Non-pharmacological Approaches to Cognitive Enhancement

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Contents

1 Introduction 418
1.1 Exercise 418
1.2 Enrichment 419
2 Non-pharmacological Cognitive Enhancement in Animals 419
2.1 Exercise as a Cognitive Enhancer in Rodents 419
2.2 Enrichment as a Cognitive Enhancer in Rodents 420
2.3 The Potential Mechanisms Underlying Exercise and Enrichment-Induced Cognitive Enhancement 421
2.3.1 Neurotrophins and Growth Factors 421
2.3.2 Synaptogenesis and Neurogenesis 422
2.3.3 Angiogenesis and Vascular Growth Factors 424
3 Non-pharmacological Cognitive Enhancement in the Healthy Human 425
4 Cognitive Enhancement in the Cognitively Impaired 426
4.1 Age-Related Cognitive Decline and Dementia 427
4.2 Parkinson's Disease, Schizophrenia and Depression 428
5 Conclusions 430
References 430

Abstract

Pharmaceuticals and medical devices hold the promise of enhancing brain function, not only of those suffering from neurodevelopmental, neuropsychiatric or neurodegenerative illnesses, but also of healthy individuals. However, a number of lifestyle interventions are proven cognitive enhancers, improving

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attention, problem solving, reasoning, learning and memory or even mood. Several of these interventions, such as physical exercise, cognitive, mental and social stimulation, may be described as environmental enrichments of varying types. Use of these non-pharmacological cognitive enhancers circumvents some of the ethical considerations associated with pharmaceutical or technological cognitive enhancement, being low in cost, available to the general population and presenting low risk to health and well-being. In this chapter, there will be particular focus on the effects of exercise and enrichment on learning and memory and the evidence supporting their efficacy in humans and in animal models will be described.

Keywords
Cognitive enhancement • Physical activity • Environmental enrichment • Neurogenesis • BDNF

1 Introduction

1.1 Exercise

Physical inactivity is a risk factor for development of several non-communicable diseases including cardiovascular disease, type 2 diabetes and certain types of cancer and is associated with a decrease in life expectancy (Lee et al. 2012). While regular exercise enhances and preserves general health, it also confers specific benefits on the nervous system that result in measurable cognitive improvement. Such improvements have been seen both in cognitively impaired and in healthy subjects, indicating the potential of exercise to act as a neurotherapeutic (Lautenschlager et al. 2008), a neuroprotectant (Kramer and Erickson 2007a; Rovio et al. 2005) and an enhancer of normal cognitive performance (Griffin et al. 2011). While most forms of exercise promote good health, it appears that aerobic exercise is a more robust enhancer of brain health when compared with static or resistance exercise. The use of rodent models is allowing the cellular and molecular mechanisms underlying these improvements to be characterised (Voss et al. 2013). Increased expression of several growth factors, particularly brain-derived neurotrophic factor (BDNF), is consistently associated with exercise-induced cognitive enhancement (Vaynman and Gomez-Pinilla 2006), while the ability of exercise to remodel brain morphology via angiogenesis, synaptogenesis and neurogenesis may underpin its cognitive-enhancing efficacy (Lista and Sorrentino 2010).

1.2 Enrichment

Environmental enrichment in laboratory rodents is easily defined; it simply means the addition of sources of stimulation to the standard housing environment. Depending on the experiment, this may include sources of social stimulation, such as an increased number of cagemates, physical stimulation such as running wheels or a larger cage environment in which to move around or mental stimulation such as provision of novel objects and toys or participation in learning experiments (van Praag et al. 2000). When reviewing the literature on environmental enrichment, one must be mindful of the profound effects of exercise on brain function; thus care must be taken to distinguish between experimental conditions that include opportunities to engage in increased physical activity, such as provision of running wheels or participation in treadmill running, and those that do not (Bechara and Kelly 2013). What does enrichment mean in the case of humans? Possible sources of enrichment include mental stimulation such as reading, playing chess, solving puzzles or engagement in formal education, social stimulation such as participation in group activities and interaction with family, friends, neighbours and the wider community or, more recently, participation in targeted cognitive training, including computerized training programmes. Again, animal models are proving useful in characterising the biological underpinnings of the cognitive effects of enrichment, at least some of which may be shared with exercise (Pang and Hannan 2013; Brown et al. 2003).

2 Non-pharmacological Cognitive Enhancement in Animals

2.1 Exercise as a Cognitive Enhancer in Rodents

There is a vast and growing literature reporting the ability of exercise to enhance cognitive function, especially learning and memory, in animals and humans (Voss et al. 2013; Gomez-Pinilla and Hillman 2013). The use of rats and mice as experimental subjects has allowed the mechanisms underlying exercise-induced cognitive enhancement to be investigated at cellular and molecular levels. The many published studies have employed different forms of exercise including forced treadmill running and voluntary wheel running, while various tasks such as object recognition memory, spatial learning in mazes and contextual fear conditioning have been used to assess cognitive performance (Voss et al. 2013). At the cellular level, the impact of exercise on forms of synaptic plasticity, particularly long-term potentiation (LTP), has been widely investigated. Exercise appears to have particularly powerful effects on the function of the hippocampus, a region of the medial temporal lobe crucial to spatial navigation and memory formation and one of the few brain regions in which new neurons can develop, a process known as adult hippocampal neurogenesis. The fact that exercise acts as a powerful stimulator of neurogenesis in the dentate gyrus subfield of the hippocampus may explain, at least

in part, its profound effects on hippocampus-dependent memory (van Praag et al. 1999b; Creer et al. 2010).

Short-term and long-term exercise protocols, using both forced and voluntary exercise, result in enhanced cognitive performance and synaptic plasticity in rodents at different stages of the life span. Voluntary wheel running enhances LTP and spatial learning in the Morris water maze (van Praag et al. 1999a) and spatial pattern separation (Creer et al. 2010) in young adult mice, while wheel running enhances LTP (Farmer et al. 2004) water maze learning (Vaynman et al. 2004b; Gomez-Pinilla et al. 2008; Ding et al. 2006), fear conditioning (Hopkins and Bucci 2010b) and recognition memory (Hopkins and Bucci 2010a) in young rats. One week of forced treadmill running improves expression of LTP and recognition memory in young rats (Bechara et al. 2014; O'Callaghan et al. 2007; Griffin et al. 2009), while several months of forced exercise enhances water maze learning in the young (Cassilhas et al. 2012) and aged (O'Callaghan et al. 2009; Albeck et al. 2006) rat. It must be noted that in some studies exercise failed to enhance cognitive function (Kennard and Woodruff-Pak 2012), suggesting that the effects of exercise on cognition may depend on variable factors such as the duration of exercise exposure, the modality of the exercise undertaken (forced versus voluntary) and the intensity of the exercise, along with the nature and difficulty of the cognitive task (Berchtold et al. 2010). However, the overall weight of evidence gives powerful support to the hypothesis that exercise is a cognitive enhancer in both young and aged rodents (Vaynman and Gomez-Pinilla 2006).

2.2 Enrichment as a Cognitive Enhancer in Rodents

A complex cage environment that includes provision of running wheels is proven to enhance learning in laboratory rodents (Rosenzweig and Bennett 1996; van Praag et al. 2000, 2002; Pang and Hannan 2013). Such enrichment can also protect against the normal decline in memory associated with ageing and a number of different neurological and psychological pathologies such as depression, Huntington's disease and Alzheimer's disease in both humans and animal models (Mora et al. 2007; Laviola et al. 2008; Brenes et al. 2009; Nithianantharajah and Hannan 2011). Animals housed in enriched environments have improved recognition and spatial memory compared with standard housed controls, while enrichment can rescue cognitive deficits induced by experimentally induced ischaemia or surgical lesions (Gobbo and O'Mara 2004; Mandolesi et al. 2008). It has been suggested that enrichment in early adulthood and throughout one's life might increase the resilience of the brain in old age, resulting in the concept of 'cognitive reserve' (Nithianantharajah and Hannan 2009).

Each different stimulatory factor present in a typical enriched environment may contribute to the resulting improvement in cognitive function; indeed, it has been suggested that different aspects of the environment can induce the same improvements via dissociable pathways (Olson et al. 2006). Several studies have assessed the effects of enrichment in the absence of exercise on various aspects of

cognitive function. This type of enrichment is linked with reduced anxiety in rodents (Galani et al. 2007) and has been shown to enhance object recognition and spatial memory in a time-dependent manner in the rat; continuous housing in an enriched environment was necessary for at least 3 weeks before cognitive benefit was detectable (Birch et al. 2013). Other studies have shown that enrichment induces cognitive benefit in middle-aged, but not young, mice, indicating that enrichment may have the particular ability to improve memory where cognitive impairment exists (Harburger et al. 2007a, b). Such observations have also been reported in rats, indicating that enrichment in the absence of exercise may be an efficacious cognitive enhancer in aged animals (Kumar et al. 2012), but a less robust enhancer of cognition in young animals (Gobbo and O'Mara 2004). These observations may be of translational relevance; it is gratifying to note that cognitive stimulation may enhance brain function in older subjects, where participation in regular physical activity may be difficult due to frailty or illness.

2.3 The Potential Mechanisms Underlying Exercise and Enrichment-Induced Cognitive Enhancement

2.3.1 Neurotrophins and Growth Factors

Numerous studies have shown that exercise significantly increases the expression of the neurotrophic factor BDNF in the hippocampus and several neocortical regions (Molteni et al. 2002; Neeper et al. 1996; Vaynman et al. 2004a; Griffin et al. 2009; Ding et al. 2011). BDNF plays a vital role in neurodevelopment, but is now accepted to be a key regulator of synaptic plasticity in the developing and adult brain (Bekinschtein et al. 2014). Exogenous BDNF can induce a form of LTP (Bramham and Panja 2014) and improve hippocampus-dependent learning (Griffin et al. 2009; Bechara et al. 2014), potentially via its ability to stimulate plasticity-related intracellular signalling pathways following binding to its receptor, TrkB (Bekinschtein et al. 2014). BDNF can depolarize neurons, leading to increased neurotransmitter release and therefore rapid modulation of neuronal communication (Lessmann 1998). Some studies have noted significant changes in BDNF mRNA expression within as little as 2 h following exercise (Huang et al. 2006; Soya et al. 2007). Since BDNF expression can be upregulated rapidly and it is released in an activity-dependent manner, it has been proposed that BDNF mediates the rapidly observed aspects of cognitive enhancement induced by exercise (Bechara et al. 2014). It has also been suggested that exercise may increase the brain's resistance to damage and degeneration through the ability of BDNF to regulate neuronal growth and survival (Neeper et al. 1996). Other growth factors may mediate exercise-induced improvements in cognitive function. Some evidence suggests that nerve growth factor (NGF) expression in the hippocampus is increased following exercise (Neeper et al. 1996), and exercise has been shown to ameliorate the age-related decline in expression of both BDNF and NGF, concomitant with improved spatial learning (O'Callaghan et al. 2009). NGF, though first identified as a key regulator of embryonic development of the nervous system, also

plays important roles in the adult nervous system, including modulation of hippocampal plasticity (Conner et al. 2009). Enrichment in the absence of exercise also induces a neurotrophic response in the hippocampus, with exposure to an enriched environment increasing expression of NGF (Birch et al. 2013), but not BDNF (Bindu et al. 2007; Kumar et al. 2012). Exogenous NGF has been shown to mimic the cognitive effects of enrichment in young rats (Birch and Kelly 2013). Peripherally produced growth factors such as insulin-like growth factor 1 (IGF-1) may be a link between the systemic and the central changes induced by exercise. IGF-1 receptors are abundantly expressed in the hippocampus and blocking these receptors during exercise has been shown to inhibit exercise-induced enhancements in memory (Ding et al. 2006). Furthermore, spatial memory impairments displayed by serum IGF-1 deficient mice are ameliorated by exogenous IGF-1 administration (Trejo et al. 2008).

2.3.2 Synaptogenesis and Neurogenesis

The formation of new synapses is likely to be critical to storage of new information in the brain and is among the neuroplastic changes induced by physical activity and enrichment. There are several reports of increased expression of the synaptic vesicle proteins synaptophysin and synapsin-I following exercise and some evidence indicates that exercise-induced synaptogenesis may be a BDNF-dependent process (Vaynman et al. 2004a; Ding et al. 2006; Quirie et al. 2012). Voluntary running increases the density of dendritic spines in granule and CA1 pyramidal neurons of the dentate gyrus and layer III pyramidal neurons of the entorhinal cortex (Stranahan et al. 2007), while both forced and voluntary running increase mossy fibre sprouting (Toscano-Silva et al. 2010). Voluntary wheel running increases the expression of the AMPA receptor subunits GluR2/3 and phosphorylation of the NMDA receptor subunits GluN1 and GluN2B (Dietrich et al. 2005), providing further evidence that enhancement of synaptic efficacy may underpin the cognitive enhancements induced by exercise. Enrichment in the absence of physical activity increases expression of synaptic vesicle proteins, indicating that cognitive and social stimulation can also stimulate synaptogenesis (Birch et al. 2013).

Adult hippocampal neurogenesis is defined as the process of generating functional neurons from neuronal precursors in the subgranular zone of the dentate gyrus (Ming and Song 2011). The process involves proliferation of neural precursor cells and their differentiation, migration and integration into the granule cell network of the dentate gyrus (Aimone et al. 2006), a process that takes 3–4 weeks. The majority of proliferating cells are not integrated into the hippocampal circuitry and undergo apoptosis; thus neurogenesis depends on increased cell proliferation in tandem with conditions conducive to cell survival. By the time adult-born neurons are 4–8 weeks old, they are preferentially recruited into circuits supporting spatial memory compared with existing granule cells, consistent with their decreased threshold for plasticity (Kee et al. 2007). Therefore, as adult-generated neurons mature they are increasingly likely to be incorporated into circuits supporting spatial memory (Kee et al. 2007). Although the contribution of neurogenesis to hippocampus-dependent learning and memory has yet to be fully

elucidated, it is being increasingly accepted that neurogenesis may be of functional relevance to learning and memory (Gage and Temple 2013). Exercise is by far the most robust neurogenic stimulus yet identified (van Praag 2009). Considering the time frame of the entire process, neurogenesis is a longer-term neuroplastic effect of exercise compared with the rapidly induced effects of exercise on synaptic transmission and plasticity. However, the onset of the neurogenic effect of exercise is rapid with cell genesis reportedly peaking following 3 days of voluntary exercise (Kronenberg et al. 2006) and remaining elevated for up to 32 days before returning to baseline. Numerous other studies have shown that both voluntary and forced exercise can induce an increase in cell proliferation in the dentate gyrus, the survival of neural progenitor cells and their differentiation into neurons rather than glial cells (van Praag et al. 1999a; Fabel et al. 2003; Van der Borght et al. 2009; Wu et al. 2008; Creer et al. 2010). A direct comparison of both exercise modalities indicated that forced exercise is a significantly more robust neurogenic stimulus compared with wheel running, an observation that may explain some of the conflicting results reported in the literature relating to exercise and cognition (Leasure and Jones 2008). The potent effects of exercise on neurogenesis have been observed in the hippocampus of young, middle-aged and aged animals indicating that the brain retains at least some neurogenic ability throughout the life span (van Praag et al. 1999a, 2005; Wu et al. 2008).

Both exercise and cognitive enrichment can bring about similar improvements in learning and memory, at least in aged animals, but it is unclear whether they do so via similar neuroplastic mechanisms, including neurogenesis. An early study in this area demonstrated that enrichment affected cell survival and not cell proliferation whereas exercise increased cell division and net neuronal survival in mice (van Praag et al. 1999a). It has been proposed that enrichment does not stimulate an increase in proliferation per se but promotes increased survival of neuronal progenitor cells and hence increases the number of young neurons available to functionally integrate into neuronal networks (Kempermann and Gage 1999). This would suggest that cell survival and cell proliferation may be regulated by differing mechanisms that can be affected by behavioural and environmental factors (Olson et al. 2006). In contrast, enrichment in the absence of exercise has been shown to increase hippocampus-dependent learning, cell proliferation, but not survival, in the dentate gyrus of the rat (Birch et al. 2013). Another recent study failed to observe any effect of enrichment alone on neurogenesis, but no cognitive measures were assessed in parallel (Gregoire et al. 2014). The relative contribution of the different aspects of an enriched environment to the cognitive enhancement that it stimulates is a complex question that has yet to be answered, but it seems that exercise is the most important element, at least in the case of young animals (Kobilo et al. 2011). Where a cognitive impairment exists, as in the aged or diseased brain, there may be greater capacity for other environmental stimuli such as social and cognitive stimulation to induce a cognitive benefit (Lazarov et al. 2010).

2.3.3 Angiogenesis and Vascular Growth Factors

Physical exercise influences the vasculature, with vasodilation the most obvious and rapid change. Although the brain was originally believed to maintain a constant blood supply in the face of changes in mean arterial pressure, there is now overwhelming evidence to support an exercise-induced increase in cerebral blood flow, possibly due to an increase in brain metabolism (Querido and Sheel 2007). At a cellular level, physical activity has been linked with angiogenesis, the growth of new capillaries from pre-existing blood vessels, in several brain regions including the hippocampus, motor cortex and cerebellum (Isaacs et al. 1992; Swain et al. 2003; Clark et al. 2009; Van der Borght et al. 2009). Vascular endothelial growth factor (VEGF), a hypoxia-inducible secreted protein, plays an important role in the angiogenic effects of exercise (Ferrara 2009; van Praag 2009). VEGF expression is increased in skeletal muscle and hippocampus following a single bout of moderate intensity exercise (Tang et al. 2010), while pharmacological blockade of angiogenesis in the hippocampus impairs spatial learning in the water maze (Kerr et al. 2010). However, other studies report minimal effects of exercise on VEGF expression in the hippocampus suggesting that this angiogenic growth factor must cross the blood–brain barrier (BBB) to induce angiogenesis in the brain (Fabel et al. 2003). Some reports indicate that the BBB permeability may increase in response to exercise, providing a potential route for signaling proteins to enter the brain parenchyma from the circulation (Sharma et al. 1991; Watson et al. 2006). It has also been suggested that increased circulation may permit delivery of more nutrient metabolites, hormones, growth factors and oxygen to the hippocampus while also facilitating metabolic waste disposal, leading to increased cell survival and enhanced neurogenesis (Olson et al. 2006). In humans, cerebral blood volume changes in the dentate gyrus have been correlated with aerobic fitness and cognitive function (Pereira et al. 2007). Collectively, these experiments show that the hippocampus displays remarkable angiogenic plasticity and that the cerebral vasculature responds to physical activity; thus vascular adaptations could be another key mechanism underlying exercise-induced improvement in cognitive function. Unsurprisingly, it appears that angiogenesis may be a more important factor in mediating exercise-induced cognitive enhancement when compared with enrichment in the absence of exercise. However, there is some evidence of modest angiogenic activity in the hippocampus of environmentally enriched rats (Ekstrand et al. 2008). Environmental enrichment that includes access to exercise equipment is widely reported to induce angiogenesis, and it is likely that the major angiogenic stimulus in such complex environments is increased physical activity.

The positive effects of exercise on cognitive function have been attributed to a number of neuroplastic changes in the hippocampus including increased expression of and signaling via growth factors, enhanced synaptic plasticity, synaptogenesis, angiogenesis and neurogenesis. At least some of the cellular mechanisms underlying each of these changes are likely to be shared. For example, administration of BDNF, VEGF and IGF-1 has been shown to increase neurogenesis in the dentate gyrus, while peripheral blockade of VEGF abolishes exercise-induced hippocampal neurogenesis (Fabel et al. 2003). Certainly, it appears that several growth factors

whose expression is upregulated by exercise and enrichment have both angiogenic and neurogenic properties, and that both processes may be necessary for at least some of the cognitive-enhancing effects of these non-pharmacological lifestyle factors to be manifested.

3 Non-pharmacological Cognitive Enhancement in the Healthy Human

Regular exercise confers long-term benefits on brain health, but evidence exists to show that those with healthy brain function may also reap short-term cognitive benefits of physical activity. A single bout of exercise can improve cognitive performance in subject groups that are not cognitively impaired (Tomporowski 2003; Lambourne and Tomporowski 2010; Chang et al. 2012). In young healthy adults, high-intensity running is reported to improve vocabulary learning (Winter et al. 2007), while cycling improves performance of the frontal lobe-dependent Stroop colour-word task (Ferris et al. 2007) and the hippocampus-dependent face-name pairs (Griffin et al. 2011) and map recognition tasks (Grego et al. 2005). Aerobic and resistance exercise make different physiological demands on the cardiovascular, musculoskeletal, endocrine and respiratory systems and have been reported to exert different effects on cognitive function; for example aerobic, but not resistance, exercise enhances working memory in young people (Pontifex et al. 2009). This suggests that exercise-induced enhancements in cognitive function are likely to be dependent on exercise modality, intensity and duration as well as the physical fitness of subjects (Grego et al. 2004). During prolonged exercise, fatigue-related factors such as heat stress, dehydration and hypoglycaemia can impair short-term memory (Cian et al. 2001) while fatigue-related increases in circulating cortisol and adrenaline reduced event-related potentials, a measure of cortical activity (Grego et al. 2004). Thus it appears that exercise can enhance or impair cognitive performance in a manner dependent on exercise intensity and duration. Certainly, acute bouts of exercise can confer a cognitive advantage, at least in the short term, since the persistence of these rapid exercise-induced effects is as yet unknown (Griffin et al. 2011; Schmidt-Kassow et al. 2013). Physical activity in children is linked with cognitive development; exercise appears to be of particular benefit to development of executive function (Tomporowski et al. 2011). In addition to physical activity, both cognitive and social stimulation are crucial for normal development in childhood. Additional cognitive stimulation for children from lower socioeconomic backgrounds, at home or in a preschool setting, can significantly improve their academic achievements (Crosnoe et al. 2010).

Evidence from experiments in animals has provided insights into the mechanisms by which exercise may enhance brain function in humans. There are several reports of an increase in circulating BDNF concentration in response to exercise (Gold et al. 2003; Rojas Vega et al. 2006; Goekint et al. 2008; Tang et al. 2008; Rasmussen et al. 2009; Cho et al. 2012); in some studies, a parallel

enhancement of cognitive function was observed (Ferris et al. 2007; Griffin et al. 2011). These changes in BDNF concentration appear to be detectable only after aerobic exercise, since resistance training has no such effect (Schiffer et al. 2009; Goekint et al. 2010); hence it may be the case that the inability of resistance exercise to increase BDNF concentration underlies its inability to enhance cognitive function in several studies. Several studies indicate that circulating NGF and IGF-1 do not increase in response to exercise (Gold et al. 2003; Schiffer et al. 2009; Griffin et al. 2011).

The cellular origin of the exercise-induced BDNF response remains to be elucidated. Several reports indicate that the brain itself may be the main contributor of BDNF to the circulation during endurance exercise (Seifert et al. 2010; Rasmussen et al. 2009) although muscle (Matthews et al. 2009), endothelial cells (Nakahashi et al. 2000) and platelets (Fujimura et al. 2002) are also potential sources. The correlation between exercise, cognitive function and BDNF is strong, but the functional relationship between these elements is not yet understood. Based on data from the animal literature, it may be speculated that candidate mechanisms mediating the effects of exercise in humans would include short-term effects on plasticity induced by neurotrophins, angiogenesis, synaptogenesis and neurogenesis. For obvious reasons, direct assessment of these measures in humans is technically difficult; however, it has recently been confirmed that adult hippocampal neurogenesis occurs in humans (Spalding et al. 2013). MRI analysis has revealed that exercise increases blood volume in the dentate gyrus concomitant with improved cognitive function (Pereira et al. 2007); the authors suggest that this may be a correlate of neurogenesis.

4 Cognitive Enhancement in the Cognitively Impaired

Every human will experience some form of physical and mental decline in old age but for many, age-related cognitive decline progresses from mild cognitive impairment to vascular dementia, Alzheimer's disease (AD) and other forms of dementia that impair or even destroy quality of life and the ability to live independently. Others struggle with the cognitive impairment that accompanies Parkinson's Disease (PD), depression, schizophrenia and other mental disorders. The identification and implementation of strategies that promote healthy aging and that improve cognitive performance in specific patient groups, such as physical activity and mental and social stimulation, is thus of broad societal and economic benefit. Worryingly, recent data on lifestyle trends in the United States show that, on average, individuals older than 15 years of age spend almost 55 % of their leisure time watching television, compared with 20 % of free time spent engaging in cognitively stimulating activities such as reading or socializing and only 6 % of their leisure time exercising (American Time Use Study, U.S. Bureau of Labor Statistics 2013); similar trends have been observed globally (Heath et al. 2012; Olafsdottir et al. 2014), with parallel increases in overweight and obesity. Given the impact that a cognitively and physically active lifestyle can have on the health of

the mind and body, a lack of stimulation may be causing detrimental effects in the general population that will impact on future mental health.

4.1 Age-Related Cognitive Decline and Dementia

The link between a healthy lifestyle and a healthy old age is indisputable and exercise is a key element of this relationship. The decreased incidence of cognitive impairment and dementia observed in elderly persons who undertake regular physical activity is strong evidence of the neuroprotective effects of exercise (Geda et al. 2010; Laurin et al. 2001; Colcombe et al. 2004). In older adults without dementia the volume of the hippocampus shrinks 1–2 % annually (Raz et al. 2005); such atrophy increases the risk of memory impairment in late adulthood (Jack et al. 2010). The smaller hippocampal volume and poorer memory performance associated with increasing age are paralleled by reduced levels of serum BDNF (Erickson et al. 2010). Exercise in those aged over 65 years reduces the incidence of dementia relative to sedentary controls (Rovio et al. 2005; Larson et al. 2006), and higher levels of aerobic fitness have also been associated with increased hippocampal volume in elderly adults (Erickson et al. 2009), indicating the importance of physical fitness throughout the life span. A 1-year aerobic intervention was shown to increase hippocampal volume by 2 %, effectively offsetting the age-related loss in volume by 1–2 years and improving memory, providing evidence that exercise can act as a neurotherapeutic as well as a neuroprotectant (Erickson et al. 2011). This improvement in function was associated with higher circulating BDNF in these subjects. Meta-analyses of the literature that reveal the rehabilitating effects of exercise in elderly patients suffering from dementia and Alzheimer's disease (Heyn et al. 2004; Farina et al. 2014; Kramer and Erickson 2007b) underline the capacity of exercise to reverse as well as prevent cognitive decline. Cerebral vasoactivity has been correlated with aerobic capacity in older adults, providing a possible physiological mechanism by which exercise impacts cognitive function in old age (Barnes et al. 2013b). The animal literature shows a specific benefit of enrichment and exercise in aged animals (O'Callaghan et al. 2009) and in mouse models of Alzheimer's disease (Valero et al. 2011), delaying or reversing the impairments in neurogenesis and resulting in prevention or reversal of cognitive impairment (Speisman et al. 2013; Lazarov et al. 2010).

Clearly, there may be certain people who are unable to participate in exercise for reasons of frailty, physical infirmity or circumstance and the fact that social and intellectual enrichment can also protect against, delay or reverse age-related cognitive decline is of particular relevance to such individuals. One comprehensive study showed that participation in cognitively stimulating activity by elderly members of Catholic religious orders was associated with a decreased incidence of AD (Wilson et al. 2002c), while participation in leisure activities such as reading and playing board games is correlated with a lower risk of development of dementia in the elderly (Verghese et al. 2003; Wilson et al. 2002b). The number of years spent in formal education is negatively correlated with the risk of dementia (Anstey

et al. 2000); conversely, loneliness, social isolation, depression and apathy are increasingly acknowledged risk factors for development of age-related cognitive impairment and dementia (Robert et al. 2008; Shankar et al. 2013; Holwerda et al. 2014; Wilson et al. 2002a). Computerized training programmes are a relatively recently developed source of targeted cognitive stimulation that may enhance brain plasticity in older subjects (Mahncke et al. 2006; Tardif and Simard 2011). These programmes variously target spatial skills, attention, visual skills, working memory and other cognitive functions (Schmiedek et al. 2010; Smith et al. 2009; Nouchi et al. 2012). However, the persistence of these effects and the transfer of the learned skills to real-life situations have not yet been demonstrated.

Taken together, the weight of evidence suggests that in populations with existing cognitive impairment, physical and intellectual activity may help to delay the progression toward more severe dementia. A randomized control trial of the effects of 12 weeks of mental and physical activity in inactive, community-residing older adults with cognitive complaints resulted in significant improvements in global cognitive function in all participants, regardless of whether the exercise intervention was aerobic or anaerobic or whether the mental stimulation consisted of challenging, computer-based activity or watching educational DVDs (Barnes et al. 2013a). These results suggest that regular participation in any type of stimulating physical or mental activity can translate to functional improvement in such groups. It is a reassuring illustration of the capacity of the brain to remain plastic throughout the life span and that exercise or novel intellectual activities begun late in life can result in improved cognitive outcome.

4.2 Parkinson's Disease, Schizophrenia and Depression

The well-known motor symptoms that characterize Parkinson's disease (PD) are often accompanied by cognitive impairment. Despite the motor impairments suffered by PD patients, many retain the ability to participate in exercise activity (Earhart 2013), in some cases resulting in demonstrable cognitive benefit. In a community-dwelling group of PD patients, regular walking resulted in improved motor function, cognition and general quality of life (Uc et al. 2014), while exercise improved cued reaction time, indicative of cognitive improvement, in another group of PD patients (Ebersbach et al. 2014). Another study demonstrated that exercise can increase BDNF in the circulation of PD patients (Frazzitta et al. 2014). A systematic review of the literature has identified a cognitive benefit of exercise training in PD patients, but highlights the need for further research in this promising area (Hindle et al. 2013). With regard to other forms of cognitive enhancement, computer-based cognitive training has benefitted learning and memory in PD patients (Naismith et al. 2013). Exercise and enrichment in animal models of PD can benefit cognitive performance (Faherty et al. 2005; Pothakos et al. 2009; Petzinger et al. 2013) and increase BDNF expression in the brain (Tuon et al. 2012).

Schizophrenia is a major psychiatric disorder whose negative symptoms include cognitive impairments affecting memory, executive functioning and attention.

Pharmacotherapy with antipsychotic medication is of course the most effective treatment for the positive symptoms of this disorder, but there may be cognitive benefit to patients of interventions such as exercise therapy as an adjunct to pharmacotherapy and psychotherapy. Some reports indicate that exercise increases hippocampal volume (Vancampfort et al. 2014; Pajonk et al. 2010) and improves verbal, visual and working memory (Vancampfort et al. 2014; Pajonk et al. 2010; Oertel-Knochel et al. 2014) in people with schizophrenia. In contrast, computer-based brain training improved performance of computer-based tasks, but did not translate to general cognitive benefit in schizophrenic patients (Dickinson et al. 2010). The ability to employ exercise as a cognitive enhancer in those suffering from schizophrenia may be confounded by their lower reported levels of activity (Laursen et al. 2012) and lower cardiorespiratory fitness (Ozbulut et al. 2013). However, participation in sports has been shown to positively affect physical and psychiatric symptoms in schizophrenic patients (Takahashi et al. 2012). Aberrant neurogenesis has been implicated in schizophrenia and thus this process may be a viable clinical target; postmortem analysis demonstrated that cell proliferation was diminished in the dentate gyrus of people who suffered from schizophrenia (Reif et al. 2006), while there is evidence that antipsychotic drugs have neurogenic properties (Keilhoff et al. 2012). Evidence from studies in a mouse model of schizophrenia indicates the ability of exercise to increase neurogenesis and improve behavioural deficits (Wolf et al. 2011).

Depression, and its accompanying cognitive impairment, may present as a primary psychiatric disorder or may be comorbid with conditions such as AD, PD or schizophrenia. Depression is often associated with low levels of physical activity; adults with depression are reported to spend significantly less time in either light or moderate physical activity than non-depressed adults (Song et al. 2012). There is a vast and growing literature on the potential benefits of exercise in the prevention (Mammen and Faulkner 2013) and treatment (Cooney et al. 2013) of depression. Indeed, the UK National Institute for Health and Clinical Excellence recommends structured exercise, three times a week for 10–14 weeks, for the treatment of mild to moderate depression (NICE guidelines [CG90], 2009). A recent Cochrane Review revealed that exercise is associated with a greater reduction in symptoms of depression compared with no treatment, placebo, or active control interventions such as relaxation or meditation (Cooney et al. 2013); though the authors emphasize that the benefits are of small magnitude, any reduction in clinical symptoms is to be welcomed. Reduced expression of BDNF in the brain is associated with depression, a finding that has led to the examination of the efficacy of interventions that may upregulate BDNF as antidepressant strategies (Castren and Rantamaki 2010). While antidepressant medication increases BDNF expression (Russo-Neustadt and Chen 2005), exercise, alone or in combination with antidepressant treatment, is reported to increase BDNF expression and reduce depressive symptoms in animal models of depression (Marais et al. 2009; Sigwalt et al. 2011; Russo-Neustadt et al. 2001; Garza et al. 2004). Antidepressant drugs are also potent stimulators of neurogenesis (Duman et al. 2001; Ota and Duman 2013); thus neurogenesis has been suggested as a key biological mechanism mediating

their cognitive effects (Ernst et al. 2006). The links between exercise, BDNF, neurogenesis and cognitive function in the healthy brain are mirrored in depression and major depressive disorder and may explain the ability of exercise to ameliorate at least some of the cognitive dysfunction associated with depression (Ota and Duman 2013).

5 Conclusions

While interventions such as exercise and enrichment are effective cognitive enhancers in their own right, they may also be useful adjuncts to pharmacological treatments of disease, as is the case in depression. Elucidation of the cellular mechanisms underlying cognitive enhancements induced by these non-pharmacological interventions may allow novel molecular drug targets that exploit the same cellular pathways to be developed.

Clinicians routinely recommend or prescribe exercise to those with conditions such as obesity, diabetes and cardiovascular disease. The proven ability of exercise and other forms of environmental stimulation to protect against or treat cognitive impairment associated with normal aging or specific neurodegenerative or neuropsychiatric disorders render these interventions of potential clinical importance. It may be envisaged that current recommendations of physical, mental or social activity for the purpose of maintaining general health may translate to prescription of activity for the specific benefit of brain health. However the optimal type, intensity, frequency and duration of exercise that will benefit specific populations or patient groups have not yet been identified.

While some of these non-pharmacological approaches have shown specific benefits to cognition, especially learning and memory, a generally healthy lifestyle that includes regular exercise, social engagement and mental stimulation has wider impacts on the general health of the individual that also benefits society as a whole. The side effects of the non-pharmacological strategies for cognitive enhancement outlined here are broadly positive.

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