:369–377

Mahar MT, Murphy SK, Rowe DA, Golden J, Shields AT, Raedeke TD (2006) Effects of a classroom-based program on physical activity and on-task behavior. Med Sci Sports Exerc 38:2086–2094

McCarthy G, Donchin E (1981) A metric for thought: a comparison of P300 latency and reaction time. Science 211:77–80

McNaughten D, Gabbard C (1993) Physical exertion and the immediate mental performance of sixth-grade children. Percept Mot Skills 77:1155–1159

Meyer DE, Kieras DE (1997) A computational theory of executive cognitive processes and multitask performance: Part 1. Basic mechanisms. Psychol Rev 104:3–65

Miltner WHR, Lemke U, Weiss T, Holroyd C, Scheffers MK, Coles MGH (2003) Implementation of error-processing in the human anterior cingulated cortex: a source analysis of the magnetic equivalent of the error-related negativity. Biol Psychol 64:157–166

Miyake A, Friedman NP, Emerson MJ, Witzki AH, Howerter A (2000) The unity and diversity of executive functions and their contributions to complex "frontal lobe" tasks: a latent variable analysis. Cogn Psychol 41:49–100

Nakamura Y, Nishimoto K, Akamatu M, Takahashi M, Maruyama A (1999) The effect of jogging on the P300 event related potentials. Clin Neurophysiol 39:71–74

Nieuwenhuis S, Ridderinkhof KR, Blom J, Band GPH, Kok A (2001) Error-related brain potentials are differentially related to awareness of response errors: evidence from an antisaccade task. Psychophysiology 38:752–760

Norman DA, Shallice T (1986) Attention to action: willed and automatic control of behavior. In: Davidson RJ, Schwartz GE, Shapiro D (eds) Consciousness and self-regulation, vol 4, Advances in research and theory. Plenum, New York, NY, pp 1–18

Olshansky SJ, Passaro DJ, Hershow RC, Layden J, Carnes BA et al (2005) A potential decline in life expectancy in the United States in the 21st century. N Engl J Med 352:1138–1145

Paas FGWC, Adam JJ (1991) Human information processing during physical exercise. Ergonomics 34:1385–1397
Polich J (1987) Task difficulty, probability and inter-stimulus interval as determinants of P300 from auditory stimuli. Clin Neurophysiol 63:251–259
Polich J (2003) Overview of P3a and P3b. In: Polich J (ed) Detection of change: event-related potential and fMRI findings. Kluwer, Boston, pp 83–98
Polich J (2007) Updating P300: an integrative theory of P3a and P3b. Clin Neurophysiol 118:2128–2148
Polich J, Kok A (1995) Cognitive and biological determinants of P300: an integrative review. Biol Psychol 41:103–146
Polich J, Martin S (1992) P300, cognitive capability, and personality. Pers Individ Dif 13:533–543
Polich J, Howard L, Starr A (1983) P300 latency correlates with digit span. Psychophysiology 20:665–669
Polich J, Lardon MT (1997) P300 and long-term physical exercise. Clin Neurophysiol 103:493–498
Pontifex MB, Hillman CH (2007) Neuroelectric and behavioral indices of interference control during acute cycling. Clin Neurophysiol 118:570–580
Pontifex MB, Hillman CH (2008) Neuroelectric measurement of cognition during aerobic exercise. Methods 45:271–278
Pontifex MB, Hillman CH, Fernhall B, Thompson KM, Valentini TA (2009a) The effect of acute aerobic and resistance exercise on working memory. Med Sci Sports Exerc 41:927–934
Pontifex MB, Hillman CH, Polich JP (2009b) Age physical fitness, and attention: P3a P3b. Psychophysiology 46:379–387
Pontifex MB, Raine LB, Johnson CR, Chaddock L, VanPatter M, Voss MW et al (2011) Cardiorespiratory fitness and the flexible modulation of cognitive control in preadolescent children. J Cogn Neurosci 23:1332–1345
Ridderinkhof KR, de Vulgt Y, Bramlage A, Spaan M, Elton M, Snel J, Band GPH (2002) Alcohol consumption impairs detection of performance errors in mediofrontal cortex. Science 298:2209–2211
Rogers RD, Monsell S (1995) Costs of a predictable switch between simple cognitive tasks. J Exp Psychol 124:207–231
Scisco JL, Leynes PA, Kang J (2008) Cardiovascular fitness and executive control during task-switching: an ERP study. Int J Psychophysiol 69:52–60
Sibley BA, Etnier JL (2003) The relationship between physical activity and cognition in children: a meta-analysis. Pediatr Exerc Sci 15:243–256
Smith PJ, Blumenthal JA, Hoffman BM, Cooper H, Strauman TA, Welsh-Bohmer K, Browndyke JN, Sherwood A (2010) Aerobic exercise and neurocognitive performance: a meta-analytic review of randomized controlled trials. Psychosom Med 72:239–252
Strong WB, Malina RM, Blimke CJR, Daniels SR, Dishman RK, Gutin B, Hergenroeder AC et al (2005) Evidence based physical activity for school-age youth. J Pediatr 146:732–737
Stroth S, Kubesch S, Dieterle K, Ruchsow M, Heim R, Kiefer M (2009) Physical fitness, but not acute exercise modulates event-related potential indices for executive control in healthy adolescents. Brain Res 1269:114–124
Sutton S, Braren M, Zubin J, John ER (1965) Evoked-potential correlates of stimulus uncertainty. Science 150:1187–1188
Talsma D, Kok A (2001) Nonspatial intermodal selective attention is mediated by sensory brain areas: evidence from event-related potentials. Psychophysiology 38:736–751
Themanson JR, Hillman CH (2006) Cardiorespiratory fitness and acute aerobic exercise effects on neuroelectric and behavioral measures of action monitoring. Neuroscience 141:757–767
Themanson JR, Hillman CH, Curtin JJ (2006) Age and physical activity influences on action monitoring during task switching. Neurobiol Aging 27:1335–1345
Themanson JR, Pontifex MB, Hillman CH (2008) Fitness and action monitoring: evidence for improved cognitive flexibility in young adults. Neuroscience 157:319–328
Tipper SP, Brehaut JC, Driver J (1990) Selection of moving and static objects for the control of spatially directed action. J Exp Psychol Hum Percept Perform 16:492–504

Tomporowski PD (2003a) Cognitive and behavioral responses to acute exercise in youths: a Review. Pediatr Exerc Sci 15:348–359
Tomporowski PD (2003b) Effects of acute bouts of exercise on cognition. Acta Psychol 112:297–324
van Boxtel GJ, Brunia CH (1994) Motor and non-motor aspects of slow brain potentials. Biol Psychol 38:37–51
van Veen V, Carter CS (2002) The timing of action-monitoring processes in the anterior cingulated cortex. J Cogn Neurosci 14:593–602
Vaynman S, Gomez-Pinilla F (2006) Revenge of the "sit": how lifestyle impacts neuronal and cognitive health though molecular systems that interface energy metabolism with neuronal plasticity. J Neurosci Res 84:699–715
Verleger R (1997) On the utility of P3 latency as an index of mental chronometry. Psychophysiology 34:131–156
Vogel EK, Luck SJ (2000) The visual N1 component as an index of a discrimination process. Psychophysiology 37:190–203
Weerts TC, Lang PJ (1973) The effects of eye fixation and stimulus and response location on the contingent negative variation (CNV). Biol Psychol 1:1–19
Wild-Wall N, Hohnsbein J, Falkenstein M (2007) Effects of ageing on cognitive task preparation as reflected by event-related potentials. Clin Neurophysiol 118:558–569
Yagi Y, Coburn KL, Estes KM, Arruda JE (1999) Effects of aerobic exercise and gender on visual and auditory P300, reaction time, and accuracy. Eur J Appl Physiol 80:402–408
Yeung N, Botvinick MM, Cohen JD (2004) The neural basis of error detection: conflict monitoring and the error-related negativity. Psychol Rev 111:931–959

Chapter 19
Relationship Between Exercise and Cognitive Processing Studied by MRI in Elderly People

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Abstract This chapter provides an overview of the research on the effects of exercise, physical activity, and fitness on brain function in aged adults. The studies described in this chapter use functional magnetic resonance imaging techniques along with cognitively challenging tasks to investigate how the functioning of brain circuits changes with age and how they are moderated by exercise. The research described in this chapter suggests that age-related changes in brain function remain tractable and that exercise has the capacity to alter brain networks and improve function, even in aged adults. The results from these studies suggest that physical activity and exercise are effective methods for enhancing brain function in late adulthood and that exercise is a promising method for preventing and even treating cognitive impairment in late life.

19.1 Introduction

Developmental changes in intellectual and cognitive function roughly follow an inverted u-shaped function. Gradual improvements in complex cognition occur in childhood and early adolescence and peak during late adolescence and early adulthood. Unfortunately, cognitive function often undergoes a progressive decline after middle adulthood, sometimes becoming so severe that it leads to dementia in late life. This general u-shaped function, however, is not followed ubiquitously. That is, there is significant individual variability in both the rate of cognitive improvements in young adulthood and the rate of decline in late adulthood (Kramer and Erickson 2007). Indeed, some people age quite successfully with minimal decline in cognitive

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function, while others experience more precipitous decline. This individual variability allows us to ask some important questions. For example, we can ask what are the factors that contribute to the individual variation in the development and decline of cognition. We could also ask if there are any methods for reducing cognitive decline in late adulthood and of enhancing our prospects for retaining our memories and cognitive function throughout our lives.

These are important questions to answer from several perspectives. First, these questions address some historic themes about biological determinism versus biological potential in human psychology. Is age-related cognitive decline an inevitable consequence of aging without any hope of prevention or reversal? Or is there potential for changing the trajectory, preventing cognitive decline from occurring and even reversing impairment that is manifest? Although there is no magic bullet cure for Alzheimer's disease or dementia, recent research suggests that there might be methods to reduce the risk of developing dementia and experiencing age-related cognitive decline (Erickson et al. 2010). First, such a finding (as will be described in detail below) suggests that we have a biological potential for securing the maintenance of cognition into late life. Second, understanding the factors that contribute to individual variability in cognitive function will have profound effects on public health and policy. It is common for physicians, health-care workers, and family members to treat aged individuals as if cognitive decline were "normal" and dementia in late life is to be expected. Such stereotypes of aging lead to discriminatory behaviors and ageism in both health care and public policy. Knowing that cognitive decline in late life might not be inevitable could significantly alter the way in which age-related stereotypes are manifested and could reduce the costs and emotional unrest associated with caring for and treating individuals with cognitive impairment.

Despite significant individual variation in cognitive function, there is, on average, decreased cognitive prowess throughout adulthood (Hertzog et al. 2009). Mirroring the pattern of cognitive decline is deterioration in brain matter. Brain atrophy in late life precedes and leads to cognitive decline, yet atrophy does not occur uniformly throughout the brain. The greatest rates of atrophy occur in prefrontal and medial temporal lobe regions including entorhinal and hippocampal regions and the dorsolateral prefrontal cortex (Raz et al. 2005; Kennedy et al. 2009), while less atrophy is usually detected in visual, motor, and sensorimotor cortices (Fjell and Walhovd 2010). Cortical and subcortical atrophy in late life is accompanied by changes in brain function as assessed by functional neuroimaging tools such as functional magnetic resonance imaging (fMRI). Because of the increased rates of atrophy and shrinkage of cortical tissue, it would be reasonable to predict that older adults may exhibit attenuated patterns of brain activity; however, functional imaging studies have instead found complex modulations in activity based upon the complexity and demands of the task, the brain regions being examined, and the age of the participants (Park and Reuter-Lorenz 2009). In addition to this apparent complexity in the functional architecture of the aged brain, there is also significant individual variation in the extent and magnitude of brain activity in late adulthood with some people showing minimal differences and others showing substantial differences when compared to younger adults. Although this variation is recognized in the field, explaining

the causes for the variation has been a challenge because large sample sizes are usually required to reliably assess correlations with lifestyle or genetic factors (Hedden and Gabrieli 2004). Nonetheless, several studies have reported that variation in brain function can be explained in terms of lifestyles and genetic factors. These studies suggest that brain function remains tractable throughout the life span such that both cognitive and physical activity training can alter the patterns of activity (Erickson and Kramer 2009; Lustig et al. 2009). Such findings are promising and suggest that the historically held views of the aged brain as an inevitable downward trajectory are overly simplistic. In fact, the aged brain retains a substantial amount of plasticity and can be rather easily modified (Erickson and Kramer 2009).

Physical activity has emerged as one method to enhance cognition throughout the life span and prevent cognitive decline, even in older adults who have had a lifetime of being sedentary (Hillman et al. 2008). In addition, recent work using fMRI has found that the regions that support complex cognitive function act differently in higher fit older adults compared to their lesser fit counterparts and that exercise training changes brain activity patterns in predictable and meaningful ways. In this chapter, the research examining the influence of physical activity and exercise on cognitive and brain function using fMRI will be described and critiqued with a focus on the dynamics of cognition in late adulthood and how changes in brain function resulting from exercise influence theories of brain plasticity in late life.

19.2 What Is Cognition and How Is It Measured?

The term "cognition" has been used as an umbrella term that includes any thought process from basic perception to action and behavior (see also Chap. 6) and is often considered to be nonspecific and too inclusive. Instead, cognitive psychologists and researchers divide cognition into different types or domains based on the particular process or type of information being tested. Research in cognitive psychology has identified several different cognitive domains such as executive function, visual perception and attention, and spatial processing. However, even these more specific domains and components of cognition do not fully capture the variety and complexity of mental processes. For example, memory function is one of the more salient domains of cognition, especially in an aged cohort in which memory decline is reported as one of the greatest fears associated with getting older (Hertzog et al. 2009). However, memory function is multifaceted with many different types including episodic memory, semantic memory, working memory, and procedural memory. In fact, memory for verbal material is often considered to be different from memory of nonverbal or spatial material, while memories of particular events (episodic memory) are different from memory of facts and knowledge (semantic memory). Such a wide array of different types of memory makes it challenging to broadly refer to "memory" deficits in late adulthood or to loosely refer to the effects of physical activity on "memory." In fact, early stages of Alzheimer's disease are more commonly associated with deficits in episodic memory with relatively little

impairment in procedural and implicit forms of memory, suggesting that it is crucial to specify what types of memory are being measured and discussed in relation to age-related impairments. Converging neuroscientific evidence for the presence of different subtypes of memory function and other forms of cognition comes from demonstrating that different cognitive domains and types of cognition rely on the integration of different networks and brain regions (Raichle 2010). For example, episodic memory and relational memory are often considered to be dependent on hippocampal function, while procedural memory is often considered to be dependent on basal ganglia function (Graybiel 2008). Although such categorically distinct dissociations may be oversimplified, they strengthen the argument that precise definitions are needed when testing associations with age or physical activity and also stress the importance of rigorous experimental designs that isolate specific cognitive domains.

Both cross-sectional and longitudinal studies of aging have demonstrated that cognitive performance declines across the adult life span (Salthouse et al. 1996). Indeed, this is the case regardless of whether cognitive performance is assessed in a laboratory environment in which individuals respond to simple visual or auditory stimuli or participate in real-world tasks such as driving (Birren and Schroots 1996; Mead and Fisk 1998). There is, however, an important distinction between two different types of processes that differ in their susceptibility to adult aging. It has generally been observed that knowledge-based or crystallized abilities (i.e., the extent to which a person has absorbed the content of culture) such as verbal knowledge and comprehension continue to be maintained or improve throughout the life span. This is in contrast to process-based or fluid abilities (i.e., reasoning, speed, and other basic abilities not dependent on experience), which display earlier and more substantial age-related declines (Baltes et al. 1999).

19.3 Age-Related Cognitive Decline and What fMRI Has Taught Us

Executive control processes that are dependent on frontal lobe function have been observed to display early and disproportionate age-related declines. Executive control processes are usually considered “higher level” and include several subdomains such as maintenance of goals, inhibiting prepotent and impulsive behaviors, coordinating multiple tasks, switching between tasks, and maintaining and manipulating items in working memory. For example, older adults show disproportionate age-related deficits on tasks that require inhibition of prepotent responses such as in the Stroop task (Milham et al. 2002), the antisaccade task (Nieuwenhuis et al. 2000), and the response compatibility paradigms (Colcombe et al. 2005), all of which are frequently employed to measure inhibitory control, a domain of executive function. In these tasks, older adults are not only slower to respond to presented stimuli but are disproportionately slower to respond to the more challenging conditions. In the congruent condition of the Stroop task (see also Chap. 6), color words are printed in

the corresponding ink color (e.g., the word RED in red ink), so the inhibitory demands of this condition are significantly reduced because the word and ink color match. On the other hand, the incongruent condition of the Stroop task, in which the word and ink color do not match (e.g., the word RED in green ink), requires participants to inhibit their prepotent response to respond to the printed word and instead respond to the ink color that is in conflict with the meaning of the word. By examining the differences in reaction time of the incongruent condition relative to the congruent condition, an interference score can be calculated for each participant that is a measure of inhibitory function: lower interference scores are a sign of better inhibitory control, and higher rates of interference are a sign of poorer inhibitory control. Using these measures, older adults are not only slower across both conditions, but also have higher interference rates when compared to younger adults, suggesting that older adults suffer from deficits in inhibitory control (Milham et al. 2002). Indeed, deficits in inhibitory function are considered to be one common explanation for many age-related cognitive deficits including memory, perception, and task coordination (Hasher and Zacks 1988).

Age-related deficits in inhibitory control are associated with dysfunctional patterns of brain activity in anterior regions including the dorsolateral prefrontal cortex and the anterior cingulate cortex. These two regions make up a circuit that supports attentional processing with the prefrontal regions involved in maintenance of an attentional "set" in working memory and the anterior cingulate cortex involved in monitoring performance during conditions that elicit greater response conflict. Using the Stroop task and fMRI with both younger and older adults, Milham et al. (2002) reported that older adults had decreased activity in the dorsolateral prefrontal cortex relative to younger adults, suggesting an age-related impairment in the implementation of attentional control and/or the maintenance of an attentional set in working memory. On the other hand, older adults also showed increased activity in the anterior cingulate cortex for both the congruent and incongruent conditions, while younger adults showed the more typical pattern of activation for only the incongruent condition in which response conflict is greatest. An age-related increase in activity in the anterior cingulate cortex for both congruent and incongruent conditions suggests that older adults are utilizing additional neural resources even to perform easier tasks that should require minimal cognitive resources. Increased brain activity for easier conditions might leave fewer neural resources available to allocate to more demanding tasks, resulting in disproportionately poorer performance and increased interference effects (Park and Reuter-Lorenz 2009).

Deficits have also been reported when adults are required to perform two or more tasks at the same time or to rapidly shift emphasis among tasks (Bherer et al. 2008; Erickson et al. 2007). Yet several studies have found that performance on these tasks can be easily and rapidly changed with only minimal amounts of cognitive training. That is, cognitive training paradigms in which older adults experience adaptive feedback and practice of the tasks for 3 weeks or longer have demonstrated that age-related differences in performance can be reduced and are often associated with changes in brain function. For example, Erickson et al. (2007) found that brain function is modifiable in late adulthood after only 3 weeks of cognitive

training. In a dual-task paradigm, Erickson et al. (2007) discovered that age-related differences in prefrontal function were eliminated and older adults that were trained showed identical patterns of activity to that of younger adults. These findings support the idea that older adults retain the capacity for brain plasticity and only minimal amounts of training are capable of altering how neural resources are allocated to handle task demands.

Age-related cognitive and functional brain deficits are often considered to be a normal consequence of aging. However, there are two lines of evidence that question the definition of "normal" age-related patterns of decline. First, as described above, a number of recent studies have trained older adults on tasks that normally show aging deficits (e.g., dual-task) and demonstrate that older adults show rapid improvements in performance (Kramer et al. 1999; Bherer et al. 2006, 2008) accompanied by significant changes in prefrontal function that are positively correlated with task performance (Erickson et al. 2007). Thus, deficits that are frequently dismissed as "normal" can be reversed with only a few weeks of training. Second, studies that investigate individual differences in cognitive and brain function have consistently revealed that variation in performance and brain function tends to increase with advancing age. Sources of this variation probably include genetic polymorphisms for neurotransmitters or trophic factors involved in neurocognitive function (Erickson et al. 2008), lifestyles such as diet and physical activity, and intellectual engagement including education, museum attendance, and reading activity. This literature suggests that healthy lifestyles and intellectual curiosity are important factors that contribute to cognitive function in late adulthood.

19.4 Effects of Physical Activity, Cardiorespiratory Fitness, and Exercise on Cognition

Aging research has demonstrated significant variability in the rate and progression of cognitive decline, yet executive function and episodic memory domains frequently show disproportionately faster rates of decline. Nonetheless, because of the substantial individual variability in cognitive dysfunction in late adulthood, several studies began asking whether there were measureable lifestyle factors that contribute to this variation. In some of the earliest research addressing this question, Spirduso (1975) reported that older racquet sportsmen outperformed their non-exercising peers on several simple, choice, and movement tasks, suggesting that greater physical activity and/or fitness is associated with attenuated cognitive decline. Based on this cross-sectional research, the conclusion that the trajectory of age-related cognitive decline remains modifiable was a significant discovery in terms of understanding the potential for cognitive and brain plasticity. Spirduso et al. followed this with another cross-sectional study showing that older adults who were runners outperformed adults who were non-runners on several different cognitive measures including tasks of processing speed (Spirduso and Clifford 1978). Since then, numerous studies have reported positive associations between greater fitness

levels and enhanced memory, fluid intelligence, speed of processing, and visual attention in older adults (for a review, see Etnier et al. 1997).

Epidemiological studies have reported that greater amounts of physical activity are often associated with less cognitive decline and a reduced risk of developing dementia later in life. For example, Podewils et al. (2005) studied the relationship between physical activity and dementia in 3,375 individuals over the course of 5.4 years. Physical activity was assessed by a self-report questionnaire in which participants were asked about the frequency and duration of 15 types of physical activities over the past 2 weeks. The authors found an inverse relationship between Alzheimer's disease and the number of physical activities performed by the participants. Other epidemiological studies have found similar protective effects of physical activity on cognitive function in late life (e.g., Andel et al. 2008; Dik et al. 2003; Weuve et al. 2004; Yaffe et al. 2001).

These studies provide intriguing support for the relationship between physical activity and cognition; however, these studies cannot establish causal links between these constructs. To establish causality between exercise and cognitive function, randomized controlled trials are needed. In one such design, Kramer et al. (1999) assigned participants to either an aerobic exercise intervention group (brisk walking) or a control group (stretching and toning). Both groups visited the laboratory 3 days a week for 45 min at a time and received the same amount of social interaction. A comprehensive neuropsychological battery was administered both before and after spending 6 months in their respective exercise programs. Over the 6-month period, Kramer et al. found that the walking group showed enhanced executive and inhibitory control, as indexed by task switching, stopping, and selective attention tasks (see also Chap. 6), compared to the stretching and toning control group. In contrast, the walking intervention failed to elevate performance on cognitive tasks that were nonexecutive in nature. These results suggested (a) that 6 months of moderate-intensity exercise could improve cognitive function, (b) that the benefits of exercise on cognitive function may be specific to tasks of executive and inhibitory control, and (c) that older adults retain their capacity for plasticity, including executive processes which show the greatest rate of decline.

Consistent with these results, a meta-analysis of 18 randomized exercise trials found that the effect of exercise on cognition is both general and specific (Colcombe and Kramer 2003). As described by Colcombe and Kramer (2003), the effects of exercise are general in the sense that most cognitive functions are improved with several months of exercise, yet specific, considering that executive and inhibitory functions show greater improvements compared to other cognitive domains. A more recent meta-analysis of 29 randomized trials found similar results of exercise training on cognitive function in adults over the age of 18 (Smith et al. 2010). Similarly, in several critical reviews of the exercise–cognition literature, it was argued that moderate-intensity exercise several days a week for a few months is sufficient for detecting cognitive improvements (Erickson and Kramer 2009; Hillman et al. 2008; Bielak et al. 2010). The effect of exercise interventions on cognition also appears to extend to populations with cognitive impairment. In one meta-analysis of 12 randomized exercise trials, Heyn et al. (2004) reported that exercise improves

cognitive function in individuals with cognitive impairment with a similar effect size to that reported in Colcombe and Kramer (2003). Although the effect of exercise on cognitive performance in populations with manifest impairment is in its infancy (Kramer and Erickson 2007), several recent randomized trials of exercise have shown significant promise for its ability to enhance cognition (Lautenschlager et al. 2008; Baker et al. 2010).

19.5 Using fMRI to Study the Effects of Exercise on Cognitive Function

One of the challenges of using fMRI to measure changes in brain function resulting from exercise is that the fMRI signal is inherently based on blood flow elicited by neural activity, making it difficult to determine whether exercise is simply affecting the vascularization of tissue or is having a more direct effect on neurons. In other words, since exercise and aerobic fitness influence the vascularization of neural tissue (see Hillman et al. 2008), differences in the fMRI signal as a function of fitness might be simply due to improved circulation rather than improvements in brain function per se. Although this might present as a difficult situation to resolve, several different studies (Colcombe et al. 2004; Voss et al. 2010a; Prakash et al. 2011) have successfully examined task-related interactions with measures of fitness and/or exercise. *Main effects* of fitness and exercise on brain activity could be interpreted in relation to vascularization differences, but a task × fitness *interaction* is more likely to be related to the supporting processing units (neurons) rather than vascularization. In any case, it is important for research using fMRI to carefully examine the interpretations of exercise and fitness in terms of either the neural or vascular consequences.

There have been several studies that have used fMRI to investigate the effects of exercise or fitness on brain function in older adults—see Table 19.1 (Colcombe et al. 2004; Rosano et al. 2010; Smith et al. 2010; Prakash et al. 2011). In the first study, Colcombe et al. (2004) used an event-related fMRI design to examine whether exercise would improve brain function during a modified flanker task (see also Chap. 6), used to assess attentional control (i.e., Eriksen and Eriksen 1974). In this task, participants were presented with five arrows on a screen and urged to selectively attend to the central arrow. Further, they were asked to respond to the direction that the center arrow was pointing while ignoring the direction of the flanking arrows (Colcombe et al. 2004). Participants would press a right button if the center arrow pointed right and a left button if the center arrow pointed left. Similar to the Stroop task described above, there were two conditions that differed in the degree of response conflict and interference: (1) a congruent condition in which all five arrows pointed in the same direction and (2) an incongruent condition in which the four flanking arrows pointed in the opposite direction of the center arrow (see Fig. 19.1). The incongruent condition is more difficult because participants need to inhibit

Table 19.1 A description of fMRI studies examining brain function in relation to physical activity and fitness

Study (year)	Sample size ($mean_{age}$)	Method	Summary of finding
Colcombe et al. (2004)	Cross-sectional = 41 *High fit*: (66.2) *Low fit*: (67.9) Intervention = 29 *Exercisers*: (67.9) *Stretchers*: (66.7)	*Design*: Cross-sectional and randomized controlled trial *Measures*: fMRI, VO_2 peak, and Rockport	High fit (Study 1) or aerobically trained (Study 2) older adults show greater task-related activity in prefrontal and parietal cortices during selective attention task
Rosano et al. (2010)	*Exercisers*: 20 (80.8) *Educational control*: 10 (81.5)	*Design*: Cross-sectional follow-up physical activity intervention *Measures*: fMRI, self-report of physical activity	Two years after intervention, exercisers demonstrated better cognitive performance and greater brain activity during digit symbol task
Smith et al. (2011)	*Low-risk AD/sedentary*: 17 (73.3) *Low-risk AD/active*: 17 (74.3)	*Design*: Cross-sectional *Measures*: fMRI, CBF, and connectivity	High physical activity and high risk for AD was associated with greater activity during a semantic memory task. Physical activity moderated risk status on brain activity
Prakash et al. (2011)	70 (65.0)	*Design*: Cross-sectional *Measures*: fMRI, VO_2 peak, and Rockport; cognitive testing	Higher fitness levels were associated with better Stroop performance and increased activity in prefrontal and parietal cortices, but not posterior regions

responding according to the flanking arrows and focus and respond to the direction of the center arrow. The flanker task is considered to be a measure of attentional control and shares similar properties to the Stroop task in that it requires inhibitory control, filtering of irrelevant information, and responding in the presence of conflicting material. Older adults are often slower on the incongruent condition and show higher interference rates compared to younger adults; exercise interventions for 6 months have shown that exercise improves performance on the flanker task (Kramer et al. 1999).

In the second study, Colcombe et al. used fMRI to examine how exercise elicits improvements in performance on the flanker task. In the first part of this study, older adults were scanned using an event-related protocol during performance of the flanker task, and brain activity for incongruent versus congruent conditions was

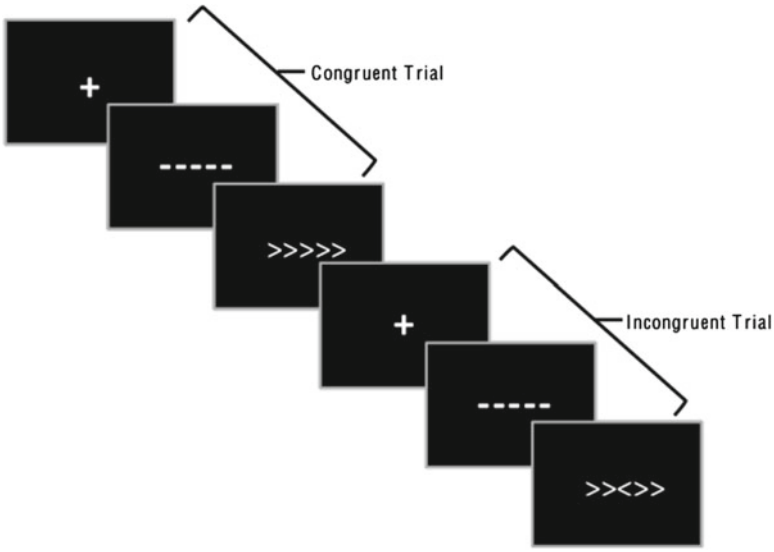

Fig. 19.1 Colcombe et al. (2004) used a modification of the Eriksen flanker paradigm. Each trial consisted of a series of three panes: first, a fixation crosshair which remained on-screen for 13.5 s; second, a 500-ms pre-cue to alert participants that the stimulus would soon appear; and third, the stimulus presentation, either a congruent or incongruent trial, which remained on-screen for 2,000 ms

found as a function of cardiorespiratory fitness levels. Cardiorespiratory fitness was measured by an estimated $\dot{V}O_2$ score calculated from the one-mile Rockport walk test. They found that higher fit older adults had increased brain activity in the right dorsolateral prefrontal cortex relative to less fit older adults (Fig. 19.2). The right dorsolateral prefrontal cortex supports attentional control operations including the maintenance of an attentional set in working memory and response conflict resolution (Banich et al. 2000). Greater prefrontal activity as a function of higher fitness levels corresponds to the hypothesis that fitness is associated with enhanced cognition because of direct associations with enhanced brain function. However, in addition to the greater brain activity in the dorsolateral prefrontal cortex in higher fit older adults, less activity was observed in the anterior cingulate cortex. That is, higher fit older adults demonstrated less activity in the anterior cingulate cortex during the incongruent condition of the flanker task (Fig. 19.2). Such decreased levels of activity in relation to higher fitness levels are also in line with the prediction that higher fit older adults perform better and experience less conflict. Colcombe et al.'s (2004) finding was provocative but was limited because of the cross-sectional design. Accordingly, they asked whether similar differences in brain activity could be elicited following an exercise intervention. Older adult participants were randomly assigned to either a 6-month moderate-intensity walking intervention or to a stretching and toning control group. Both groups received the same amount of social interaction from experimenters by coming into the laboratory 3 days/week for

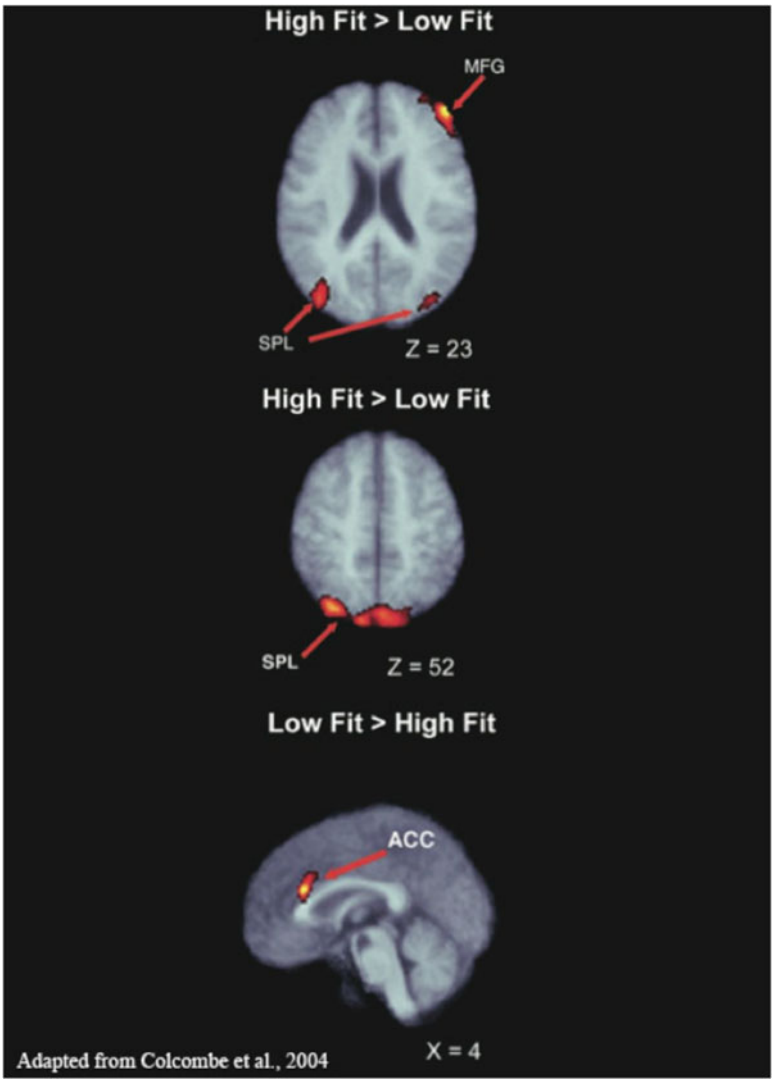

Fig. 19.2 Areas showing differences in cortical recruitment as a function of cardiovascular fitness (adapted from Colcombe et al. 2004)

approximately 45 min. Trained exercise leaders monitored the exercise sessions, and subjects were instructed to maintain their activity levels so that their heart rate was within 60–70% of their age-based maximum. fMRI testing using the same flanker task as described above was conducted both before and after the 6-month intervention. They found that the exercise intervention was effective at increasing fitness levels. They also found, consistent with the results from study one, that the exercise intervention increased activity in the dorsolateral prefrontal cortex and

decreased activity in the anterior cingulate cortex and that these changes in activity were specific to the exercising group. Interestingly, these changes in brain function during the flanker task corresponded to improvements in performance. That is, the exercising group showed a reduction in interference rates over the 6-month period, while the stretching and toning control group did not. These results indicate that (1) 6 months of exercise is sufficient for altering brain function in late adulthood; (2) the most significant changes in activity are found for the most challenging conditions (i.e., incongruent conditions) that rely the most on executive and inhibitory control; (3) the fMRI patterns from cross-sectional designs and randomized clinical trials are greatly overlapping, suggesting that the cross-sectional effects of fitness are likely due to variation in exercise rather than some other third variable; and (4) brain function is related to fitness and exercise in a meaningful way, with significant changes occurring in the regions that support executive function such as the prefrontal cortex, anterior cingulate cortex, and parietal regions. Overall, this study was important as it was the first to demonstrate that aerobic exercise is capable of improving brain function in older adults by using fMRI.

But how does exercise or cardiorespiratory fitness influence brain function? That is, what are the mediating paths by which exercise enhances brain function? From a biological perspective, it is customary to define the term *mechanism* as the molecular processes that give rise to the system-level changes influencing cognitive function; however, mechanisms can exist on multiple levels. For example, using cognitive neuroscience tools, we could ask how different brain regions are affected by physical activity and how they work together to enhance cognitive function. This question asks whether physical activity enhances cognition by changing or improving the connectivity of particular brain regions. In fact, it is likely that the brain works as an integrated network to give rise to cognition and that prior fMRI research (e.g., Colcombe et al. 2004) was simply capturing the regions of the brain associated with exercise and fitness and not *how* exercise was changing the communication between regions.

With increasing age, there is a steady decrease in the "connectedness" of the brain. That is, aging is associated with a decline in how effectively different regions of the brain are connected with each other and how efficiently regions communicate. The most common network examined is the so-called default mode network, a network of brain regions that are active during resting conditions (Andrews-Hanna et al. 2007). The default mode network is thought to be involved in internally directed cognition, homeostatic processes, or the monitoring of the environment (Andrews-Hanna et al. 2007). Studies with cognitively healthy older adults and those with Alzheimer's disease and mild cognitive impairment find that the default mode network is significantly disrupted in anterior brain regions, indicating that the brain becomes less coherent and functionally connected in late life. Since exercise and physical activity are associated with a reduction in the prevalence of cognitive impairment and enhanced cognitive function in late adulthood, it is possible that exercise enhances the communication and functional connectivity between regions, thereby producing a more efficient and stable brain. In fact, new evidence now suggests that this may be the case (see Voss et al. 2010a, b).

An alternative, but not mutually exclusive, way in which exercise might be influencing brain communication is through the ability of prefrontal regions to modulate activity in posterior regions. In fact, models of selective attention predict that focused attention to task-relevant information should result in an increase in brain activity in regions that process the task-relevant information, a process often referred to as top-down attentional control. For example, Corbetta et al. (1991) reported that directing attention to certain features of a visual stimulus such as color, shape, or speed increased brain activity in distinct areas of visual cortex that were specialized for processing the particular feature. Therefore, a common component of theories of selective attention and attentional control includes the finding that visual attention can modulate activity in striate and extrastriate regions of cortex for a variety of task-relevant stimulus dimensions (Erickson et al. 2009). Furthermore, both enhancement and suppressive processes have been found in striate and extrastriate regions and are considered to be essential components of a push–pull mechanism for attentional selection and filtering task-irrelevant information (see Erickson et al. 2009). From a basic perspective, a focus on task-relevant information should result in increased activity in regions that process the task-relevant stimulus features, while selective filtering of other stimulus features should result in suppression of activity in regions that process those ignored dimensions of the stimuli. Several studies have now found results consistent with this prediction (Corbetta and Shulman 2002; de Fockert et al. 2001). Could exercise enhance cognition, and in particular measures of selective attention such as Stroop and flanker task performance (Kramer et al. 1999), by improving the top-down modulation of striate and extrastriate cortices?

Recent evidence suggests that older adults experience a deficit in modulating striate and extrastriate brain regions during tasks that require selective attention. For example, Gazzaley et al. (2005) reported that older adults experienced a deficit in the suppression of cortical activity in extrastriate brain regions when they were supposed to be ignoring task-irrelevant information. Moreover, the extent to which older adults failed at inhibiting, or suppressing, activity in posterior brain regions was related to poorer working memory performance. These results suggest that inhibitory deficits in late adulthood can be partially attributed to deficits in top-down modulatory processes.

Whether cardiorespiratory fitness moderates an age-related deficit in top-down suppression, or enhancement of posterior brain regions, has only recently been investigated using a modified version of the Stroop task (Prakash et al. 2011). The Stroop task was chosen because prior studies have linked the interference and costs with suppression and enhancement of activity in color and word related areas in the ventral visual cortex (Erickson et al. 2009). Erickson et al. (2009) localized color-sensitive areas and word/letter-sensitive areas of visual cortex and then examined whether modulation of these regions occurred during the performance of a Stroop task in a group of younger adults. They reported that during performance of the incongruent condition, the condition with the highest cognitive demand, there was increased activity in regions sensitive to color, indicating an attentional enhancement in target processing regions. In addition, they also found an enhancement of

activity in one region sensitive to word processing, suggesting greater processing of the distractor dimension. These results were important because they demonstrated top-down modulation during the Stroop task, enabling other research to better predict how the brain would respond as a function of cardiorespiratory fitness.

Prakash et al. (2011) predicted that older adults would show deficits in top-down modulation of color-sensitive and word/letter-sensitive regions of cortex during the Stroop task but that higher levels of cardiorespiratory fitness would ameliorate this deficit. However, an alternative hypothesis for the benefits of cardiorespiratory fitness on brain function is that the effects of fitness are specific to the prefrontal cortex and that they are unrelated to, or not mediated by, changes in top-down control over the processing of posterior brain regions. Prakash et al. (2011) examined this hypothesis and used a sample of 70 community-dwelling adults without dementia between 60 and 75 years of age who were capable of performing a cardiorespiratory fitness and MRI testing session. Cardiorespiratory fitness was quantified by $\dot{V}O_2$ peak, the gold standard measure of aerobic fitness. Using a similar approach to localize color-sensitive regions and word/letter-sensitive areas of visual cortex as described above (Erickson et al. 2009), they found that during the most demanding condition of the Stroop task, there was enhancement of activity in color-sensitive and word/letter-sensitive areas, suggesting that top-down modulation plays an important role in performance for both older and younger adults. However, inconsistent with their original prediction, Prakash et al. (2011) did not find any evidence that higher levels of cardiorespiratory fitness moderated the top-down modulation of visual cortical regions during the incongruent condition of the Stroop task. Instead, they found that higher levels of cardiorespiratory fitness were associated with enhanced functioning of prefrontal and parietal cortices during the Stroop task with no differences occurring in visual areas. These results suggest that cardiorespiratory fitness primarily enhances attentional function by influencing the functioning of the anterior cortical regions and not by altering the efficacy of top-down attentional control processes (Prakash et al. 2011). These results are important as they shed light on how cardiorespiratory fitness is enhancing cognition and selective attention. That is, aerobic fitness is associated with enhanced cognition by increasing brain function in areas that support executive function including the prefrontal and parietal cortices and resting-state connectivity (Voss et al. 2010a, b) but not the modulatory processes that give rise to attentional enhancement. In short, enhancement of top-down modulation processes does not appear to be influenced by fitness.

Thus far, we have primarily discussed two fMRI studies that have examined the effect of either cross-sectional measures of cardiorespiratory fitness or 6 months of an exercise regimen on brain function (Colcombe et al. 2004; Prakash et al. 2011). However, we could also ask what the long-term effects of an exercise intervention are on prefrontal brain activity in older adults. Rosano et al. (2010) addressed this research question in an fMRI study that used a sample of 30 older adult participants at an average age of 80 years. Twenty of the participants had successfully completed a 1-year single-blind physical activity intervention that consisted of aerobic, strength, balance, and flexibility exercises, with walking as the primary mode of

exercise. The other ten subjects had participated in an educational control group that received educational sessions on health topics such as nutrition, medication, foot care, and prevention services. Two years following the end of the physical activity intervention, participants who reported remaining active returned for an fMRI session. During the fMRI session, participants completed a modified digit-symbol substitution task, a commonly employed measure of processing speed. Rosano et al. (2010) found that those individuals who remained more physically active had greater activity in dorsolateral prefrontal cortices, posterior parietal regions, and the anterior cingulate cortex compared to their peers who engaged in the health education course. These results suggest that physical activity enhanced brain activity and that sustained physical activity after the termination of an experimental regimen was associated with elevated brain function. One caveat of this study is that people who maintained physical activity over the 2-year interval between termination of the intervention and fMRI scanning may have had superior executive and cognitive skills, thereby allowing them to maintain and execute goals to exercise regularly. Nonetheless, these results are intriguing and suggest that there may be long-term consequences of physical activity on measures of brain function in late life.

Late life is associated with an escalating risk of experiencing cognitive impairment. One of the risk factors for developing Alzheimer's disease is the presence of the apolipoprotein epsilon 4 allele (APOE 4). Individuals homozygous for the APOE 4 allele are at the greatest risk for developing dementia, but those with a single allele are also at a heightened risk. One of the nagging questions in the field is whether exercise or cardiorespiratory fitness could act to moderate the effect of the APOE 4 allele on cognitive function, risk for dementia, or brain function. This research question was recently addressed in an fMRI study with a group of older adults that were scanned during a semantic memory task and genotyped for the APOE 4 allele (Smith et al. 2011). In this study, physical activity was assessed by self-report via the Stanford Brief Activity Survey, an assessment of habitual patterns of physical activity. There were four groups in a cross-sectional design, with 17 participants per group: (1) a low-risk/low physical activity group, (2) a low-risk/high physical activity group, (3) a high-risk/low physical activity group, and (4) a high-risk/high physical activity group. Using an event-related fMRI paradigm during a semantic memory task using a famous name discrimination task, the authors found significant interactions between physical activity and genetic risk for Alzheimer's disease such that high physical activity increased brain function in the high-risk group more than in the other groups. Overall, these results suggest that physical activity increases brain activity in memory-related brain areas in genetically at-risk older adults. Although provocative, these results do not address whether extended and habitual physical activity would reduce cognitive impairment by enhancing activity in memory-related regions.

The fMRI results from Smith et al. (2011) suggest that future studies need to examine both lifestyle factors such as physical activity and exercise along with genetic risk factors that could be moderating the effects of exercise on brain and cognition in order to gain a complete and more thorough understanding of how the brain changes with age and how these factors contribute to individual variation.

For example, there are other genes that could be moderated by exercise, such as a gene that regulates the secretion of brain-derived neurotrophic factor (BDNF), a molecule produced by neurons that is upregulated by exercise and is involved in learning, memory, and the production of new neurons in the dentate gyrus of the hippocampus. There is some evidence that the BDNF gene explains some individual variation in cognitive function in both older and younger adults (Erickson et al. 2008), but whether physical activity or exercise moderates this effect remains unknown.

19.6 Conclusions and Future Directions

In this chapter, we have reviewed the research that has used fMRI to examine the neural circuits that are impacted by physical activity and fitness (Rosano et al. 2010; Smith et al. 2011; Prakash et al. 2011) and that these changes may occur as the result of an exercise intervention (Colcombe et al. 2004). Although this research is in its infancy, we can draw several important conclusions from it: (1) physical activity and fitness are associated with enhanced brain activity in several different areas of the brain, but most of these regions are located in anterior regions such as the dorsolateral prefrontal cortex and anterior cingulate cortex; (2) fitness and exercise are not associated with a global increase in function for all tasks, but rather a disproportionate increase in activity for the most challenging conditions, suggesting that the effects of physical activity are most apparent when the cognitive demands and cognitive resources are being significantly taxed; and (3) individual variation in age-related brain function can be attributed to individual variation in the physical activity levels or fitness levels of the participants. These three main findings are important as they demonstrate the power of combining measures of physical activity and fitness with brain measurements such as fMRI to enhance our understanding of the aged brain.

Although these prior studies have strengths, they also have some significant weaknesses. First, only one of these studies has examined the effect of a randomized exercise intervention on brain function using multiple neuroimaging sessions (Colcombe et al. 2004). This greatly limits the extent to which causal claims can be made regarding the role of physical activity on brain function. Second, there is significant variation in the way physical activity and fitness are measured and quantified, including both self-report and objective measures. More consistency and use of objective measures will be important for future studies to remove any possibility that the fMRI results are confounded by inaccurate estimates of physical activity from self-report measures. Third, only one study has examined and postulated how the activity differences are influenced by variation in connectivity and communication between regions (Prakash et al. 2011). It is clear that brain areas work in concert with other areas to support complex cognitive processes. It will be important for future studies to examine how these regions are working together to promote enhanced cognitive function. Fourth, these prior studies have failed to systematically examine how variation in gray matter volume and white matter integrity

influences the activity patterns observed. Indeed, combining the results from both structural MRI methods and functional MRI methods is going to be necessary to fully capture the importance of physical activity and exercise on brain function. Finally, statistical models that explicitly examine the way in which brain circuits mediate the cognitive enhancements observed with exercise and fitness remains an important matter for future studies to investigate.

Overall, the studies discussed in this chapter suggest that the brain retains some degree of plasticity well into late adulthood and that physical activity and exercise can take advantage of this plasticity. It will be important for future studies to examine how much exercise is needed to detect these effects, how long the effects are retained after termination of exercise routines, and whether the effects apply to populations with neurological or psychiatric impairments. Given the increasing aging population along with the expected increase in the prevalence of age-related neurological diseases, exercise has emerged as a promising and low-cost method to prevent cognitive impairment in late adulthood.

References

Andel R, Crowe M, Pedersen NL, Fratiglioni L, Johansson B, Gatz M (2008) Physical exercise at midlife and risk of dementia three decades later: a population-based study of Swedish twins. J Gerontol A Biol Sci Med Sci 63:62–66

Andrews-Hanna JR, Snyder AZ, Vincent JL, Lustig C, Head D, Raichle ME, Buckner RL (2007) Disruption of large-scale brain systems in advanced aging. Neuron 56:924–935

Baker LD, Frank LL, Foster-Schubert K, Green PS, Wilkinson CW, McTiernan A et al (2010) Effects of aerobic exercise on mild cognitive impairment: a controlled trial. Arch Neurol 67:71–79

Baltes PB, Staudinger UM, Lindenberger U (1999) Lifespan psychology: theory and application to intellectual functioning. Annu Rev Psychol 50:471–507

Banich MT, Milham MP, Atchley RA, Cohen NJ, Webb A, Wszalek T et al (2000) Prefrontal regions play a predominant role in imposing an attentional 'set': evidence from fMRI. Brain Res Cogn Brain Res 10:1–9

Bherer L, Kramer AF, Petersen MS, Colcombe S, Erickson KI, Becic E (2006) Testing the limits of cognitive plasticity in older adults: application to attentional control. Acta Psychol 123:261–278

Bherer L, Kramer AF, Peterson MS, Colcombe S, Erickson KI, Becic E (2008) Transfer effects in task-set cost and dual-task cost after dual-task training in older and younger adults: further evidence for cognitive plasticity in attentional control in late adulthood. Exp Aging Res 34:188–219

Bielak AM (2010) How can we not 'lose it' if we still don't understand how to 'use it'? Unanswered questions about the influence of activity participation on cognitive performance in older age – a mini-review. Gerontology 56:507–519

Birren JE, Schroots JF (1996) History, concepts, and theory in the psychology of aging. In: Schaie K, Birren J (eds) Handbook of the psychology of aging, 3rd edn. Academic, San Diego, CA, pp 3–23

Colcombe SJ, Kramer AF (2003) Fitness effects on the cognitive function of older adults: a meta-analytic study. Psychol Sci 14:125–130

Colcombe SJ, Kramer AF, Erickson KI, Scalf P, McAuley E, Cohen NJ et al (2004) Cardiovascular fitness, cortical plasticity, and aging. Proc Natl Acad Sci USA 101:3316–3321

Colcombe SJ, Kramer AF, Erickson KI, Scalf P (2005) The implications of cortical recruitment and brain morphology for individual differences in inhibitory function in aging humans. Psychol Aging 20:363–375

Corbetta M, Shulman GL (2002) Control of goal-directed and stimulus-driven attention in the brain. Nat Rev Neurosci 3:201–215
Corbetta M, Miezin FM, Dobmeyer S, Shulman GL, Petersen SE (1991) Selective and divided attention during visual discriminations of shape, color, and speed: functional anatomy by positron emission tomography. J Neurosci 11:2383–2402
de Fockert JW, Rees G, Frith CD, Lavie N (2001) The role of working memory in visual selective attention. Science 291:1803–1806
Dik M, Deeg DJ, Visser M, Jonker C (2003) Early life physical activity and cognition at old age. J Clin Exp Neuropsychol 25:643–653
Erickson KI, Kramer AF (2009) Aerobic exercise effects on cognitive and neural plasticity in older adults. Br J Sports Med 43:22–24
Erickson KI, Colcombe SJ, Wadhwa R, Bherer L, Peterson MS, Scalf PE et al (2007) Training-induced plasticity in older adults: effects of training on hemispheric asymmetry. Neurobiol Aging 28:272–283
Erickson KI, Kim JS, Suever BL, Voss MW, Francis BM, Kramer AF (2008) Genetic contributions to age-related decline in executive function: a 10-year longitudinal study of COMT and BDNF polymorphisms. Front Hum Neurosci 2:11
Erickson KI, Prakash RS, Kim JS, Sutton BP, Colcombe SJ, Kramer AF (2009) Top-down attentional control in spatially coincident stimuli enhances activity in both task-relevant and task-irrelevant regions of cortex. Behav Brain Res 197(1):186–197
Erickson KI, Raji CA, Lopez OL, Becker JT, Rosano C, Newman AB et al (2010) Physical activity predicts gray matter volume in late adulthood: the Cardiovascular Health Study. Neurology 75:1415–1422
Eriksen BA, Eriksen CW (1974) Effects of noise letters upon the identification of a target letter in a nonsearch task. Percept Psychophys 16:143–149
Etnier JL, Salazar W, Landers DM, Petruzzello SJ, Han M, Nowell P (1997) The influence of physical fitness and exercise upon cognitive functioning: a meta-analysis. J Sport Exerc Psychol 19:249–277
Fjell AM, Walhovd KB (2010) Structural brain changes in aging: courses, causes, and cognitive consequences. Rev Neurosci 21:187–221
Gazzaley A, Cooney JW, McEvoy K, Knight R, D'Esposito M (2005) Top-down enhancement and suppression of the magnitude and speed of neural activity. J Cogn Neurosci 17:507–517
Graybiel AM (2008) Habits, rituals, and the evaluative brain. Annu Rev Neurosci 31:359–387
Hasher L, Zacks RT (1988) Working memory, comprehension, and aging: a review and a new view. In: Bower GH (ed) The psychology of learning and motivation, vol 22. Academic, New York, pp 193–225
Hedden T, Gabrieli DE (2004) Insights into the ageing mind: a view from cognitive neuroscience. Nat Rev Neurosci 5:87–96
Hertzog C, Kramer AF, Wilson RS, Lindenberger U (2009) Enrichment effects on adult cognitive development: can the functional capacity of older adults be preserved and enhanced? Psychol Sci Public Interest 9:1–65
Heyn P, Abreu BC, Ottenbacher KJ (2004) The effects of exercise training on elderly persons with cognitive impairment and dementia: a meta-analysis. Arch Phys Med Rehabil 85:1694–1704
Hillman CH, Erickson KI, Kramer AF (2008) Be smart, exercise your heart: exercise effects on brain and cognition. Nat Rev Neurosci 9:58–65
Kennedy KM, Erickson KI, Rodrigue KM, Voss MW, Colcombe SJ, Kramer AF et al (2009) Age-related differences in regional brain volumes: a comparison of optimized voxel-based morphometry to manual volumetry. Neurobiol Aging 30:1657–1676
Kramer AF, Erickson KI (2007) Capitalizing on cortical plasticity: influence of physical activity on cognition and brain function. Trends Cogn Sci 11:342–348
Kramer AF, Hahn S, Cohen NJ, Banich MT, McAuley E, Harrison CR et al (1999) Ageing, fitness and neurocognitive function. Nature 400:418–419

Lautenschlager NT, Cox KL, Flicker L, Foster JK, van Bockxmeer FM, Xiao J et al (2008) Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. JAMA 300:1027–1037

Lustig C, Shah P, Seidler R, Reuter-Lorenz PA (2009) Aging, training, and the brain: a review and future directions. Neuropsychol Rev 19:504–522

Mead S, Fisk AD (1998) Measuring skill acquisition and retention with an ATM simulator: the need for age-specific training. Hum Factors 40:516–523

Milham MP, Erickson KI, Banich MT, Kramer AF, Webb A, Wszalek T, Cohen NJ (2002) Attentional control in the aging brain: insights from an fMRI study of the Stroop task. Brain Cogn 49:277–296

Nieuwenhuis S, Ridderinkhof KR, de Jong R, Kok A, van der Molen MW (2000) Inhibitory inefficiency and failures of intention activation: age-related decline in the control of saccadic eye movements. Psychol Aging 15:635–647

Park DC, Reuter-Lorenz P (2009) The adaptive brain: aging and neurocognitive scaffolding. Annu Rev Psychol 60:173–196

Podewils LJ, Guallar E, Kuller LH, Fried LP, Lopez OL, Carlson M, Lyketsos CG (2005) Physical activity, APOE genotype, and dementia risk: findings from the Cardiovascular Health Cognition Study. Am J Epidemiol 161:639–651

Prakash RS, Voss MW, Erickson KI, Lewis JM, Chaddock L, Malkowski E et al (2011) Cardiorespiratory fitness and attentional control in the aging brain. Front Hum Neurosci 4:229

Raichle M (2010) Two views of brain function. Trends Cogn Sci 14:180–190

Raz N, Lindenberger U, Rodrigue KM, Kennedy KM, Head D, Williamson A et al (2005) Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. Cereb Cortex 15:1676–1689

Rosano C, Venkatraman VK, Guralnik J, Newman AB, Glynn NW, Launer L et al (2010) Psychomotor speed and functional brain MRI 2 years after completing a physical activity treatment. J Gerontol A Biol Sci Med Sci 65:639–647

Salthouse TA, Hancock HE, Meinz EJ, Hambrick DZ (1996) Interrelations of age, visual acuity, and cognitive functioning. J Gerontol B Psychol Sci Soc Sci 51B:317–330

Smith PJ, Blumenthal JA, Hoffman BM, Cooper H, Strauman TA, Welsh-Bohmer K et al (2010) Aerobic exercise and neurocognitive performance: a meta-analytic review of randomized controlled trials. Psychosom Med 72:239–252

Smith JC, Nielson KA, Woodard JL, Seidenberg M, Dungerian S, Antuono P et al (2011) Interactive effects of physical activity and APOE-e4 on BOLD semantic memory activation in healthy elders. Neuroimage 54:635–644

Spirduso WW (1975) Reaction and movement time as a function of age and physical activity level. J Gerontol 30:435–440

Spirduso WW, Clifford P (1978) Replication of age and physical activity effects on reaction and movement time. J Gerontol 33:26–30

Voss MW, Erickson KI, Prakash RS, Chaddock L, Malkowski E, Alves H et al (2010a) Functional connectivity: a source of variance in the association between cardiorespiratory fitness and cognition? Neuropsychologia 48:1394–1406

Voss MW, Prakash RS, Erickson KI, Basak C, Chaddock L, Kim JS et al (2010b) Plasticity of brain networks in a randomized intervention trial of exercise training in older adults. Front Aging Neurosci 2:1–17

Weuve J, Kang JH, Manson JE, Breteler MM, Ware JH, Grodstein F (2004) Physical activity, including walking, and cognitive function in older women. JAMA 292:1454–1461

Yaffe K, Barnes D, Nevitt M, Lui L, Covinsky K (2001) A prospective study of physical activity and cognitive decline in elderly women. Arch Intern Med 161:1703–1708

Chapter 20
Cross-sectional Studies on the Influence of Exercise on Brain Structure, Functional Activation, and Cognition in Health and Disease

Agnes Flöel and Stefan Knecht

Abstract The aim of this chapter is to demonstrate if and how the beneficial influence of physical activity on cognitive function and the prevention of its decline in age, postulated in basic science studies, can be substantiated in prospective epidemiological and cross-sectional studies. Moreover, we will elucidate the mechanisms underlying these lifestyle-related modulations of cognitive functions in elderly individuals, including cerebral gray matter volume and white matter integrity, functional connectivity between brain areas, neurotrophic factors, as well as potential interactions with genetic factors.

20.1 Introduction

Cross-sectional studies suggest a decreased risk of cognitive decline and dementia for subjects who exercise regularly; structural and functional imaging studies have started to elucidate underlying mechanisms. Interaction with genetic factors, as well as other lifestyle choices, may account for interindividual differences in cognitive response to exercise.

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20.2 Behavioral Effects of Physical Activity in Observational Studies

An accumulating body of epidemiological studies have suggested decreased risk of cognitive decline and dementia for subjects who exercise regularly (Abbott et al. 2004; Barnes et al. 2003; Hillman et al. 2006; Laurin et al. 2001; Lytle et al. 2004; Podewils et al. 2005; Scarmeas et al. 2001; van Gelder et al. 2004; Weuve et al. 2004; Yaffe et al. 2001). For example, a large study by Laurin et al. (2001) examined more than 6,000 elderly people over a period of 5 years, with a total of 4,600 completing the 5-year follow-up. Physical activity was measured with questionnaires, and no objective fitness measurements were included. Outcome measures were the presence of mild cognitive impairment (MCI) without dementia, Alzheimer's disease (AD), or vascular dementia. They found significantly lower odd ratios for cognitive impairment and AD in subjects with higher levels of physical activity. Interestingly, for both MCI and AD, they noted a dose–response curve: the more activity, the smaller the odds for developing cognitive impairment or dementia. Further, Barnes et al. (2003) conducted a community-based study in adults aged 55 and older and included a total of 349 healthy participants without cognitive impairment at baseline. Importantly, individuals with cardiovascular disease or musculoskeletal disability, who may be restricted in the amount of exercise they can participate in, were not included. Moreover, this study measured physical fitness using a standard treadmill exercise test, rather than self-reported measures of physical activity. As outcome measures, they included tests of memory (California Verbal Learning Test) and attention/executive function (Trail-Making Test, Part B; the Stroop Interference Test; and the Digit Symbol Test) and also calculated a measure of global cognitive function. The authors found that baseline measurements of cardiorespiratory fitness were positively associated with preservation of cognitive function over a 6-year period. A recent meta-analysis (Hamer and Chida 2009) of 16 prospective studies on the association of physical activity and risk for all types of dementia or AD found that the pooled calculated relative risk between the most active group compared with the least active one was 0.72 for all types of dementia (95% CI, 0.60–0.86; $p > 0.0001$) and 0.55 for AD (95% CI, 0.36–0.84; $p = 0.006$). Two further studies found similar associations for physical activity and the risk of MCI (Etgen et al. 2010; Geda et al. 2010). Taken together, multiple studies have provided evidence to indicate that increased participation in physical activity or higher levels of fitness relate to a decreased risk of cognitive impairment including AD. Note, however, that a healthy lifestyle, of which physical activity is only one aspect, may be more strongly related to cognitive function. Our own group (Floel et al. 2008) has shown that a healthy lifestyle, including not only physical exercise but also dietary habits, BMI, smoking, and alcohol consumption (merged into a "lifestyle index"), was associated with better verbal episodic memory performance, even after adjusting for age, sex, education, and blood pressure. This composite index had a stronger relationship with verbal episodic memory scores than any single one of the factors.

Conversely, other observational studies have failed altogether to find a positive relationship between physical activity and cognition (Sturman et al. 2005; Verghese et al. 2003; Wilson et al. 2002; Yamada et al. 2003). For example, two studies examined the relation of physical activities to cognition. Specifically, Wilson et al. (2002) examined a biracial community in Chicago, where 6,000 persons aged 65 years and older participated in an interview. As part of the interview, persons rated current frequency of participation in seven cognitive activities (e.g., reading a newspaper) and nine physical activities (e.g., walking for exercise, as assessed by questionnaires) from which composite measures of cognitive and physical activity frequency were derived, ranging from 1.3 to 4.7, with higher scores indicating more frequent activity. Four years later, 842 of those judged free of AD at baseline were sampled for a detailed clinical evaluation of incident disease. It was found that a one-point increase in cognitive-activity score was associated with a 64% reduction in risk of incident AD, but weekly hours of physical activity were not related to disease risk.

Verghese et al. (2003) examined the relation between leisure activities, which included both cognitively stimulating and physically stimulating activities, and the risk of dementia in a prospective cohort of subjects 75 years of age who resided in the community and did not have dementia at baseline. Cox proportional-hazards analysis was used to evaluate the risk of dementia according to the baseline level of participation in leisure activities, with adjustment for age, sex, educational level, presence or absence of chronic medical illnesses, and baseline cognitive status. They found that only the cognitive-activity score was significantly associated with a reduced risk of dementia but not the physical-activity score. The association with the cognitive-activity score persisted after the exclusion of the subjects with possible preclinical dementia at baseline. Results were similar for AD and vascular dementia.

An important potential shortcoming of cross-sectional studies is the difficult-to-answer question of whether increased participation in leisure activities lowers the risk of dementia or participation in leisure activities declines during the preclinical phase of dementia. Some studies have tried to at least partially overcome this limitation. For example, Laurin et al. (2001), who found a cross-sectional correlation between higher level of physical activity and lower risk of dementia, specifically assessed the possibility that lower physical activity could be a consequence of cognitive impairment or dementia at its preclinical state rather than a risk factor: The authors reanalyzed their data excluding subjects who reported early cognitive symptoms in the first 2 years of follow-up and found practically unchanged results. However, even this analysis cannot overcome the correlational limitation, and controlled interventional trials are needed to address this issue.

To sum up, the majority of observational studies found a positive relationship between physical activity and cognition, or conversely lower rates of MCI and dementia for those that were more physically active over the observation period. However, a minority of studies reported a lack of a relationship, demonstrating the need for more research on this topic. This inconsistency in the literature could be due to a number of factors, including the way fitness and activity were defined

(subjective, questionnaire; objective, ergometer); how well the authors controlled for other lifestyle factors, including diet but also social and intellectual stimulation; the role of duration, intensity, and frequency of activity; the outcome parameter chosen (e.g., executive vs. memory); the specific population under study (with regard to social status and age); and finally the influence of genetics (Etnier et al. 2007; Podewils et al. 2005; Rovio et al. 2005b; Schuit et al. 2001).

20.3 Mechanisms of the Influence of Physical Activity on Behavior: Brain Structure, Functional Activation, and Neurotrophins

In a first study, Colcombe et al. (2003) assessed the relationship between aerobic fitness and cerebral gray matter density using voxel-based morphometry (VBM). VBM is a magnetic resonance (MR)-based method to determine structural properties of the brain. Data from nonhuman exercise models suggest that the changes in gray matter volume seen in our study may be due to changes in synaptic interconnections, axonal integrity, and capillary bed growth (Pereira et al., 2007). However, it should be pointed out that little is known about the relationship between the gray matter changes identified by VBM and the underlying cellular changes. In the study by Colcombe et al., MR images were examined for systematic variation in tissue density as a function of age, aerobic fitness, and a number of other health markers. They found robust declines in tissue densities as a function of age in the frontal, parietal, and temporal cortices. Moreover, losses in these areas were substantially reduced as a function of cardiovascular fitness, even when the results were statistically controlled for other moderator variables. Note that these authors used gray matter density, rather than the more commonly recommended (Good et al. 2001) gray matter volume in VBM analysis. Thus, the results are not directly comparable to most studies using VBM measures.

In 2004, Colcombe et al. published a study (see also Chap. 19) in which elderly participants were first cross-sectionally examined for physical fitness and brain activation using functional MRI during a modified flanker task in which they were asked to respond to a central arrow cue embedded in an array of five arrows that pointed either to the left or right (Colcombe et al. 2004). They subsequently underwent a physical activity intervention for 6 months prior to being tested again. In the cross-sectional part of the study, it was demonstrated that the individuals who tested high in cardiovascular fitness showed significantly greater activation in several cortical regions associated with effective attentional control, including right medial frontal gyrus, superior frontal gyrus, and superior parietal lobe, and significantly less activity in the anterior cingulate cortex (ACC). Thus, increased cardiovascular fitness was associated with increased task-related activity in the regions of cortex thought to be necessary for successful task completion. Moreover, subjects who entered the testing situation with a relatively high level of aerobic fitness showed a reduced amount of activity in the ACC, a region associated with the presence of

behavioral conflict and the need to adapt attentional control processes. Thus, higher cardiovascular fitness seems to be associated with more effective attentional control during complex tasks, possibly leading to better performance in demanding activities of daily living.

While Colcombe et al. (2004) only assessed attentional functions in their study, other authors focused on the impact of aerobic fitness on memory functions. For example, Erickson et al. (2009) found evidence for an association of aerobic fitness with hippocampal volume and spatial memory in elderly humans. They investigated whether individuals with higher levels of aerobic fitness displayed greater volume of the hippocampus and better spatial memory performance than individuals with lower fitness levels. Furthermore, in exploratory analyses, they assessed whether hippocampal volume mediated the relationship between fitness and spatial memory. Using a region-of-interest analysis on MRI in 165 nondemented older adults, they found a triple association such that higher fitness levels were associated with larger left and right hippocampi after controlling for age, sex, and years of education, and larger hippocampi and higher fitness levels were correlated with better spatial memory performance. Furthermore, they demonstrated that hippocampal volume partially mediated the relationship between higher fitness levels and enhanced spatial memory. This study was the first to demonstrate that higher levels of aerobic fitness were associated with increased hippocampal volume in older humans, and may translate to better memory function, similar to what has been shown in the animal literature (see also Chap. 17).

The studies described so far focused on cerebral gray matter density and volume. Other studies looked into the integrity of cerebral white matter (WM) fibers, using fractional anisotropy (FA) via diffusion tensor imaging (DTI). FA is a measure of the deviation from isotropy that shows the degree to which the diffusion tensor is "anisotropic," and high FA is found in the brain regions that contain white matter fibers because the water molecules move more easily parallel to the fibers (Ciccarelli et al. 2008). For example, Marks et al. (2007) studied cerebral WM integrity with regard to aerobic fitness in the elderly. In 28 individuals, they found that greater aerobic fitness was related to greater WM integrity in the uncinate fasciculus and the cingulum, indicating more efficient processing of information. Other authors looked at both gray matter volume and white matter integrity: Gordon et al. (2008) found evidence of beneficial effects of physical activity on both gray matter volume and WM integrity. They analyzed volumetric differences in cerebrospinal fluid and gray and white matter, along with neuropsychological data, in adults differing in age, fitness, and education. Cognitive performance was correlated with fitness and education. In the structural MRI analyses, they found that fitness in the elderly correlated with preserved gray matter volume and WM integrity, as determined by VBM, in the areas that showed the most age-related decline in general, most notably gray and white matter in medial-temporal, parietal, and frontal areas. A further study (Ho et al. 2011) also found that greater physical activity was associated with greater average tissue volumes in white matter of the corona radiata extending into the parietal–occipital junction in a sample of 226 healthy elderly, after controlling for age, sex, and education. However, they also

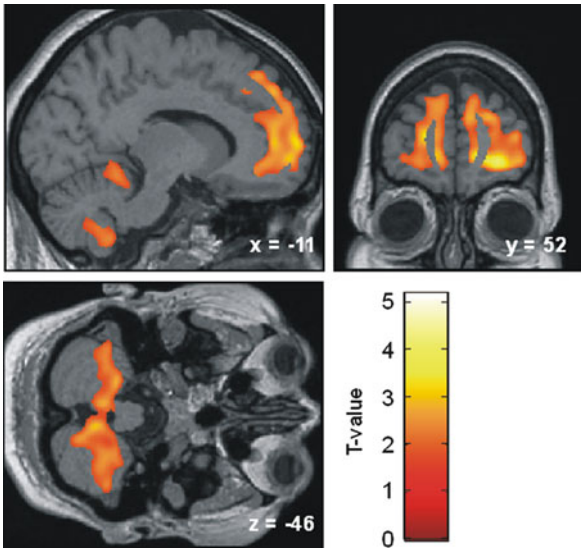

Fig. 20.1 Regions where gray matter volume was significantly associated with total physical activity. The two clusters are illustrated where gray matter volume was significantly correlated with physical activity levels (corrected for age, sex, education, depression, alcohol consumption, and smoking, $p < 0.05$; FWE corrected cluster extent threshold). A color-coded statistical parametric map is superimposed on the normalized T1-weighted image of one of the subjects (from Floel et al. 2010, with permission)

found that body mass index (BMI) was highly correlated with physical activity (and education). When BMI was included with physical activity and education in the same model, only the BMI effects remained significant. Thus, BMI may be a key factor explaining some of the observed relationship between physical activity and brain structure. Finally, Floel et al. (2010) combined extensive neuropsychological testing with assessment of physical activity, aerobic fitness, and neurotrophic factors in addition to cerebral gray matter volume. They found that physical activity, but not cardiovascular fitness, was associated with better memory encoding in a word list learning task, after controlling for age and sex. Higher levels of physical activity were associated with increased gray matter volume in prefrontal and cingulate cortex as assessed by MR-based VBM (see Fig. 20.1). Moreover, serum levels of the neurotrophic factor (see also Chap. 8) granulocyte-colony stimulating factor (G-CSF) were higher in individuals with higher levels of physical activity, pointing to a possible mediating factor between physical activity and increases in gray matter brain volume. However, these findings need to be substantiated in further studies: Cross-sectional data on the association of neurotrophin levels with physical activity are still scarce and remain controversial. In fact, some studies even suggested that increased levels of cardiorespiratory fitness and habitual exercise are associated with lower resting levels of serum brain-derived neurotrophic factor (BDNF) in healthy humans (Currie et al. 2009).

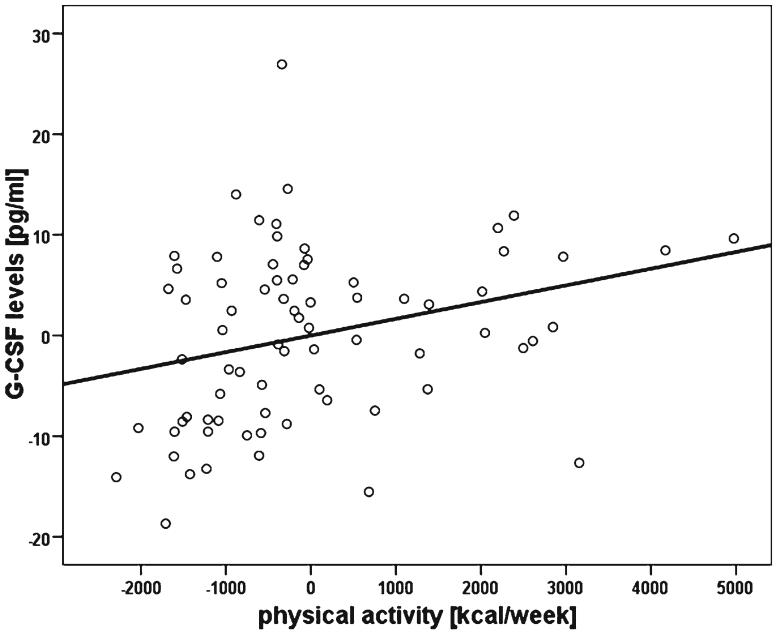

Fig. 20.2 Positive association of level of physical activity with G-CSF levels (*$p<0.05$). The *graph* shows residuals of G-CSF levels after correcting for age, sex, education, depression, alcohol consumption, and smoking plotted against physical activity levels. Weighted least squares regression instead of ordinary least squares regression was used because of heteroscedasticity (from Floel et al. 2010, with permission)

Results from short-term interventions suggest that vigorous exercise in young healthy subjects leads to an increase in BDNF release in peripheral blood, with more sustained BDNF levels after intense exercise related to better short-term success on a learning task (Winter et al. 2007). These findings are corroborated by a study examining the effects of 4 weeks of aerobic exercise training in patients with multiple sclerosis. Here a small increase in BDNF (Schulz et al. 2004) was noted, again pointing to the possibility that exercise leads to at least a short-term increase in neurotrophic factors. However, after a 6-month intervention of physical activity in MCI patients, reduced circulating levels of BDNF were noted (Baker et al. 2010).

The cited human studies are in line with animal experiments that found the most pronounced effect of exercise on BDNF in the first few days after the start of an exercise regime, tailing off after about 4 weeks of training (Gomez-Pinilla et al. 2001; Molteni et al. 2002). Thus, with regular low-intensity physical activity, some neurotrophin concentrations may remain on a permanently slightly higher level like G-CSF (Floel et al. 2010) (see Fig. 20.2), while others like BDNF may not (Baker et al. 2010; Currie et al. 2009).

The association of cardiorespiratory fitness with cognitive function, as well as brain structure, has also been studied in other chronic diseases of the central nervous

system, including multiple sclerosis (Prakash et al. 2010; White and Castellano 2008). Here exercise-induced cerebral plasticity may support functional reorganization in the presence of disease-induced brain lesions. Prakash et al. (2010) found a positive association between cardiorespiratory fitness and regional gray matter volumes, using VBM, in midline cortical structures including the medial frontal gyrus, anterior cingulate cortex and the precuneus, and higher focal FA values in the left thalamic radiation and right anterior corona radiata. Both preserved gray matter volume and white matter tract integrity were associated with better performance on measures of processing speed. They interpreted their finding as suggestive that fitness exerts a prophylactic influence on the structural decline observed early on, preserving neuronal integrity in multiple sclerosis.

20.4 Gene–Environment Interactions

Genetic factors interact with both susceptibility to cognitive decline and the impact of lifestyle factors on cognition (Anttila et al. 2004; Dufouil et al. 2000; Kivipelto et al. 2008; Lindenberger et al. 2008; Rovio et al. 2005a; Zhang et al. 2009). The polymorphism most extensively studied so far is APOE ε2–4. This polymorphism has shown to influence the incidence of AD, the conversion rate of MCI to AD (Lopez et al. 2003; Tervo et al. 2004), and the response of AD patients to drugs currently approved for the treatment of AD (acetylcholinesterase inhibitors) (Cacabelos 2008). Moreover, a study in 2001 first demonstrated that sedentary individuals with APOE ε4 genotype were of particular risk for cognitive decline (Schuit et al. 2001). Studies conducted in the following years have generally pointed in a similar direction: Etnier et al. (2007) examined 90 community-dwelling older women for several cognitive parameters, aerobic fitness, and APOE genotype and found that individuals with a high-risk genotype benefit the most from being more aerobically fit. Rovio et al. (2005b) examined 1,449 persons at baseline in 1972 and 21 years later. Here in this sample, 117 individuals had some form of dementia, with 76 individuals being diagnosed with AD. Multiple logistic regression analysis showed that leisure-time physical activity at least twice a week during midlife was associated with a reduced risk of dementia and AD, after adjusting for several factors including APOE genotype; however, this association was particularly strong in the APOE ε4 carriers. Podewils et al. (2005) studied 3,375 men and women, and physical activity was determined by the modified Minnesota Leisure-Time Activity Questionnaire. Approximately 5.4 years later during follow-up, participants in the highest quartile of physical energy expenditure had a trend-wise lower risk of dementia compared with those in the lowest quartile, and participants engaging in ≥4 activities had a significantly lower risk of dementia compared with those engaging in 0–1 activity. These associations were driven by the carriers of the APOE ε4 allele, which showed a stronger association, while the non-APOE ε4 carriers alone failed to show a significant association. Epidemiological studies even showed evidence that midlife physical activity has a more pronounced positive effect on dementia risk in APOE ε4 carriers (Kivipelto et al. 2008).

These findings are consonant with the hypothesis that homozygous "at-risk" allele carriers of specific plasticity-related polymorphisms tend to more strongly respond to lifestyle interventions in general (Witte et al. 2010). Our own previous study that assessed the effect of the "at-risk" genotype COMT Val158Met on the cognitive response to a dietary intervention (caloric restriction, or increase in unsaturated fatty acids) demonstrated that cognitive effects of dietary interventions are dependent on COMT Val158Met genotype: Homozygous Val/Val-carriers had significantly lower memory scores than Met-carriers at baseline. Dietary intervention-induced memory improvements of Val/Val-carriers were significantly greater than those of Met-carriers.

Data from another common learning-relevant single nucleotide polymorphism (SNP), which has been linked to memory performance and hippocampal processing, BDNF Val66Met (Egan et al. 2003), support this idea: Carriers of the Met-allele, associated with lower BDNF levels, experienced greater advantages in their depressive symptoms due to exercise than carriers of the Val-allele (Mata et al. 2010).

20.5 Open Issues

20.5.1 Immediate and Long-Term Effects

Beneficial effects of physical activity on cognitive function have been observed immediately after a bout of activity and following months of activity participation (see also Chaps. 17–19). While immediate effects may involve exercise-associated increases in dopamine, G-CSF, and BDNF (Winter et al. 2007), long-term effects have been reported to involve changes in vascular–metabolic parameters like inflammatory biomarkers, reduction in blood pressure, decrease in body mass index, and increase in insulin sensitivity (Mora et al. 2007). As of yet, it is unclear if vascular–metabolic parameters are also immediately affected by exercise or, conversely, if hormones are also affected on a long-term basis. If neither were the case, it would be prudent to henceforth distinguish more strictly between immediate and long-term mechanisms and possibly effects of physical activity.

20.5.2 Exercise or Fitness

Usually, regular exercise will contribute to cardiovascular—and, as we have seen, cognitive—fitness. Increased fitness will render a given exercise less demanding and stressful. The situation is further complicated by individuals who, presumably by specific genetic predispositions, demonstrate good performance in treadmill tests despite a predominantly sedentary lifestyle (Bouchard et al. 1992).

Mattson has suggested in 2000 that physical activity may activate signaling pathways involving a mild stress response and production of neurotrophic factors.

This pathway may promote survival and plasticity of neurons and may enhance cognition (Mattson 2000). If exercise benefits cognition by exerting a "mild stress," then exercise should be most beneficial to those who are the least fit. To maintain the beneficial effects of exercise, people would have to increase either their intensity or the duration of their exercise regimen.

20.6 Outlook

20.6.1 Interventional Trials

The cross-sectional results presented in this chapter do not go beyond implying an association between increased fitness level, or increased aerobic activity, and the respective outcome measures including cognitive function, brain structure, and brain activation. For more information on interventional trials, see also Chaps. 17 and 19.

20.6.2 Comprehensive Assessment of Mechanisms

Early studies have used a more comprehensive assessment of mechanisms underlying the proposed beneficial effects of activity on function and structure of the brain (Colcombe et al. 2004, 2006; Erickson et al. 2011) including neurotrophin levels (Floel et al. 2010). However, further factors should also include the effects of physical activity on glucose/insulin metabolism and markers of inflammation, which have been demonstrated to mediate beneficial effects of dietary interventions on brain functions (Mattson 2000; Wersching et al. 2010; Witte et al. 2009).

20.6.3 Combination of Interventions

The majority of studies have assessed one lifestyle factor—physical activity—in isolation and have tried to control for other factors. However, different lifestyle factors, involving also dietary habits, social interaction, and psychological well-being, may not be strictly separable but may in fact act in unison. Some studies have tried to involve not only one lifestyle factor but have tried to develop comprehensive lifestyle indexes to assess, for example, the risk of coronary heart disease (Stampfer et al. 2000), diabetes mellitus (Kurth et al. 2006), and stroke (Hu et al. 2001). Our own group (Floel et al. 2008) first assessed the relation between a composite lifestyle index and cognition in an apparently healthy elderly population. The combined lifestyle index demonstrated an association between healthy behavior and memory that was stronger than any of the individual lifestyle factors in isolation (for more details, see Sect. 20.2 above). In addition, we found both positive and inverse correlations between lifestyle components,

suggesting multiple interrelations within those factors. These findings support the hypothesis that the effects of individual lifestyle factors on cognition are complexly interrelated (pleiotropic effect) with certain healthy behaviors "neutralizing" the effect of unhealthy behaviors (Mattson 2000; Vaynman and Gomez-Pinilla 2006). For example, lifestyle components like exercise, healthy dietary habits, or moderate alcohol consumption may activate systems that act on metabolism and plasticity, like neurotrophic factors. Thus, they may ameliorate the oxidative stress that our brains accumulate as the result of a diet low in antioxidants and high in saturated fatty acids or by means of smoking (Duan et al. 2001; Vaynman and Gomez-Pinilla 2006).

Since we now have accumulating evidence on the beneficial effect of physical activity in humans, it is time to study the impact of a combined approach systematically, since synergistic beneficial effects of lifestyle interventions on progression to and treatment of dementia have been suggested (Solfrizzi et al. 2008). It was, for example, found that exercise potentiated the positive effects of dietary omega-3 fatty-acid supplementation on synaptic membranes, NMDA-receptors, and learning (Chytrova et al. 2010). Enriched environment settings in the animal literature often comprised exercise and cognitive stimulation in the "enriched environment group" (Ambrée et al. 2006; Costa et al. 2007; Galvan and Bredesen 2007; Görtz et al. 2008; Herring et al. 2009; Lazarov et al. 2005; Lewejohann et al. 2009).

20.6.4 Gene–Environment Interactions

Genetic factors interact with both susceptibility to cognitive decline and the impact of lifestyle factors on cognition (Anttila et al. 2004; Dufouil et al. 2000; Lindenberger et al. 2008; Rovio et al. 2005a; Zhang et al. 2009). So far, gene–environment interactions are only beginning to be understood, and the significance of functional polymorphisms for the response to lifestyle-based therapies in individuals with already manifest cognitive impairment is largely unknown (see Solfrizzi et al. 2008, for review). Thus, there is currently not enough information to individualize preventive strategies against cognitive decline in the elderly or to avoid conversion of MCI to AD. One set of recommendations, derived from a certain population, may not be valid in a different population or in subjects with differing genetic background. Here future studies should recruit specific cohorts of patients either carrying or not carrying respective polymorphisms, to directly compare the impact of the polymorphism on cognition and response to therapy (Cheeran et al. 2008; Mattay et al. 2003; Witte et al. 2010).

References

Abbott RD, White LR, Ross GW, Masaki KH, Curb JD, Petrovitch H (2004) Walking and dementia in physically capable elderly men. JAMA 292:1447–1453

Ambrée O, Leimer U, Herring A, Görtz N, Sachser N, Heneka MT et al (2006) Reduction of amyloid angiopathy and Abeta plaque burden after enriched housing in TgCRND8 mice: involvement of multiple pathways. Am J Pathol 169:544–552

Anttila T, Helkala E-L, Viitanen M, Kåreholt I, Fratiglioni L, Winblad B et al (2004) Alcohol drinking in middle age and subsequent risk of mild cognitive impairment and dementia in old age: a prospective population based study. BMJ (Clin Res Ed) 329:539

Baker LD, Frank LL, Foster-Schubert K, Green PS, Wilkinson CW, McTiernan A et al (2010) Effects of aerobic exercise on mild cognitive impairment: a controlled trial. Arch Neurol 67:71–79

Barnes DE, Yaffe K, Satariano WA, Tager IB (2003) A longitudinal study of cardiorespiratory fitness and cognitive function in healthy older adults. J Am Geriatr Soc 51:459–465

Bouchard C, Dionne FT, Simoneau JA, Boulay MR (1992) Genetics of aerobic and anaerobic performances. Exerc Sport Sci Rev 20:27–58

Cacabelos R (2008) Pharmacogenomics and therapeutic prospects in dementia. Eur Arch Psychiatry Clin Neurosci 258(Suppl 1):28–47

Cheeran B, Talelli P, Mori F, Koch G, Suppa A, Edwards M et al (2008) A common polymorphism in the brain derived neurotrophic factor gene (BDNF) modulates human cortical plasticity and the response to rTMS. J Physiol 586(Pt 23):5717–5725

Chytrova G, Ying Z, Gomez-Pinilla F (2010) Exercise contributes to the effects of DHA dietary supplementation by acting on membrane-related synaptic systems. Brain Res 1341:32–40

Ciccarelli O, Catani M, Johansen-Berg H, Clark C, Thompson A (2008) Diffusion-based tractography in neurological disorders: concepts, applications, and future developments. Lancet Neurol 7(8):715–727, 7 Aug 2008

Colcombe SJ, Erickson KI, Raz N, Webb AG, Cohen NJ, McAuley E et al (2003) Aerobic fitness reduces brain tissue loss in aging humans. J Gerontol A Biol Sci Med Sci 58:176–180

Colcombe SJ, Kramer AF, Erickson KI, Scalf P, McAuley E, Cohen NJ et al (2004) Cardiovascular fitness, cortical plasticity, and aging. Proc Natl Acad Sci USA 101:3316–3321

Colcombe SJ, Erickson KI, Scalf PE, Kim JS, Prakash R, McAuley E et al (2006) Aerobic exercise training increases brain volume in aging humans. J Gerontol A Biol Sci Med Sci 61:1166–1170

Costa DA, Cracchiolo JR, Bachstetter AD, Hughes TF, Bales KR, Paul SM et al (2007) Enrichment improves cognition in AD mice by amyloid-related and unrelated mechanisms. Neurobiol Aging 28:831–844

Currie J, Ramsbottom R, Ludlow H, Nevill A, Gilder M (2009) Cardio-respiratory fitness, habitual physical activity and serum brain derived neurotrophic factor (BDNF) in men and women. Neurosci Lett 451:152–155

Duan W, Lee J, Guo Z, Mattson MP (2001) Dietary restriction stimulates BDNF production in the brain and thereby protects neurons against excitotoxic injury. J Mol Neurosci 16:1–12

Dufouil C, Tzourio C, Brayne C, Berr C, Amouyel P, Alpérovitch A (2000) Influence of apolipoprotein E genotype on the risk of cognitive deterioration in moderate drinkers and smokers. Epidemiology 11:280–284

Egan MF, Kojima M, Callicott JH, Goldberg TE, Kolachana BS, Bertolino A et al (2003) The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell 112:257–269

Erickson KI, Prakash RS, Voss MW, Chaddock L, Hu L, Morris KS et al (2009) Aerobic fitness is associated with hippocampal volume in elderly humans. Hippocampus 19:1030–1039

Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, Chaddock L et al (2011) Exercise training increases size of hippocampus and improves memory. Proc Natl Acad Sci USA 108:3017–3022

Etgen T, Sander D, Huntgeburth U, Poppert H, Forstl H, Bickel H (2010) Physical activity and incident cognitive impairment in elderly persons: the INVADE study. Arch Intern Med 170:186–193

Etnier JL, Caselli RJ, Reiman EM, Alexander GE, Sibley BA, Tessier D et al (2007) Cognitive performance in older women relative to ApoE-epsilon4 genotype and aerobic fitness. Med Sci Sports Exerc 39:199–207

Floel A, Witte AV, Lohmann H, Wersching H, Ringelstein EB, Berger K et al (2008) Lifestyle and memory in the elderly. Neuroepidemiology 31:39–47

Floel A, Ruscheweyh R, Kruger K, Willemer C, Winter B, Volker K et al (2010) Physical activity and memory functions: are neurotrophins and cerebral gray matter volume the missing link? Neuroimage 49:2756–2763

Galvan V, Bredesen DE (2007) Neurogenesis in the adult brain: implications for Alzheimer's disease. CNS Neurol Disord Drug Targets 6:303–310
Geda YE, Roberts RO, Knopman DS, Christianson TJ, Pankratz VS, Ivnik RJ et al (2010) Physical exercise, aging, and mild cognitive impairment: a population-based study. Arch Neurol 67:80–86
Gomez-Pinilla F, Ying Z, Opazo P, Roy RR, Edgerton VR (2001) Differential regulation by exercise of BDNF and NT-3 in rat spinal cord and skeletal muscle. Eur J Neurosci 13:1078–1084
Good CD, Johnsrude IS, Ashburner J, Henson RN, Friston KJ, Frackowiak RS (2001) A voxel-based morphometric study of ageing in 465 normal adult human brains. Neuroimage 14:21–36
Gordon BA, Rykhlevskaia EI, Brumback CR, Lee Y, Elavsky S, Konopack JF et al (2008) Neuroanatomical correlates of aging, cardiopulmonary fitness level, and education. Psychophysiology 45:825–838
Görtz N, Lewejohann L, Tomm M, Ambrée O, Keyvani K, Paulus W et al (2008) Effects of environmental enrichment on exploration, anxiety, and memory in female TgCRND8 Alzheimer mice. Behav Brain Res 191:43–48
Hamer M, Chida Y (2009) Physical activity and risk of neurodegenerative disease: a systematic review of prospective evidence. Psychol Med 39:3–11
Herring A, Ambrée O, Tomm M, Habermann H, Sachser N, Paulus W et al (2009) Environmental enrichment enhances cellular plasticity in transgenic mice with Alzheimer-like pathology. Exp Neurol 216:184–192
Hillman CH, Motl RW, Pontifex MB, Posthuma D, Stubbe JH, Boomsma DI et al (2006) Physical activity and cognitive function in a cross-section of younger and older community-dwelling individuals. Health Psychol 25:678–687
Ho AJ, Raji CA, Becker JT, Lopez OL, Kuller LH, Hua X et al (2011) The effects of physical activity, education, and body mass index on the aging brain. Hum Brain Mapp 32(9):1371–1382
Hu FB, Manson JE, Stampfer MJ, Colditz G, Liu S, Solomon CG et al (2001) Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. N Engl J Med 345:790–797
Kivipelto M, Rovio S, Ngandu T, Kareholt I, Eskelinen M, Winblad B et al (2008) Apolipoprotein E epsilon4 magnifies lifestyle risks for dementia: a population-based study. J Cell Mol Med 12:2762–2771
Kurth T, Moore SC, Gaziano JM, Kase CS, Stampfer MJ, Berger K et al (2006) Healthy lifestyle and the risk of stroke in women. Arch Intern Med 166:1403–1409
Laurin D, Verreault R, Lindsay J, MacPherson K, Rockwood K (2001) Physical activity and risk of cognitive impairment and dementia in elderly persons. Arch Neurol 58:498–504
Lazarov O, Robinson J, Tang Y-P, Hairston IS, Korade-Mirnics Z, Lee VMY et al (2005) Environmental enrichment reduces Abeta levels and amyloid deposition in transgenic mice. Cell 120:701–713
Lewejohann L, Reefmann N, Widmann P, Ambrée O, Herring A, Keyvani K et al (2009) Transgenic Alzheimer mice in a semi-naturalistic environment: more plaques, yet not compromised in daily life. Behav Brain Res 201(1):99–102
Lindenberger U, Nagel IE, Chicherio C, Li SC, Heekeren HR, Backman L (2008) Age-related decline in brain resources modulates genetic effects on cognitive functioning. Front Neurosci 2:234–244
Lopez OL, Jagust WJ, Dulberg C, Becker JT, DeKosky ST, Fitzpatrick A et al (2003) Risk factors for mild cognitive impairment in the Cardiovascular Health Study Cognition Study: part 2. Arch Neurol 60:1394–1399
Lytle ME, Vander Bilt J, Pandav RS, Dodge HH, Ganguli M (2004) Exercise level and cognitive decline: the MoVIES project. Alzheimer Dis Assoc Disord 18:57–64
Marks BL, Madden DJ, Bucur B, Provenzale JM, White LE, Cabeza R et al (2007) Role of aerobic fitness and aging on cerebral white matter integrity. Ann N Y Acad Sci 1097:171–174
Mata J, Thompson RJ, Gotlib IH (2010) BDNF genotype moderates the relation between physical activity and depressive symptoms. Health Psychol 29(2):130–133
Mattay VS, Goldberg TE, Fera F, Hariri AR, Tessitore A, Egan MF et al (2003) Catechol O-methyltransferase val158-met genotype and individual variation in the brain response to amphetamine. Proc Natl Acad Sci USA 100:6186–6191
Mattson MP (2000) Neuroprotective signaling and the aging brain: take away my food and let me run. Brain Res 886:47–53

Molteni R, Ying Z, Gomez-Pinilla F (2002) Differential effects of acute and chronic exercise on plasticity-related genes in the rat hippocampus revealed by microarray. Eur J Neurosci 16:1107–1116
Mora S, Cook N, Buring JE, Ridker PM, Lee IM (2007) Physical activity and reduced risk of cardiovascular events: potential mediating mechanisms. Circulation 116:2110–2118
Pereira AC, Huddleston DE, Brickman AM, Sosunov AA, Hen R, McKhann GM et al (2007) An in vivo correlate of exercise-induced neurogenesis in the adult dentate gyrus. Proc Natl Acad Sci USA 104(13):5638–5643 Epub 20 Mar 2007
Podewils LJ, Guallar E, Kuller LH, Fried LP, Lopez OL, Carlson M et al (2005) Physical activity, APOE genotype, and dementia risk: findings from the Cardiovascular Health Cognition Study. Am J Epidemiol 161:639–651
Prakash RS, Snook EM, Motl RW, Kramer AF (2010) Aerobic fitness is associated with gray matter volume and white matter integrity in multiple sclerosis. Brain Res 1341:41–51
Rovio S, Kåreholt I, Helkala E-L, Viitanen M, Winblad B, Tuomilehto J et al (2005a) Leisure-time physical activity at midlife and the risk of dementia and Alzheimer's disease. Lancet Neurol 4:705–711
Rovio S, Kareholt I, Helkala EL, Viitanen M, Winblad B, Tuomilehto J et al (2005b) Leisure-time physical activity at midlife and the risk of dementia and Alzheimer's disease. Lancet Neurol 4:705–711
Scarmeas N, Levy G, Tang MX, Manly J, Stern Y (2001) Influence of leisure activity on the incidence of Alzheimer's disease. Neurology 57:2236–2242
Schuit AJ, Feskens EJ, Launer LJ, Kromhout D (2001) Physical activity and cognitive decline, the role of the apolipoprotein e4 allele. Med Sci Sports Exerc 33:772–777
Schulz KH, Gold SM, Witte J, Bartsch K, Lang UE, Hellweg R et al (2004) Impact of aerobic training on immune-endocrine parameters, neurotrophic factors, quality of life and coordinative function in multiple sclerosis. J Neurol Sci 225:11–18
Solfrizzi V, Capurso C, D'Introno A, Colacicco AM, Santamato A, Ranieri M et al (2008) Lifestyle-related factors in predementia and dementia syndromes. Expert Rev Neurother 8:133–158
Stampfer MJ, Hu FB, Manson JE, Rimm EB, Willett WC (2000) Primary prevention of coronary heart disease in women through diet and lifestyle. N Engl J Med 343:16–22
Sturman MT, Morris MC, Mendes de Leon CF, Bienias JL, Wilson RS, Evans DA (2005) Physical activity, cognitive activity, and cognitive decline in a biracial community population. Arch Neurol 62:1750–1754
Tervo S, Kivipelto M, Hanninen T, Vanhanen M, Hallikainen M, Mannermaa A et al (2004) Incidence and risk factors for mild cognitive impairment: a population-based three-year follow-up study of cognitively healthy elderly subjects. Dement Geriatr Cogn Disord 17:196–203
van Gelder BM, Tijhuis MA, Kalmijn S, Giampaoli S, Nissinen A, Kromhout D (2004) Physical activity in relation to cognitive decline in elderly men: the FINE Study. Neurology 63:2316–2321
Vaynman S, Gomez-Pinilla F (2006) Revenge of the "sit": how lifestyle impacts neuronal and cognitive health through molecular systems that interface energy metabolism with neuronal plasticity. J Neurosci Res 84:699–715
Verghese J, Lipton RB, Katz MJ, Hall CB, Derby CA, Kuslansky G et al (2003) Leisure activities and the risk of dementia in the elderly. N Engl J Med 348:2508–2516
Wersching H, Duning T, Lohmann H, Mohammadi S, Stehling C, Fobker M et al (2010) Serum C-reactive protein is linked to cerebral microstructural integrity and cognitive function. Neurology 74:1022–1029
Weuve J, Kang JH, Manson JE, Breteler MM, Ware JH, Grodstein F (2004) Physical activity, including walking, and cognitive function in older women. JAMA 292:1454–1461
White LJ, Castellano V (2008) Exercise and brain health – implications for multiple sclerosis: Part 1 – neuronal growth factors. Sports Med 38:91–100
Wilson RS, Bennett DA, Bienias JL, Aggarwal NT, Mendes de Leon CF, Morris MC et al (2002) Cognitive activity and incident AD in a population-based sample of older persons. Neurology 59:1910–1914
Winter B, Breitenstein C, Mooren FC, Voelker K, Fobker M, Lechtermann A et al (2007) High impact running improves learning. Neurobiol Learn Mem 87:597–609

Witte AV, Fobker M, Gellner R, Knecht S, Floel A (2009) Caloric restriction improves memory in elderly humans. Proc Natl Acad Sci USA 106:1255–1260

Witte AV, Jansen S, Schirmacher A, Young P, Floel A (2010) COMT Val158Met polymorphism modulates cognitive effects of dietary intervention. Front Aging Neurosci 2:146

Yaffe K, Barnes D, Nevitt M, Lui LY, Covinsky K (2001) A prospective study of physical activity and cognitive decline in elderly women: women who walk. Arch Intern Med 161:1703–1708

Yamada M, Kasagi F, Sasaki H, Masunari N, Mimori Y, Suzuki G (2003) Association between dementia and midlife risk factors: the Radiation Effects Research Foundation Adult Health Study. J Am Geriatr Soc 51:410–414

Zhang H, Kranzler HR, Poling J, Gruen JR, Gelernter J (2009) Cognitive flexibility is associated with KIBRA variant and modulated by recent tobacco use. Neuropsychopharmacology 34(12):2508–2516

Part V
Effects of Exercise on Affective Processing

Chapter 21
The Effects of Exercise on Brain Cortical Function and Its Implication on Mental Health and Mood

Stefan Schneider and Heiko K. Strüder

Abstract In this chapter, we will review present theories connecting exercise-related changes to brain cortical activity and changes in mood. Current models in neuropsychology as the model of frontal asymmetry and the transient hypofrontality theory propose that mood improvements after acute exercise are dependent on deactivation patterns especially in (pre-)frontal cortex areas. Moreover, there is good evidence that improvements in mood, as well as accompanying neuropsychological changes, are linked to an individual dose–response relationship as well as individual exercise preferences, which connects well to the psychological model of "flow."

> People without clinical mood disorders rank exercise near the top among the behaviors they use to self-manage their moods
>
> (Thayer et al. 1994).

21.1 Introduction

While regular physical activity is primarily recommended for its beneficial effects on cardiorespiratory health and fitness, habitual exercisers often cite the positive effect of exercise and physical activity on mood and general well-being. There is a growing body of evidence to support the positive psychological effects of exercise. Nevertheless, the neurophysiological mechanisms underlying the link between exercise and acute changes in mood are not clear, but it is likely that changes in the concentration of different neurotransmitters (Buckworth and Dishman 2002; Hollmann and Strüder 2003) and alterations in central neural activity (Hall et al. 2007) play a determining role.

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Already 15 years ago, Yeung (1996) reviewed 81 studies that investigated the influence of a single bout of exercise on mood and mental state. The vast majority (85%) of these studies found an improvement in mood and mental state with exercise, and this benefit seems to be dependent on the duration and intensity of the exercise (Ekkekakis and Lind 2006; Lind et al. 2005). In spite of a general agreement that exercise improves mood and cognitive performance, there is an ongoing debate regarding dose–response effects of exercise (Ekkekakis et al. 2000; Ekkekakis and Petruzzello 1999). Recent evidence suggests that the transition from aerobic to anaerobic exercise metabolism seems to have a positive impact on mood (Hall et al. 2002). Furthermore, there is a consensus that changes in mood should be monitored on an individual level, as experiments on a group level might blur these effects (Ekkekakis and Petruzzello 1999; Schneider et al. 2009b).

In the last 5 years, there has been an increased interest in detecting the underlying neurophysiological processes of the effects of exercise on mood and cognitive performance. Research using brain imaging methods, such as positron-emission tomography (PET) or functional magnetic resonance imaging (fMRI), is still in its early stages, as imaging is difficult to conduct in exercise settings. However, it can be seen from these studies that exercise does recruit not only motor control regions but also areas regulating emotional and cognitive processes, especially in the (pre-) frontal cortex (PFC). From affective neuroscience and exercise psychobiology, it is known that the PFC plays a major role in processing emotions such as fatigue, distress, and tension (Faw 2003). Evidence suggests that the frontal cortex regulates amygdala activity via top-down projections (Mcdonald et al. 1996; Sesack et al. 1989), impacting on emotional regulation, classified as *Perceiver*, *Verbalizer*, *Motivator*, *Attender*, and *Coordinator* (Faw 2003).

In this chapter, we review current theories connecting exercise-related changes to brain cortical activity, measured by electroencephalography (EEG, for a detailed introduction to the use of EEG in exercise science, please see Chap. 9), and changes in mood. Indeed, these theories mainly focus on changes in (pre-)frontal cortical areas but also take into account that relevant changes are dependent on a dose–response relationship as well as individual exercise preferences. Finally, we attempt to relate the current discussion to the model of "flow" and suggest recommendations for further research activities.

21.2 The Model of Frontal Asymmetry

The model of frontal asymmetry has gained increased attention in the exercise literature over the last years. The model of frontal asymmetry, first put forward by Davidson in 1979 (Davidson et al. 1979), proposes that higher activity of the left PFC, in comparison to the right side, is associated with the experience and expression of positive affect and approach-related emotions. Conversely, greater right PFC activity is related in the expression and experience of negative avoidance-related emotions (Allen and Kline 2004; Harmon-Jones 2004; Schutter et al. 2008). As such,

frontal EEG asymmetry may serve as a marker of emotional anxiety and/or relaxation (Coan and Allen 2004) associated with exercise, especially as Harmon-Jones (2004) suggested that an increase in left frontal cortex activity is associated with an increase in psychological and physical well-being.

The model of frontal asymmetry is based on changes in alpha activity, which is calculated by subtracting cortical alpha activity recorded over left frontal regions (EEG electrode position F3) from cortical activity recorded over right frontal regions (EEG electrode position F4). This is accomplished either by a simple subtraction of log-transformed alpha activity (log F4 − log F3) (Woo et al. 2009) or by similar equations. For example, Vogt et al. (2010) used (right − left) / (right + left) as proposed by Kline et al. (1999).

In the last two decades, a number of studies have evaluated the effects of exercise on mood and affect using the model of frontal asymmetry. First, Petruzzello and Landers (1994) studied the link between frontal asymmetry and anxiety: After running for 30 min on a treadmill with an intensity of 75% $\dot{V}O_2$max, anxiety levels were reduced in 19 participants 10, 20, and 30 min postexercise. Moreover, preexercise EEG alpha asymmetry was significantly related to anxiety and was able to explain 30% of the variance of the postexercise anxiety. Woo et al. (2010) were able to show an increase in self-reported vigor after a 30-min steady-state treadmill exercise at three different intensity levels (below, at, and above the individual ventilatory threshold), and this effect was associated with an increase in right-sided alpha activity. Interestingly, a time-dependent dose–response relationship was reported for the same population (Woo et al. 2009): While running at a fixed intensity at the individual ventilatory threshold (approx. 60% $\dot{V}O_2$max) for 15, 30, or 45 min, the authors observed a clear effect on vigor and an increase in right frontal alpha activity only for the 30-min trial. Considering a basic model of brain activation where alpha activity is regarded as a sign for cortical relaxation, this is equivalent to an increase in left-sided activity, hence, confirming the model of frontal asymmetry. Similar results were recently reported by Vogt et al. (2010): Instead of predefining exercise duration and intensity, they calculated frontal asymmetry in a group of elderly people walking at a self-selected pace for a self-selected time frame in a natural setting and could show an increase in right frontal alpha activity and perceived physical health after exercise.

Besides this state-dependent dimension of frontal asymmetry (i.e., frontal asymmetry as an index of current affective state), a state-independent dimension of frontal asymmetry has been used to predict individual affective responses to exercise, i.e., some individuals will show greater left-sided prefrontal activity under rest conditions without emotional stimulation compared to other individuals, and this can serve as a predictor for individual responses to exercise (Coan and Allen 2004; Tomarken et al. 1992). While Schneider et al. (2009a) were able to confirm the assumption that left-dominant adolescents reported more positive affect compared to right-dominant adolescents during *moderate* exercise intensity (30 min cycle ergometry of 98 participants), no significant association was found for *hard* exercise. In contrast, Hall et al. (2007) could show that greater relative left frontal activity predicted tiredness and calmness using the Activation Deactivation Adjective

Check List during recovery from exercise, but not tension or energy during a strenuous *maximal* graded exercise test. They later acknowledged an exercise intensity specific predictability of frontal asymmetry on affective response, i.e., showing that greater relative left frontal activity preexercise predicted increased positive affect and reduced state anxiety after cycling for 30 min at 70% $\dot{V}O_2$max but not at 55% $\dot{V}O_2$max (Hall et al. 2010). Not only exercise intensity but also aerobic fitness seems to influence the relationship between resting frontal asymmetry and exercise-related affective responsivity: Petruzzello et al. (2001) showed that resting frontal EEG asymmetry predicted affect only in a high-fit group, compared to a group of low/moderate-fit participants during a 30-min treadmill exercise at 75% $\dot{V}O_2$max.

It is important to stress that according to the "approach-withdrawal model," alpha activity is inversely related to cerebral activity, and likewise, an increase of right-sided alpha activity would be interpreted as a decrease of right cortical activity. But this issue is currently under debate (Cooper et al. 2003; Schutter et al. 2008). In addition, as current results suggest relevant exercise-induced changes also in the beta frequency range, it might be necessary to extend the model of frontal asymmetry to other frequency ranges (Schneider et al. 2008). Furthermore, it was pointed out that the "approach-withdrawal model" sometimes contrasts similar valences (Harmon-Jones 2004). For example, anger is a negative valence but often evokes approach motivation. Similar lines of argumentation were raised by Hall et al. (2010), who noted that a decrease in energetic arousal was correlated with greater left-sided activity, which is in contrast to the predictions of the "valence-motivation model" but could be explained by the fact that low energetic arousal could be indicative of approach motivation, especially at higher exercise intensities. Finally, it should be taken into consideration that specific adjectives used to assess actual mood states might have slightly different significance after exercise. For example, tiredness after exercise might be experienced as positive, especially as it seems to covary with calmness (Hall et al. 2007). Also, a reduced "willingness to seek contact" (Schneider et al. 2009b) is generally negatively connoted, but after exercise, it might represent a state of inner flow.

21.3 The Transient Hypofrontality Hypothesis/the Dual-Mode Theory

Dietrich's "transient hypofrontality theory" (Dietrich 2006) assumes that exercise reduces activity within the prefrontal cortex. This hypothesis, which is based on the assumption that cerebral blood flow remains stable during exercise, postulates that an increase in oxygen consumption in motor regions results in a decrease in blood flow in nonmotor regions like the prefrontal cortex. The "transient hypofrontality theory" is supported by PET findings showing a decreased prefrontal cortex activity during exercise (Tashiro et al. 2008). Also, a study by our group (Schneider et al. 2010a) found an increase in alpha frequency immediately after exercise, indicating decreased cortical activity. The "transient hypofrontality

theory" is, however, limited by the fact that it does not explain why no other brain regions are affected as well.

Recently, Ekkekakis brought up another concept that is closely linked to the hypofrontality theory, the so-called dual-mode theory (Ekkekakis 2009; Ekkekakis and Lind 2006). Within the framework of a dose–response relationship of exercise, it postulates that with ongoing exercise intensity, cognitive processing, originating in prefrontal cortex, systematically shifts toward interoceptive processing. Thereby, the multiple subcortical processing routes directing interoceptive information to the amygdala become a primary route of affect induction (Ekkekakis and Lind 2006). Both theories postulate a shift of cortical resources *during* exercise away from regions responsible for cognitive and emotional processing. Hence, previously "overloaded" brain regions are downregulated, due to the increased computational demand of brain regions associated with exercise. After exercise, the tremendous workload will result in physical relaxation, which is associated with an increase in alpha frequency activity in the precuneus immediately after exercise (Schneider et al. 2009c). These results let the authors speculate that phases of increased physical activity and arousal might be mirrored by an increase of alpha activity in the precuneus (i.e., an increase of tonic alpha activity would be interpreted as a decrease of cortical activation and reflects a more synchronized cortical state (Miller 2007)). The precuneus in the superior parietal lobe is believed to contain a sensory-based map of one's own body (Cavanna 2007). Precuneus activation has been documented in healthy subjects engaged in self-related mental representation and episodic/autobiographical memory retrieval (Cavanna 2007). In contrast, hypometabolism in the precuneus is reported during sleep, hypnosis, vegetative state, and impaired consciousness (Cavanna 2007). Therefore, it is assumed that the precuneus belongs to the neural network subserving awareness and producing a conscious self-percept (Cavanna 2007). Tashiro et al. (2008) were able to demonstrate that the adjusted regional metabolic rate ratio is increased in sensorimotor and premotor but decreased in temporal and prefrontal cortex areas while running. Within two recent studies, Schneider et al. reported a decrease of cortical high-frequency activity (beta activity, desynchronized state of the brain, indicator for excitatory brain activity) in areas that are responsible for language processing (Brodmann areas 21/22) (Schneider et al. 2009c, 2010a), as well as an increase in alpha activity (synchronized state of the brain, indicator for decrease of brain cortical activity) in prefrontal cortex areas (Schneider et al. 2010a).

21.4 Methodological Considerations

At present, given existing inconsistencies in the literature, we are still far away from understanding the effects of exercise on mood and emotions. One of the major problems is the lack of reproducibility of results obtained in different experimental setups. Beyond differences in the experimental setup, relaxational effects of exercise seem to be linked to individuals' physical activity history and

to exercise preferences (Boutcher and Landers 1988; Shibata et al. 1997). Especially with regard to mood changes, remarkable differences can be found when testing exercise-experienced or exercise-inexperienced subjects. Every physical burden in an exercise-inexperienced population is likely to result in negative affect states simply because this population tends to dislike exercise. Secondly, it might be important to respect individual exercise preferences. It is likely that, for example, an experienced biker tested on a treadmill might show only discrete changes in mood parameters because the exercise differs from accepted customs, whereas the same person might show positive mood values after an intensive bike session. Moreover, differences may emerge from studies in laboratory versus outdoor sessions. There have been calls to normalize and standardize exercise protocols and exercise conditions in order to better understand the neurobiology of exercise. However, pertinent mood ratings are dependent on an individual exercise history, for example, the type of exercise (biking, cycling, endurance sports, team sports, etc.), but also the chosen intensity.

According to this rationale, we started to perform a first couple of experiments hypothesizing that changes in brain cortical activity are linked to preferred exercise intensities as well as to the participants exercise history: In a first study, we asked 24 recreational runners aged 21–45 to complete three outdoor running trials at a low (50–55% $\dot{V}O_2$peak), high (80–85% $\dot{V}O_2$peak), and preferred running intensity in a counterbalanced order. A preferred intensity was chosen as suggested by Ekkekakis and Petruzzello (1999). Running intensity during the low and high trials was established using individualized target heart rate zones that were determined using the linear relationship established between heart and $\dot{V}O_2$ during the initial treadmill running test. Before, immediately after, and 15 min after completion of each trial, global EEG activity and mood were recorded. EEG activity was divided into its specific frequency ranges alpha and beta. Mood states were assessed using the Mood Meter®, a tool developed to detect short-term changes in perceived physical state, perceived motivational state, and perceived psychological strain by Schneider et al. (2009b) and Kleinert (2006).

Data revealed a significant effect mainly on beta activity postexercise for the high and preferred running intensity (Fig. 21.1a, b). Interestingly high and preferred intensities did not differ concerning heart rate, lactate, perceived exhaustion measured by BORG scale, running time, and running distance. Interestingly, psychological strain and perceived motivational state showed a clear negative correlation with beta activity, i.e., a decrease in beta activity was accompanied by an increase in these two dimensions.

As this study was limited by the fact that only global field power was examined, we designed another study where 12 individuals aged 26.3 ± 3.8 years were asked to perform three kinds of exercise (treadmill, bike ergometry, arm crank ergometry). Following a graded exercise test until maximal exhaustion in each of the disciplines, participants were asked to perform six more tests consisting of 30-min exercise at 50% $\dot{V}O_2$max and 80% $\dot{V}O_2$max in each of the disciplines. EEG activity was recorded at 19 cortical sites following the international 10-20 (Jasper 1958) and localized using standardized low-resolution brain electromagnetic tomography

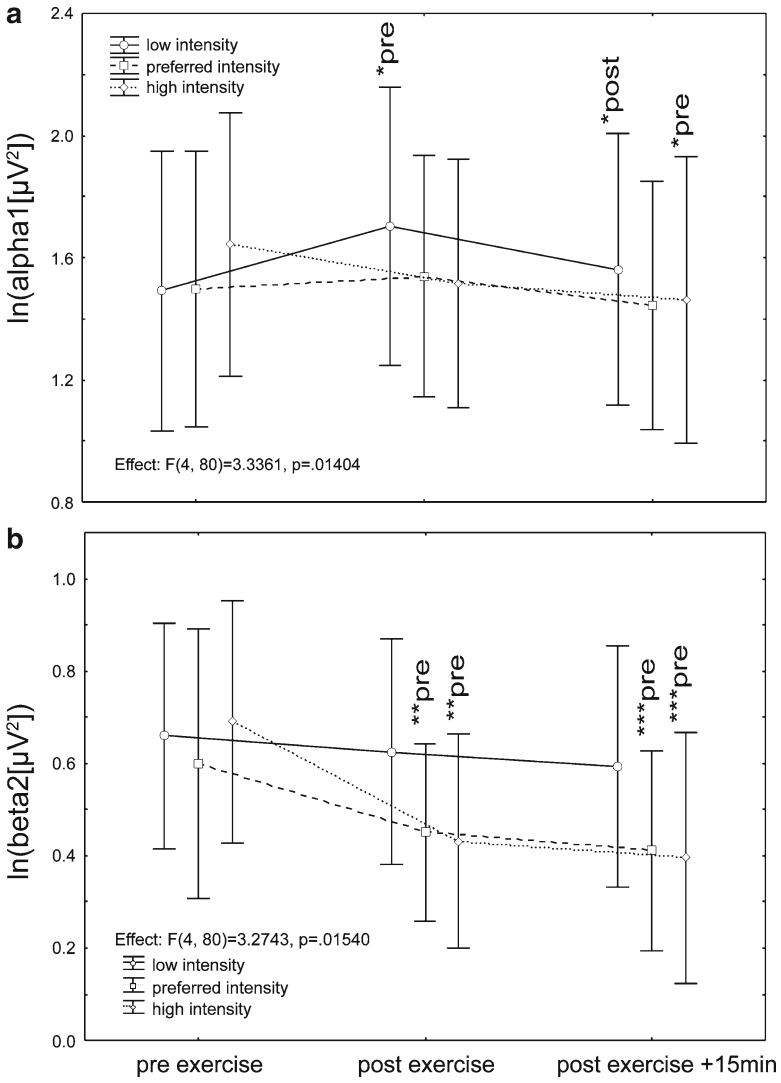

Fig. 21.1 Changes in alpha-1 (**a**) and beta-2 (**b**) activity from preexercise to immediately postexercise and 15 min postexercise for a low- and high- as well as preferred-intensity run. Whereas an increase in alpha activity could be noticed immediately postexercise in the low-intensity run, alpha activity was significantly reduced 15 min postexercise for the high-intensity run. Beta activity was significantly reduced postexercise and 15 min postexercise for the high and preferred-intensity run. *Bars* show means ±0.95 confidence intervals. *mark $p<0.05$; **$p<0.01$; ***$p<0.001$

(sLORETA) (Grech et al. 2008; Pascual-Marqui 2002; Pascual-Marqui et al. 1994, 2002) before as well as 15 and 30 min postexercise. All participants were regular runners performing a minimum of 2-h weekly training. Additionally, some of the

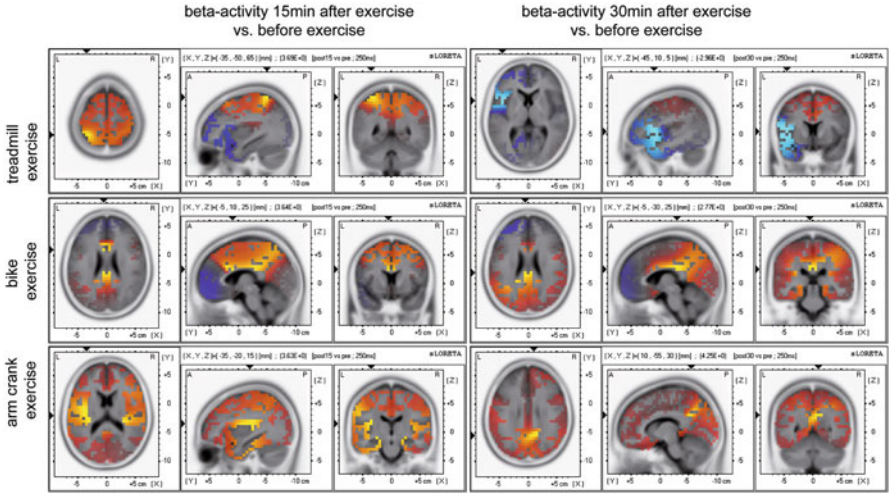

Fig. 21.2 Statistical parametric maps (SPM) of sLORETA differences in the beta-frequency band comparing 15 min postexercise versus preexercise (*left*) and 30 min postexercise versus preexercise (*right*, $n = 12$). *Red* and *yellow colors* indicate increased activity, *blue colors* decreased activity in the measurements 15 and 30 min postexercise

participants also reported cycling without exercise ambition. In contrast, none of the participants had previous experience with arm crank ergometry or similar exercise (e.g., hand biking).

As shown in Fig. 21.2, a distinct, although not significant, frontal deactivation pattern in the beta frequency range was observed 15 min after the graded treadmill and bike but not arm crank exercise test. Furthermore, 30 min postexercise, a strong decrease in left-sided frontal beta activity was observed after the treadmill condition but did not occur following the bike or arm crank exercise conditions (Fig. 21.2).

Following the 30 min of exercise at 50% $\dot{V}O_2$max and 80% $\dot{V}O_2$max, even more pronounced results were obtained: A significant ($p < 0.01$) decrease of beta activity in the frontal cortex (Brodmann areas 11, 47, 25; Fig. 21.3) was observed 15 min posttreadmill exercise at 80% $\dot{V}O_2$max, whereas no changes in frontal cortex activity could be observed after bike or arm crank exercise, nor after exercise at 50% $\dot{V}O_2$max in all of the disciplines.

These results demonstrate the impact of exercise on prefrontal cortex activity, as pointed out in the beginning of this chapter, and are also compatible with findings arguing for a dose–response relationship. Furthermore, these data also show the impact of individual exercise preference (Schneider et al. 2009b).

In conclusion, the relationship between mood, exercise, and neurophysiological changes has been a comparatively underrepresented field of research. With the advance of new technologies, the field of neuroimaging in exercise science will probably become a major research theme in the next decade. Already some major hypotheses have been developed, especially a “frontal brain theory,” a “dose–response

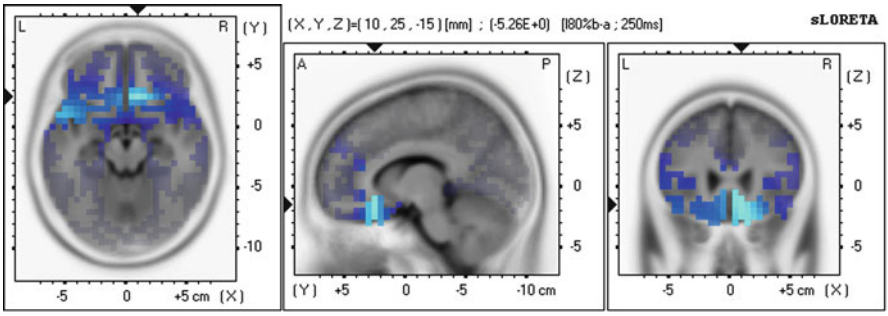

Fig. 21.3 Statistical parametric map of sLORETA differences in the beta frequency range comparing electrocortical activity after 30 min of treadmill exercise with a rest measurement prior to exercise. Orthogonal views of the cortex (not thresholded) are displayed from three perspectives (*top view*, *lateral view* from the *left*, *back view*; *L* left, *R* right, *A* anterior, *P* posterior). Coding according to three-dimensional coordinates (*X*=transversal axis, *Y*=longitudinal axis, *Z*=sagittal axis). The structural anatomy is shown in *gray*. *Blue color* indicates a decrease in beta activity from pre- to postexercise which was found to be significant in Brodmann areas 11, 47, and 25

relationship," and an "exercise preference hypothesis." Nevertheless, results of different studies show inconsistencies and are hardly reproducible. To further understand the effects of physical exercise on mental health, it is perhaps necessary to reconsider the phylogenetic relevance of physical exercise. An interesting conceptual approach, combining the psychological concept of "flow" with neurophysiological data obtained from exercise studies, was recently brought up by Dietrich (2004).

21.5 The Flow Theory as an Explanation for Changed Cortical Activation Patterns and Related Changes in Mood

The flow theory was developed in the 1970s by Mihaly Csikszentmihalyi, who used the term "flow" to describe a mental state, during which a person is fully immersed in the process of an action (Csikszentmihalyi 1991). The flow theory originated from the field of intrinsic motivation, i.e., someone is doing something just for the sake of doing it. In contrast, extrinsic motivation defines an action that is specified and motivated by an external aim. The term "flow" nowadays is widely used in different scientific disciplines and activities, as exercise (endurance sports), gaming (computer games, chess), creative tasks (maths, painting), and spiritual tasks have been associated with the flow theory (Jackson and Csikszentmihalyi 2000). Csikszentmihalyi himself described the flow experience: "My mind isn't wandering. I am not thinking about something else. I am totally involved in what I am doing. My body feels great. I don't seem to hear anything. The world seems to be cut off from me. I am less aware of myself and my problems." (Csikszentmihalyi 1982). An elite cyclist describes his flow experience as

a feeling of total unity: “You’re working with the bike. It doesn’t seem like you’re sitting on the bike, it feels like altogether, it’s just one piece of machinery working together … like you’re a part of this machine that you were born with and it’s how you move” (Jackson 1996).

Although the “flow experience” seems to be more of a psychological term in exercise science (Jackson 1996), Dietrich (2004) proposes a neurophysiological approach in which the frontal cortex plays a major role. As evolution required an integration of different (sub-)cortical structures to handle the increasing flow of information, today higher cognitive function is organized hierarchically. The frontal cortex plays a major role integrating these different subsystems and can be regarded as the constitutive entity for coordinating and integrating emotion, cognition, awareness, working memory, and action. Accordingly, it does not surprise to find a number of neurophysiological studies showing that the prefrontal cortex is highly involved into processing *explicit* information (Ashby 2002; Dehaene and Naccache 2001; Dietrich 2003). In contrast, exercise routines can be regarded as *implicitly* processed tasks that do not require prefrontal cortex control and therefore might be accompanied by a transient hypofrontality, which Dietrich assumes to be associated with the flow experience.

Nevertheless, as one of the basic components of the flow experience is a steady state between challenge and skill levels, a hypofrontality theory needs to integrate a dose–response relationship as well as an individual exercise preference: If the individual challenge level is too high, this will cause frustration; if the individual challenge level is too low, this will cause boredom. Only if challenge and skill levels are balanced, an intrinsically triggered motivation to keep on going, running, biking, etc., arises.

In contrast, unusual kinds of exercise, or intensities, which are rated as displeasing might cause negative affect and might even be perceived as stress. Therefore, only a carefully chosen and individually balanced exercise intensity allows to reach a state of flow where one does not have to care nor worry for the next step as one is immersed in the activity.

21.6 Recommendations for Experimental Studies on Mood Processing

The characterization of positive mood effects of exercise as a prerequisite for correlation with neurophysiological findings depends on an evaluation of the individuals’ attitude toward exercise. Although exercise is commonly used as a physical intervention to increase mood, there is good reason to argue that exercise might also have the opposite effect being perceived as a stressor. It is very likely that someone who is not used to exercise or does not like (a specific kind of) exercise will show a negative response. Accordingly, psychological as well as neurophysiological data will be affected by a systematic error, as not the effect of exercise, but rather an individual bias toward exercise is assessed.

The hypothesis is raised here that the positive effects of exercise on brain cortical activity and mood are related to the question whether one's motivation to exercise is intrinsic or extrinsic. This may prove to be important not only for understanding the effects of exercise on neuropsychological changes but also for designing individualized exercise recommendations. When considering exercise as a preventive tool and as a tool to avoid an explosion of health-care costs, intrinsic motivation is preferred and will be more successful. Furthermore, it is recommended to use standardized evaluation processes on exercise history and mental attitude toward exercise (including exercise intensity), as for instance the questionnaire developed by Manigandan et al. (2004). In addition, we propose to increase the number of field tests as the lab situation is perceived as a special situation and, for example, an incremental exercise test on a treadmill will show different results compared to an outdoor run.

To further investigate the effects of exercise on mood, it is important to realize that "time after exercise" plays a major role. We have recently identified that, for example, "perceived physical state" and "perceived physical health" were decreased immediately after exercise (Schneider et al. unpublished results), whereas the same variables were positively signed 20–30 min postexercise (Schneider et al. 2010b). A correlation of psychological and neurophysiological data could easily be obtained by applying two frontal electrodes (allowing to check for a transient hypofrontality as well as frontal asymmetry) and a simple profile of mood state (POMS), as recently shown by Vogt et al. (2010) during an outdoor exercise test.

References

Allen JJ, Kline JP (2004) Frontal EEG asymmetry, emotion, and psychopathology: the first, and the next 25 years. Biol Psychol 67:1–5

Ashby FG, Casale MB (2002) The cognitive neuroscience of implicit category learning. In: Jiménez (ed) Attention and implicit learning. Amsterdam & Philadelphia: John Benjamins Publishing Company, pp 109–141

Boutcher SH, Landers DM (1988) The effects of vigorous exercise on anxiety, heart rate, and alpha activity of runners and nonrunners. Psychophysiology 25:696–702

Buckworth J, Dishman RK (2002) Exercise psychology. Human Kinetics, Champaign, IL

Cavanna AE (2007) The precuneus and consciousness. CNS Spectr 12:545–552

Coan JA, Allen JJ (2004) Frontal EEG asymmetry as a moderator and mediator of emotion. Biol Psychol 67:7–49

Cooper NR, Croft RJ, Dominey SJ, Burgess AP, Gruzelier JH (2003) Paradox lost? Exploring the role of alpha oscillations during externally vs. internally directed attention and the implications for idling and inhibition hypotheses. Int J Psychophysiol 47:65–74

Csikszentmihalyi M (1982) Towards a psychology of optimal experience. In: Wheeler L (ed) Annual review of personality and social psychology. Sage, Beverly Hills, CA, pp 13–36

Csikszentmihalyi M (1991) Flow: the psychology of optimal experience. HarperCollins, New York

Davidson RJ, Schwartz GE, Saron C, Bennett J, Goleman DJ (1979) Frontal versus parietal EEG asymmetry during positive and negative affect. Psychophysiology 16:202–203

Dehaene S, Naccache L (2001) Towards a cognitive neuroscience of consciousness: basic evidence and a workspace framework. Cognition 79(1–2):1–37

Dietrich A (2003) Functional neuroanatomy of altered states of consciousness: the transient hypofrontality hypothesis. Conscious Cogn 12(2):231–256
Dietrich A (2004) Neurocognitive mechanisms underlying the experience of flow. Conscious Cogn 13:746–761
Dietrich A (2006) Transient hypofrontality as a mechanism for the psychological effects of exercise. Psychiatry Res 145:79–83
Ekkekakis P (2009) Illuminating the black box: investigating prefrontal cortical hemodynamics during exercise with near-infrared spectroscopy. J Sport Exerc Psychol 31:505–553
Ekkekakis P, Lind E (2006) Exercise does not feel the same when you are overweight: the impact of self-selected and imposed intensity on affect and exertion. Int J Obes (Lond) 30:652–660
Ekkekakis P, Petruzzello SJ (1999) Acute aerobic exercise and affect: current status, problems and prospects regarding dose-response. Sports Med 28:337–374
Ekkekakis P, Hall EE, VanLanduyt LM, Petruzzello SJ (2000) Walking in (affective) circles: can short walks enhance affect? J Behav Med 23:245–275
Faw B (2003) Pre-frontal executive committee for perception, working memory, attention, long-term memory, motor control, and thinking: a tutorial review. Conscious Cogn 12:83–139
Grech R, Cassar T, Muscat J, Camilleri KP, Fabri SG, Zervakis M, Xanthopoulos P, Sakkalis V, Vanrumste B (2008) Review on solving the inverse problem in EEG source analysis. J Neuroeng Rehabil 5:25
Hall EE, Ekkekakis P, Petruzzello SJ (2002) The affective beneficence of vigorous exercise revisited. Br J Health Psychol 7:47–66
Hall EE, Ekkekakis P, Petruzzello SJ (2007) Regional brain activity and strenuous exercise: predicting affective responses using EEG asymmetry. Biol Psychol 75:194–200
Hall EE, Ekkekakis P, Petruzzello SJ (2010) Predicting affective responses to exercise using resting EEG frontal asymmetry: does intensity matter? Biol Psychol 83:201–206
Harmon-Jones E (2004) Contributions from research on anger and cognitive dissonance to understanding the motivational functions of asymmetrical frontal brain activity. Biol Psychol 67:51–76
Hollmann W, Strüder HK (2003) Körperliche Aktivität fördert Gehirngesundheit und -leistungsfähigkeit: Übersicht und eigene Befunde. Nervenheilkunde 9:467–474
Jackson SA (1996) Toward a conceptual understanding of the flow experience in elite athletes. Res Q Exerc Sport 67:76–90
Jackson S, Csikszentmihalyi M (2000) Flow im sport. BLV Verlagsgesellschaft, München
Jasper HH (1958) The ten-twenty electrode system of the international Federation. Electroencephalogr Clin Neurophysiol Suppl 35:371–375
Kleinert J (2006) Adjektivliste zur Erfassung der wahrgenommenen körperlichen Verfassung (WKV): Skalenkonstruktion und erste psychometrische Befunde [Adjective list for assessing Perceived Physical State (PEPS). Scale construction and psychometric results]. Zeitschrift für Sportpsychologie 13(4):156–164
Kline JP, Blackhart GC, Schwartz GE (1999) Gender specificity of resting anterior electroencephalographic asymmetry and defensiveness in the elderly. J Gend Specif Med 2:35–39
Lind E, Joens-Matre RR, Ekkekakis P (2005) What intensity of physical activity do previously sedentary middle-aged women select? Evidence of a coherent pattern from physiological, perceptual, and affective markers. Prev Med 40:407–419
Manigandan C, Charles J, Divya I, Edward SJ, Aaron A (2004) Construction of exercise attitude questionnaire-18 to evaluate patients' attitudes toward exercises. Int J Rehabil Res 27:229–231
Mcdonald AJ, Mascagni F, Guo L (1996) Projections of the medial and lateral prefrontal cortices to the amygdala: a Phaseolus vulgaris leucoagglutinin study in the rat. Neuroscience 71:55–75
Miller R (2007) Theory of the normal waking EEG: from single neurones to waveforms in the alpha, beta and gamma frequency ranges. Int J Psychophysiol 64:18–23
Pascual-Marqui RD (2002) Standardized low-resolution brain electromagnetic tomography (sLORETA): technical details. Methods Find Exp Clin Pharmacol 24(Suppl D):5–12
Pascual-Marqui RD, Michel CM, Lehmann D (1994) Low resolution electromagnetic tomography: a new method for localizing electrical activity in the brain. Int J Psychophysiol 18:49–65

Pascual-Marqui RD, Esslen M, Kochi K, Lehmann D (2002) Functional imaging with low-resolution brain electromagnetic tomography (LORETA): a review. Methods Find Exp Clin Pharmacol 24(Suppl C):91–95

Petruzzello SJ, Landers DM (1994) State anxiety reduction and exercise: does hemispheric activation reflect such changes? Med Sci Sports Exerc 26:1028–1035

Petruzzello SJ, Hall EE, Ekkekakis P (2001) Regional brain activation as a biological marker of affective responsivity to acute exercise: influence of fitness. Psychophysiology 38:99–106

Schneider S, Brummer V, Carnahan H, Dubrowski A, Askew CD, Strüder HK (2008) What happens to the brain in weightlessness? A first approach by EEG tomography. Neuroimage 42:1316–1323

Schneider M, Graham D, Grant A, King P, Cooper D (2009a) Regional brain activation and affective response to physical activity among healthy adolescents. Biol Psychol 82:246–252

Schneider S, Mierau A, Diehl J, Askew CD, Strüder HK (2009b) EEG activity and mood in health orientated runners after different exercise intensities. Physiol Behav 96:706–716

Schneider S, Vogt T, Frysch J, Guardiera P, Strüder HK (2009c) School sport – a neurophysiological approach. Neurosci Lett 467:131–134

Schneider S, Askew CD, Abel T, Mierau A, Strüder HK (2010a) Brain and exercise: a first approach using electrotomography. Med Sci Sports Exerc 42:600–607

Schneider S, Brummer V, Carnahan H, Kleinert J, Piacentini MF, Meeusen R, Strüder HK (2010b) Exercise as a countermeasure to psycho-physiological deconditioning during long-term confinement. Behav Brain Res 211:208–214

Schutter DJ, Weijer AD, Meuwese JD, Morgan B, Honk JV (2008) Interrelations between motivational stance, cortical excitability, and the frontal electroencephalogram asymmetry of emotion: a transcranial magnetic stimulation study. Hum Brain Mapp 29(5):574–580

Sesack SR, Deutch AY, Roth RH, Bunney BS (1989) Topographical organization of the efferent projections of the medial prefrontal cortex in the rat: an anterograde tract-tracing study with Phaseolus vulgaris leucoagglutinin. J Comp Neurol 290:213–242

Shibata M, Shimura M, Shibata S, Wakamura T, Moritani T (1997) Determination of the optimal walking speed for neural relaxation in healthy elderly women using electromyogram and electroencephalogram analyses. Eur J Appl Physiol Occup Physiol 75:206–211

Tashiro M, Itoh M, Fujimoto T, Masud MM, Watanuki S, Yanai K (2008) Application of positron emission tomography to neuroimaging in sports sciences. Methods 45:300–306

Thayer RE, Newman JR, McClain TM (1994) Self-regulation of mood: strategies for changing a bad mood, raising energy, and reducing tension. J Pers Soc Psychol 67:910–925

Tomarken AJ, Davidson RJ, Wheeler RE, Kinney L (1992) Psychometric properties of resting anterior EEG asymmetry: temporal stability and internal consistency. Psychophysiology 29:576–592

Vogt T, Schneider S, Brummer V, Strüder HK (2010) Frontal EEG asymmetry: the effects of sustained walking in the elderly. Neurosci Lett 485:134–137

Woo M, Kim S, Kim J, Petruzzello SJ, Hatfield BD (2009) Examining the exercise-affect dose-response relationship: does duration influence frontal EEG asymmetry? Int J Psychophysiol 72(2):166–172

Woo M, Kim S, Kim J, Petruzzello SJ, Hatfield BD (2010) The influence of exercise intensity on frontal electroencephalographic asymmetry and self-reported affect. Res Q Exerc Sport 81:349–359

Yeung RR (1996) The acute effects of exercise on mood state. J Psychosom Res 40:123–141

Chapter 22
Effects of Aerobic Exercise on Mood and Human Opioidergic Activation Measured by Positron Emission Tomography

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Abstract According to the often-cited "endorphin hypothesis", endogenous opioidergic transmitter release has been postulated as the neurochemical basis of some of the psychophysical effects associated with endurance exercise, in particular mood changes. This chapter provides an overview on the applicability of positron emission tomography (PET) ligand activation studies with opioidergic tracers for imaging endogenous opioidergic transmission associated with exercise.

22.1 Introduction

Endurance exercise can induce transient affect modulation, including stress reduction (Rosch 1985), anxiolysis (Dishman 1985; Morgan 1985), and elevated mood (Janal et al. 1984; Wildmann et al. 1986). Positive mood states elicited by exercise

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can range from feelings of general well-being (Knechtle 2004; Sher 1996) to intense sensations referred to as "runners high" (Partin 1983; Wagemaker and Goldstein 1980). Neurochemically, the effects of exercise on mood have been attributed primarily to biogenic amines and endorphinergic neurotransmission (Chaouloff 1989; Francis 1983; Harber and Sutton 1984). The so-called "endorphin hypothesis" which claims that raised mood states during and after exercise result from endogenous opioid release, has been debated extensively in the literature (Dishman 1985; Hinton and Taylor 1986; Morgan 1985; Sforzo 1989), as this hypothesis is derived mainly from indirect measures like elevated postexercise levels of endorphins in plasma (Carr et al. 1981; Farrell et al. 1982; Gambert et al. 1981) or—as shown in dog experiments—in cerebrospinal fluid (Radosevich et al. 1989). Numerous exercise studies in humans have demonstrated that exercise interventions lead to significant increases of endorphins in plasma (Boecker et al. 2010); on closer inspection, however, these studies have failed to identify a tight relation between the evoked level of endorphins in plasma and the magnitude of mood changes on behavioral scales (Boecker et al. 2010). This discrepancy has been attributed to the large molecule size of opioid peptides, which hinders their passage via the blood–brain barrier (Dearman and Francis 1983). Hence, measured levels of opioid peptides in plasma following exercise challenges do not allow extrapolating upon central opioidergic tone and neither upon central transmitter actions at the opioid receptor level.

There are other issues to be considered with respect to the "endorphin hypothesis" and mood changes in athletes: although opioid antagonists like Naloxone or Naltrexone have evoked positive associations of opioid actions and mood effects in most studies (Daniel et al. 1992; Janal et al. 1984; Jarvekulg and Viru 2002), although not equivocally (Markoff et al. 1982), it is well known that the central actions of opioid peptides (e.g., endorphins, enkephalins, and dynorphin) are highly variable, with distinct behavioral effects being mediated via μ-, δ-, and κ-opioid receptors, respectively. Opioids are not exclusively linked to raised mood states, as for instance dysphoria is mediated via kappa-agonistic properties of opioids (Bruchas et al. 2010; Corbett et al. 2006; Pfeiffer et al. 1986), but μ-agonists (Lasagna et al. 1955) can also induce negative mood states; for instance, Wagner et al. (2010) reported acute dysphoria under the synthetic μ-receptor opioid agonist remifentanil, although the literature findings for μ-agonists are heterogeneous (Crozier et al. 2004).

Hence, although the existing human data argue strongly for a genuine and central role of endogenous opioids in mood regulation during and after exercise, most of the body of evidence is indirect (plasma data). Direct studies of central opioid receptor expression are indeed a major advantage of animal exercise work, and postmortem receptor studies in rats and mice have shown that acute and chronic exercise stimuli modulate central opioid receptor expression (see also Chap. 3). On the other hand, human studies have the important advantage that behavioral effects can be monitored with more precision and detail than in animal studies and, thus, opioid binding studies in athletes may provide a more complete understanding of the interaction between exercise, opioids, and mood. Here, the focus will be laid on PET as an imaging tool that allows noninvasive monitoring of both acute

neurotransmitter trafficking and chronic changes of receptor expression in humans athletes. The chapter summarizes current evidence from published PET ligand data using exercise challenges, which have generated novel insight on central opioidergic mechanisms for mood induction in endurance exercise.

22.2 Opioid Receptor PET

Ligand PET allows studying neurotransmitter systems within the central nervous system in vivo. A detailed introduction into PET methodology is given in Chap. 13. Opioid receptor ligands, which are of particular interest in exercise studies, have been synthesized with either nonspecific ([^{11}C]diprenorphine, [^{18}F]diprenorphine, nonselective antagonists) or subtype-specific ([^{11}C]carfentanil, μ-opioid receptor agonist; [^{18}F]fluoro-cyclofoxy μ/κ-opioid receptor antagonist) binding properties. The advantage of subtype-specific tracers is that information can be gained on distinct receptor subtype-specific modes of action of endogenous opioids; on the other hand, the advantage of unspecific opioid tracers like [^{18}F] diprenorphine ([^{18}F]FDPN) is that the tracer binds to the entire opioidergic system, thus providing a rather composite view of opioidergic neurotransmission evoked by exercise challenges. As the endocannabinoid system is also of great interest in the context of exercise research (Dietrich and McDaniel 2004; Sparling et al. 2003), future applications are awaited using novel compounds that label endocannabinoid receptors (Evens et al. 2009; Terry et al. 2008; Van Laere et al. 2008). For a detailed summary of the available opioidergic tracers, we refer to a recent review article from our group (Boecker et al. 2008a).

Opioid receptor compounds are labeled with ^{11}C ($t½ = 20.3$ min) or ^{18}F ($t½ = 109.7$ min) radionuclides. The advantage of the ^{18}F labeling is that it provides more flexibility due to the longer half-life, for instance allowing PET studies to be done without on-site cyclotron. Depending on the binding properties of the PET tracer, quantification of tracer binding at the opioid receptor level can be done with or without invasive arterial cannulation. The arterial cannulation allows measuring the blood flow-mediated peak brain uptake of the radiotracer, i.e., the tracer input function. In case that brain regions can be determined which have no relevant tracer binding (i.e., brain regions devoid of the subtype-specific opioid receptor to which the particular tracer binds), the arterial cannulation can be avoided. This is the case for Carfentanil, as it allows calculating specific binding in relation to the binding at the level of the receptor-free control region (occipital cortex). On the other hand, in case of ^{11}C- or ^{18}F-labeled Diprenorphine (i.e., a tracer without receptor-free brain region), most researchers prefer arterial cannulation. The scanning usually starts directly with the injection of the radiotracer, so that the dynamic acquisition captures the dynamics of the ligand distribution within the brain, from initial global (unspecific, flow-dominated) to regional (tracer specific) binding of the radiotracer. Scanning usually takes between 60 and 120 min depending on the half-life of the applied radioligand and the signal-to-noise ratio. The binding kinetics of the opioidergic tracer can

then be quantified using tracer kinetic modeling (see also Chap. 13) and region of interest approaches or statistical parametric mapping for voxel-wise statistical analyses can be used to determine relative changes in cerebral ligand binding after exercise challenges and correlate local opioid binding with behavioral measures.

22.3 Ligand Displacement Studies

PET ligand displacement studies provide a noninvasive approach for measuring endogenous neurotransmitter release under experimental challenges in humans. Ligand binding changes reflect the competition between the endogenous neurotransmitter released during the task and the exogenous ligand for specific receptor-binding sites in the brain. The first demonstration of the applicability and the inherent potential of human PET ligand displacement studies was given by Koepp et al. (1998) in a seminal paper, reporting endogenous dopaminergic release evidenced by decreased striatal ^{11}C-raclopride binding in volunteers performing a computer game. This study has demonstrated the scientific potential of correlating changes in endogenous neurotransmission with behavioral measures. Namely, striatal dopamine binding changes were correlated with task performance parameters of participants in this strategic and rewarding sensori-motor task. Thereafter, activation studies with dopamine receptor ligands were extended to pure motor tasks, and endogenous dopamine release was demonstrated during sequential finger movements in healthy subjects (Goerendt et al. 2003). In patients with Parkinson's disease, impaired dopamine release was detected using the same task and these deficits were most pronounced on the predominantly affected side (Goerendt et al. 2003). From the studies referenced above, it can be deduced that PET ligand displacement studies provide a sensitive means to measure endogenous neurotransmission at the whole-brain level. This allows characterizing disease states, which are manifested by abnormal neurotransmission in response to "sensitive" tasks that are linked to the underlying pathology. It is, however, well conceivable that this approach is not only limited to manifest disease states, but should also be sensitive in detecting "neurochemical signatures" of aberrant behavioral manifestations, for instance addictive behavior as described in the context of excessive endurance exercise (Pierce et al. 1993).

One previous PET study has investigated the effects of aerobic exercise on dopamine release in the striatum (Wang et al. 2000). The authors applied a two-scan [^{11}C]raclopride design in 12 healthy volunteers (5 women, 7 men; mean age, 32 ± 5 years) at rest and after 30 min of treadmill exercise (average speed of 8.7 ± 0.5 km/h (5.4 ± 0.3 mph) at an inclination of 3.3° ± 2°). Subjects were instructed not to perform any aerobic activity 24 h prior to PET. Dopamine D2 receptor availability was measured using the ratio of the distribution volume in the putamen to that in the cerebellum. While rat in vivo microdialysis studies (see also Chap. 4) have been able to show enhanced striatal dopamine concentrations after physical exercise (Hattori et al. 1994; Meeusen et al. 1997; Wilson and Marsden 1995), this first PET ligand activation study in human athletes did not detect any significant dopaminergic

activation at the level of the putamen. Since no psychophysical data, except analog verbal scales of fatigue, were acquired, it also remains unclear whether the treadmill running induced euphoria or other mood changes in the participants. It may also be speculated that the amount of exercise was not sufficient to induce a significant ligand displacement, or, alternatively that the group size was not high enough to disclose significant dopaminergic displacement effects at the group level. Clearly, more studies need to be conducted in the future to further examine the role of the dopaminergic system in exercise.

Beyond the dopaminergic system, PET ligand displacement studies have been published within recent years using opioidergic tracers to identify opioidergic binding changes during experimental challenges. Both increases (Zubieta and Stohler 2009) and decreases (Zubieta et al. 2001) of opioid ligand binding have been found, likewise, reflecting experimentally induced net decreases or increases of the endogenous neurotransmitter release. It has to be pointed out that not only task-induced acute endogenous neurotransmitter release will affect the postsynaptic ligand binding status, but also other mechanisms have to be considered, such as receptor internalization or receptor downregulation (Laruelle 2000) and PET is not capable of differentiating between these mechanisms.

22.4 [^{18}F]FDPN Ligand Displacement Under Exercise Conditions

To the best of our knowledge, no PET study has so far quantified basal opioid receptor-binding patterns in athletes (under resting conditions), as compared to sedentary control subjects. This is an interesting issue, as data in animals with repeated exercise exposure indicate a modulation of [3H]diprenorphine binding (Sforzo et al. 1986), putatively due to repeated bursts of opioid release upon exercise (see also Chap. 3). There are also no longitudinal human data available on long-term opioidergic binding changes as a consequence of repeated exercise interventions. Currently, only the effects of acute exercise challenges have been studied, and our group was the first to apply [^{18}F]FDPN in a group of trained athletes to test the effect of 2 h endurance running as experimental challenge (Boecker et al. 2008b). As there was no specific hypothesis which opioid receptor subtype is playing the predominant role mediating human exercise effects, we deliberately chose an opioid tracer ([^{18}F]FDPN), which has similar selectivity to μ, δ, and κ opioid receptors (Wester et al. 2000).

The study (Boecker et al. 2008b) involved ten trained male athletes (mean age 36.9 years ± 2.6), each receiving two PET scans in random order: rest (no sport 24 h prior to PET), post exercise (directly after 2 h of running). The included athletes were regular runners with a minimum of 4 h weekly training over the past 2 years (mean training duration of 8.6 ± 3.9 h, range 4–10 h). The exercise challenge was similar to natural training conditions, i.e., subjects were advised to run at their normal training pace. Heart rate was monitored continuously using commercial equipment. The two [^{18}F]FDPN PET scans were performed on separate days (mean

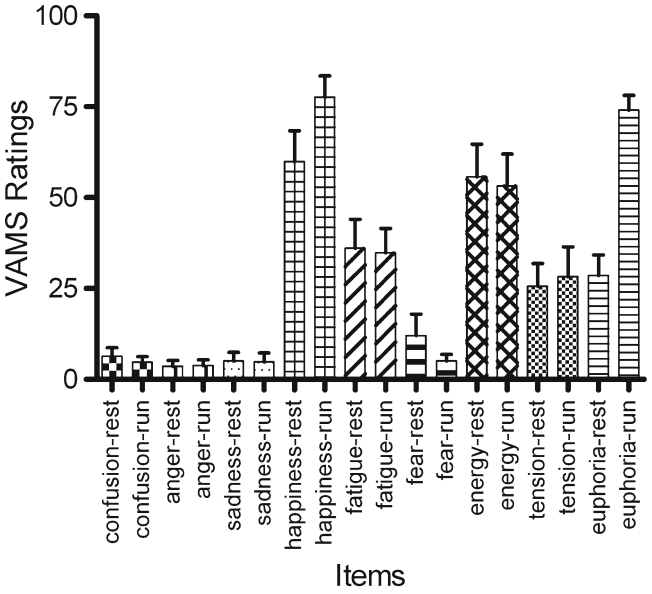

Fig. 22.1 *Box plot* of euphoria VAS scores. Mean and standard error of visual analogue mood scale (VAMS) ratings (0–100) during 2 conditions (*left column* of each item represents rest, *right column* postexercise). Differences between the conditions were significant for the items euphoria and happiness (Student's paired *t*-test, $P<0.05$, corrected for multiple comparisons). Data from Boecker et al. (2008b). Published and cited with permission from Cerebral Cortex

interval between the two scans being 4.0 ± 1.9 weeks). The average pace during running was of 11.0 ± 2.3 km/h, and the average heart rate 144 ± 7 min^{-1}. The euphoria ratings as measured using visual analog scales (VAS) of mood-related items increased significantly from 37.6 ± 19.6/100 (prior to exercise) to 73.3 ± 13.2/100 (see Fig. 22.1). VAS ratings after the PET session indicated that the euphoria ratings were still elevated as compared with baseline levels prior to exercise. This indicates a persistent behavioral effect of running and elevated mood over the course of the 2 h PET measurement.

Upon imaging, we observed a significant [^{18}F]FDPN binding reduction after physical exercise, which confirmed our a priori hypothesis and is compatible with elevated endogenous opioid release induced by the running. Prominent ligand displacement effects were seen in prefrontal/orbitofrontal cortices and limbic structures (anterior cingulate cortex (ACC) and insula), and in these regions, there was also a negative correlation between ligand binding and the individual VAS euphoria ratings (see Fig. 22.2), such that high levels of euphoria were associated with low [^{18}F]FDPN binding (i.e., indicative of raised endogenous endorphin release).

In conclusion, using [^{18}F]DPN in a two-scan approach, we were indeed able to provide evidence that outdoor running at regular training speed (i.e. aerobic exercise training) is associated with changes in central opioidergic binding: As hypothesized a priori, running was associated exclusively with decreases in opioid receptor binding,

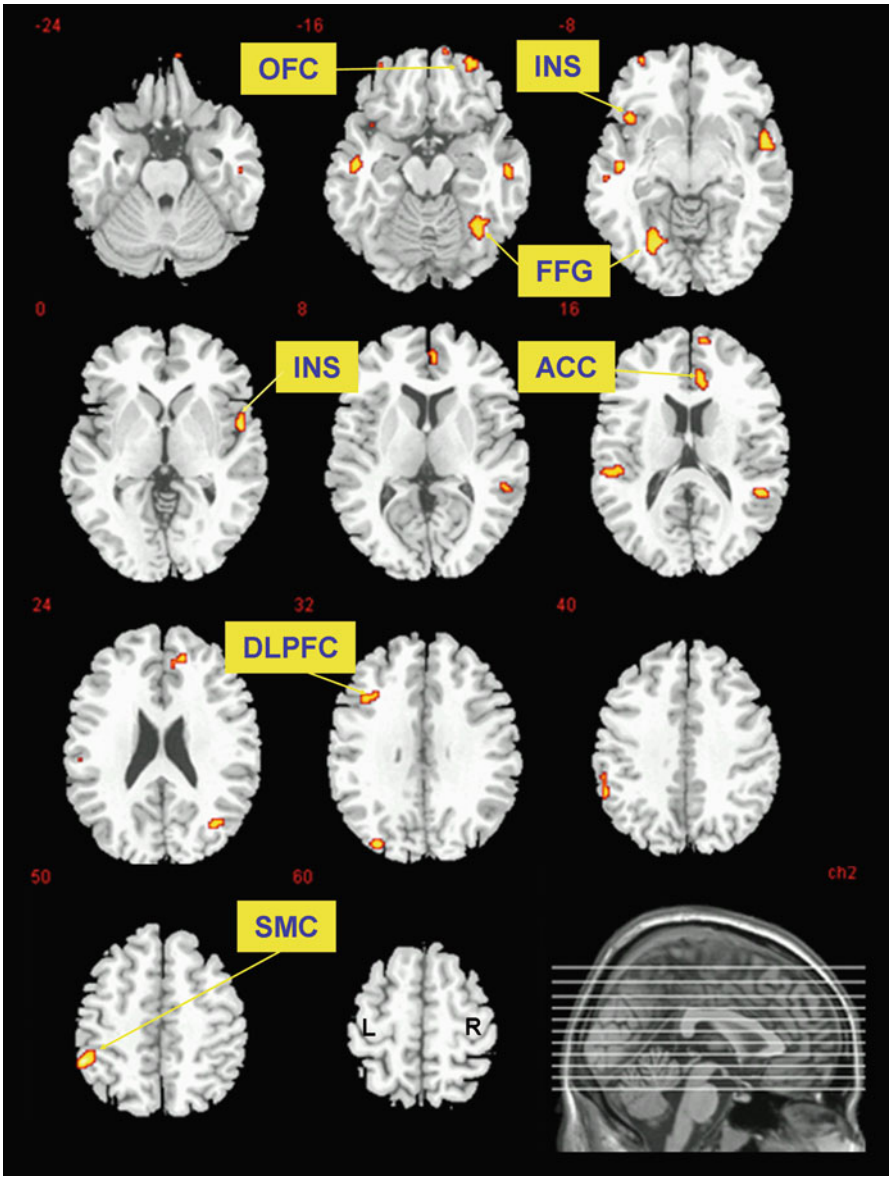

Fig. 22.2 Correlation of opioidergic binding in runners with VAS ratings of euphoria. Statistical parametric maps of the regression analysis (regions where VAS ratings of euphoria are inversely correlated with [18F]FDPN binding) in standard stereotactic space (Montreal Neurological Institute [MNI] space) are overlaid in color on axial slices of a skull-stripped normalized brain (MNI single subject brain as provided by MRIcro program). *Z* values indicate the location of the slice planes relative to the AC-PC line. For display purposes, the statistical analysis is thresholded at an uncorrected height threshold of $P<0.001$. All regions are also significant after small volume correction (10 voxel sphere). *L* left side of figure, *R* right side of figure. Data from Boecker et al. (2008b). Published and cited with permission from Cerebral Cortex

i.e., indicating elevated endogenous opioid levels post exercise. Hence, these data are compatible with the "endorphin hypothesis", which has claimed endogenous release of central acting opioids during exercise. Moreover, they extend the indirect evidence derived from peripheral plasma endorphin measurements in humans, which have only limited value as they do not allow interpolating upon central opioidergic mechanisms (Boecker et al. 2010); the major advantage of applying PET ligand activation is that it provides a more direct picture about where in the brain opioidergic effects are generated by exercise. As these studies can be performed in humans, this work is also a veritable advance to postmortem autoradiography work in animals (Sforzo et al. 1986), particularly as the neuroimaging findings can be correlated with behavioral measures, as shown here for euphoria indices.

The finding that running affects opioidergic binding particularly in areas of the brain implicated in affective processing is of particular interest (Dalgleish 2004). Indeed, displacement effects were encountered in the prefrontal cortex and in areas of the limbic system (ACC and insular/parainsular cortex), which are pivotal in the generation of affect and mood states. The location of these effects is well in accord with current theories of opioid-generated pleasure (Kringelbach and Berridge 2010) and it is tempting to conclude that this release of endogenous opioids is responsible for the perceived euphoria.

22.5 Methodological Aspects

Although the findings of the cited study by Boecker et al. (2008b) were in accord with a priori hypotheses, both in terms of the general direction of the effects (i.e., decreased ligand binding post exercise) and their specific localization (i.e., predominant effects in fronto-limbic circuitries), there are several methodological aspects that have to be considered: The small sample size of ten preselected athletes is a limitation of this study. Indeed, the recruitment was limited for reasons of radiation exposure and due to the need of arterial cannulation before both PET scans. Nevertheless, we consider the study cohort just large enough for the purpose of identifying relevant effects of running upon [^{18}F]DPN binding. Due to restrictions imposed by the national radiation protection authority, it was not possible to scan subjects under further experimental conditions, for instance walking (as low level control) or even running in a different intensity range, which might have allowed examining the relationship between exercise effort and ligand binding changes.

Another general issue to be considered in this context is the following: Exercise studies make it impossible to blind participating athletes for the type of exercise intervention; moreover, factors like reward expectancy, attention, and social reinforcement are difficult to control for (Dishman 1985). One possible way how to avoid such bias is to combine the neuroimaging during exercise challenges with a pharmacological blockade of opioid receptors (double-blind exercise intervention: opioid receptor antagonist naloxone versus placebo); however, opioid receptor

antagonists themselves influence binding patterns of opioid tracers and mood, thus interfering with the exercise displacement effects and psychophysical measures (Melichar et al. 2003).

22.6 Outlook

The summarized [^{18}F]FDPN work should be seen as an initial application of opioid ligand PET activation studies in the sports and exercise sciences (Boecker et al. 2008b); as such, this paper provides a basis for future work examining links between exercise-induced psychophysics and neurotransmitter systems in more detail. Unsolved research questions for future studies pertain to the dependence of ligand binding changes to the duration and intensity of exercise challenges, the influence of gender and training status thereupon, and the interaction between different neurotransmitter systems, e.g., the opioidergic and the dopaminergic system, in the context of mood (Kringelbach and Berridge 2010) and exercise.

Further conclusive studies on exercise measures are warranted in human athletes, as findings from studies measuring peripheral endorphin levels indicate on the one hand that the opioidergic release depends on both intensity and duration of exercise (Estorch et al. 1998; Goldfarb et al. 1990; Mougin et al. 1987; Petraglia et al. 1990), whereas on the other hand, data in dogs have disclosed that beta-endorphin increases in CSF were observed only during low-intensity exercise (Radosevich et al. 1989). In the future, it will also be important to directly relate peripheral endorphin levels with central subtype-specific opioid binding values and, finally, PET studies are awaited that determine the role of other transmitters, including the dopaminergic system (Wang et al. 2000) and the endocannabinoid system (Dietrich and McDaniel 2004; Sparling et al. 2003) in endurance exercise.

References

Boecker H, Henriksen G, Sprenger T, Miederer I, Willoch F, Valet M, Berthele A, Tolle TR (2008a) Positron emission tomography ligand activation studies in the sports sciences: measuring neurochemistry in vivo. Methods 45:307–318

Boecker H, Sprenger T, Spilker ME, Henriksen G, Koppenhoefer M, Wagner KJ, Valet M, Berthele A, Tolle TR (2008b) The runner's high: opioidergic mechanisms in the human brain. Cereb Cortex 18(11):2523–2531

Boecker H, Othman A, Mueckter S, Scheef L, Pensel M, Daamen M, Jankowski J, Schild HH, Tölle TR, Schreckenberger M (2010) Advocating neuroimaging studies of transmitter release in human physical exercise challenges studies. Open Access J Sports Med 1:167–175

Bruchas MR, Land BB, Chavkin C (2010) The dynorphin/kappa opioid system as a modulator of stress-induced and pro-addictive behaviors. Brain Res 1314:44–55

Carr DB, Bullen BA, Skrinar GS, Arnold MA, Rosenblatt M, Beitins IZ, Martin JB, McArthur JW (1981) Physical conditioning facilitates the exercise-induced secretion of beta-endorphin and beta-lipotropin in women. N Engl J Med 305:560–563

Chaouloff F (1989) Physical exercise and brain monoamines: a review. Acta Physiol Scand 137:1–13

Corbett AD, Henderson G, McKnight AT, Paterson SJ (2006) 75 years of opioid research: the exciting but vain quest for the Holy Grail. Br J Pharmacol 147(Suppl 1):S153–S162

Crozier TA, Kietzmann D, Dobereiner B (2004) Mood change after anaesthesia with remifentanil or alfentanil. Eur J Anaesthesiol 21:20–24

Dalgleish T (2004) The emotional brain. Nat Rev Neurosci 5:583–589

Daniel M, Martin AD, Carter J (1992) Opiate receptor blockade by naltrexone and mood state after acute physical activity. Br J Sports Med 26:111–115

Dearman J, Francis KT (1983) Plasma levels of catecholamines, cortisol, and beta-endorphins in male athletes after running 26.2, 6, and 2 miles. J Sports Med Phys Fitness 23:30–38

Dietrich A, McDaniel WF (2004) Endocannabinoids and exercise. Br J Sports Med 38:536–541

Dishman RK (1985) Medical psychology in exercise and sport. Med Clin North Am 69:123–143

Estorch M, Fuente T, Serra-Grima R, Flotats A, Berna L, Sanz D, Nuno de la Rosa JA, Carrio I (1998) The effect of a race 4 hours in duration on the production of beta-endorphin and adrenocorticotropic hormone. Med Clin (Barc) 111:770–773

Evens N, Muccioli GG, Houbrechts N, Lambert DM, Verbruggen AM, Van Laere K, Bormans GM (2009) Synthesis and biological evaluation of carbon-11- and fluorine-18-labeled 2-oxoquinoline derivatives for type 2 cannabinoid receptor positron emission tomography imaging. Nucl Med Biol 36:455–465

Farrell PA, Gates WK, Maksud MG, Morgan WP (1982) Increases in plasma beta-endorphin/beta-lipotropin immunoreactivity after treadmill running in humans. J Appl Physiol 52: 1245–1249

Francis K (1983) The role of endorphins in exercise: a review of current knowledge. J Orthop Sports Phys Ther 4:169–173

Gambert SR, Garthwaite TL, Pontzer CH, Cook EE, Tristani FE, Duthie EH, Martinson DR, Hagen TC, McCarty DJ (1981) Running elevates plasma beta-endorphin immunoreactivity and ACTH in untrained human subjects. Proc Soc Exp Biol Med 168:1–4

Goerendt IK, Messa C, Lawrence AD, Grasby PM, Piccini P, Brooks DJ (2003) Dopamine release during sequential finger movements in health and Parkinson's disease: a PET study. Brain 126:312–325

Goldfarb AH, Hatfield BD, Armstrong D, Potts J (1990) Plasma beta-endorphin concentration: response to intensity and duration of exercise. Med Sci Sports Exerc 22:241–244

Harber VJ, Sutton JR (1984) Endorphins and exercise. Sports Med 1:154–171

Hattori S, Naoi M, Nishino H (1994) Striatal dopamine turnover during treadmill running in the rat: relation to the speed of running. Brain Res Bull 35:41–49

Hinton ER, Taylor S (1986) Does placebo response mediate runner's high? Percept Mot Skills 62:789–790

Janal MN, Colt EW, Clark WC, Glusman M (1984) Pain sensitivity, mood and plasma endocrine levels in man following long-distance running: effects of naloxone. Pain 19:13–25

Jarvekulg A, Viru A (2002) Opioid receptor blockade eliminates mood effects of aerobic gymnastics. Int J Sports Med 23:155–157

Knechtle B (2004) Influence of physical activity on mental well-being and psychiatric disorders. Praxis (Bern 1994) 93:1403–1411

Koepp MJ, Gunn RN, Lawrence AD, Cunningham VJ, Dagher A, Jones T, Brooks DJ, Bench CJ, Grasby PM (1998) Evidence for striatal dopamine release during a video game. Nature 393:266–268

Kringelbach ML, Berridge KC (2010) The functional neuroanatomy of pleasure and happiness. Discov Med 9:579–587

Laruelle M (2000) Imaging synaptic neurotransmission with in vivo binding competition techniques: a critical review. J Cereb Blood Flow Metab 20:423–451

Lasagna L, Von Felsinger JM, Beecher HK (1955) Drug-induced mood changes in man. I. Observations on healthy subjects, chronically ill patients, and postaddicts. J Am Med Assoc 157:1006–1020

Markoff RA, Ryan P, Young T (1982) Endorphins and mood changes in long-distance running. Med Sci Sports Exerc 14:11–15

Meeusen R, Smolders I, Sarre S, de Meirleir K, Keizer H, Serneels M, Ebinger G, Michotte Y (1997) Endurance training effects on neurotransmitter release in rat striatum: an in vivo microdialysis study. Acta Physiol Scand 159:335–341

Melichar JK, Nutt DJ, Malizia AL (2003) Naloxone displacement at opioid receptor sites measured in vivo in the human brain. Eur J Pharmacol 459:217–219

Morgan WP (1985) Affective beneficence of vigorous physical activity. Med Sci Sports Exerc 17:94–100

Mougin C, Baulay A, Henriet MT, Haton D, Jacquier MC, Turnill D, Berthelay S, Gaillard RC (1987) Assessment of plasma opioid peptides, beta-endorphin and met-enkephalin, at the end of an international nordic ski race. Eur J Appl Physiol Occup Physiol 56:281–286

Partin C (1983) Runner's "high". JAMA 249:21

Petraglia F, Bacchi Modena A, Comitini G, Scazzina D, Facchinetti F, Fiaschetti D, Genazzani AD, Barletta C, Scavo D, Genazzani AR (1990) Plasma beta-endorphin and beta-lipotropin levels increase in well trained athletes after competition and non competitive exercise. J Endocrinol Invest 13:19–23

Pfeiffer A, Brantl V, Herz A, Emrich HM (1986) Psychotomimesis mediated by kappa opiate receptors. Science 233:774–776

Pierce EF, McGowan RW, Lynn TD (1993) Exercise dependence in relation to competitive orientation of runners. J Sports Med Phys Fitness 33:189–193

Radosevich PM, Nash JA, Lacy DB, O'Donovan C, Williams PE, Abumrad NN (1989) Effects of low- and high-intensity exercise on plasma and cerebrospinal fluid levels of ir-beta-endorphin, ACTH, cortisol, norepinephrine and glucose in the conscious dog. Brain Res 498:89–98

Rosch PJ (1985) Exercise and stress reduction. Compr Ther 11:10–15

Sforzo GA (1989) Opioids and exercise. An update. Sports Med 7:109–124

Sforzo GA, Seeger TF, Pert CB, Pert A, Dotson CO (1986) In vivo opioid receptor occupation in the rat brain following exercise. Med Sci Sports Exerc 18:380–384

Sher L (1996) Exercise, wellbeing, and endogenous molecules of mood. Lancet 348:477

Sparling PB, Giuffrida A, Piomelli D, Rosskopf L, Dietrich A (2003) Exercise activates the endocannabinoid system. Neuroreport 14:2209–2211

Terry G, Liow JS, Chernet E, Zoghbi SS, Phebus L, Felder CC, Tauscher J, Schaus JM, Pike VW, Halldin C, Innis RB (2008) Positron emission tomography imaging using an inverse agonist radioligand to assess cannabinoid CB1 receptors in rodents. Neuroimage 41:690–698

Van Laere K, Koole M, Sanabria Bohorquez SM, Goffin K, Guenther I, Belanger MJ, Cote J, Rothenberg P, De Lepeleire I, Grachev ID, Hargreaves RJ, Bormans G, Burns HD (2008) Whole-body biodistribution and radiation dosimetry of the human cannabinoid type-1 receptor ligand 18F-MK-9470 in healthy subjects. J Nucl Med 49:439–445

Wagemaker H, Goldstein L (1980) The runner's high. J Sports Med Phys Fitness 20:227–229

Wagner KJ, Valet M, Kochs EF, Kriner M, Tolle TR, Sprenger T (2010) The mu-opioid receptor agonist remifentanil induces acute dysphoria irrespective of its analgesic properties. J Psychopharmacol 24:355–361

Wang GJ, Volkow ND, Fowler JS, Franceschi D, Logan J, Pappas NR, Wong CT, Netusil N (2000) PET studies of the effects of aerobic exercise on human striatal dopamine release. J Nucl Med 41:1352–1356

Wester HJ, Willoch F, Tolle TR, Munz F, Herz M, Oye I, Schadrack J, Schwaiger M, Bartenstein P (2000) 6-O-(2-[18F]fluoroethyl)-6-O-desmethyldiprenorphine ([18F]DPN): synthesis, biologic evaluation, and comparison with [11C]DPN in humans. J Nucl Med 41:1279–1286

Wildmann J, Kruger A, Schmole M, Niemann J, Matthaei H (1986) Increase of circulating beta-endorphin-like immunoreactivity correlates with the change in feeling of pleasantness after running. Life Sci 38:997–1003

Wilson WM, Marsden CA (1995) Extracellular dopamine in the nucleus accumbens of the rat during treadmill running. Acta Physiol Scand 155:465–466

Zubieta JK, Stohler CS (2009) Neurobiological mechanisms of placebo responses. Ann N Y Acad Sci 1156:198–210

Zubieta JK, Smith YR, Bueller JA, Xu Y, Kilbourn MR, Jewett DM, Meyer CR, Koeppe RA, Stohler CS (2001) Regional mu opioid receptor regulation of sensory and affective dimensions of pain. Science 293:311–315

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