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REVIEW ARTICLE

Influence of Physical Exercise on Traumatic Brain Injury Deficits: Scaffolding Effect

Trevor Archer

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Abstract Traumatic brain injury (TBI) may be due to a bump, blow, or jolt to the head or a penetrating head injury that disrupts normal brain function; it presents an ever-growing, serious public health problem that causes a considerable number of fatalities and cases of permanent disability annually. Physical exercise restores the healthy homeostatic regulation of stress, affect and the regulation of hypothalamic–pituitary–adrenal axis. Physical activity attenuates or reverses the performance deficits observed in neurocognitive tasks. It induces anti-apoptotic effects and buttresses blood–brain barrier intactness. Exercise offers a unique non-pharmacologic, non-invasive intervention that incorporates different regimes, whether dynamic or static, endurance, or resistance. Exercise intervention protects against vascular risk factors that include hypertension, diabetes, cellular inflammation, and aortic rigidity. It induces direct changes in cerebrovasculature that produce beneficial changes in cerebral blood flow, angiogenesis and vascular disease improvement. The improvements induced by physical exercise regimes in brain plasticity and neurocognitive performance are evident both in healthy individuals and in those afflicted by TBI. The overlap and inter-relations between TBI effects on brain and cognition as related to physical exercise and cognition may provide lasting therapeutic benefits for recovery from TBI. It seems likely that some modification of the notion of scaffolding would postulate that physical exercise reinforces the adaptive processes of the brain that has undergone TBI thereby facilitating the development of existing networks, albeit possibly less efficient, that compensate for those lost through damage.

Keywords TBI · Pathophysiology · Exercise · Stress affect · HPA · Cognition · Vascular integrity · Neuroplasticity · Adaptation · Scaffolding

A common cause of traumatic brain injury (TBI) is the impact of a mechanical insult, an external force, to the brain that results in tissue damage, cerebral inflammation and neurodegeneration in the central nervous system (cf., Rice et al. 2003). After mechanical impact, the activation of secondary systems contributes to ischemic damage due to circulatory disturbances, compromisation of the blood–brain barrier (BBB), and excitotoxic loss of neurons (Xiong et al. 1997). It has been estimated that about 1.7 million citizens of the USA sustain TBI annually (Faul et al. 2010); the incidence in Sweden has varied from one study reporting 540 individuals per 100,000 in Western Sweden (Andersson et al. 2003), to another, 20-year-old study, reporting 249 per 100,000 in Northern Sweden (Johansson et al. 1991), while a recent National registry-based study reported about 250 per 100,000 individuals annually (Borg et al. 2011). Since psychiatric disorders are common following TBI, the timing of onset may differ according to pre-injury history with different trajectories for anxiety and depressive disorders, thereby posing implications for identifying the time individuals are most at risk for psychiatric disorders post-injury (Bryant 2011; Gould et al. 2011). TBI diagnosis covers a wide range of short- and long-term impairments in physical, cognitive, behavioral, and emotional domains, depending upon injury extent,

T. Archer (✉)
Department of Psychology, University of Gothenburg, Box 500, 430 50 Gothenburg, Sweden
e-mail: trevor.archer@psy.gu.se

T. Archer
School of Education, Psychology and Sport Science, Linnaeus University, Kalmar, Sweden

severity, and location (Albensi 2001). In mild sport-related TBI, memory problems, not least spatial navigation memory deficits and alterations in brain networks suggest widespread behavioral changes (Slobounov et al. 2010). For example regarding affective status, TBI patients report significant changes in self-concept with the post-injury self-image experienced negatively in comparison with pre-injury self-image. Their perceived change in self-identity was positively associated with depression and grief but negatively associated with self-esteem and awareness. Awareness in this context was negatively associated with self-esteem and positively associated with depression (cf. Carroll and Coetzer 2011). Anxiety following childhood TBI appears to be part of a broader problem of affective dysregulation related to a damaged dorsal frontal lobe and frontal white matter systems (Max et al. 2011). Not least, quality-of-life issues are critical to considerations of post-injury recovery (cf. Hawthorne et al. 2011).

The tragic and wasteful consequences of TBI that are expressed even under a cursory examination of the pathophysiology of TBI suggest that it is both important and of necessity that the particular benefits of physical exercise as an intervention ought to be addressed. The variable nature of TBI pathology is characterized by the deficits observed in the capacity of neurons to metabolize energy, sustain synaptic function, often with consequent cognitive–emotional and debilitating disorders that disrupt homeostatic mechanisms (Wu et al. 2011). Exercise influences the homeostatic imbalance that arises under conditions of prevailing HPA dysregulation. The anti-neurodegenerative effects of exercise emerge beneficially through expressions of neurocognitive functioning and neuroplasticity, whereas the destructive and wasteful consequences of TBI for cellular inflammation and vascular pathophysiology appear to be assuaged by carefully selected exercise/activity regimes. The notion of Scaffolding in injured/aging brains may provide a conceptual 'hub' to elucidate the unique utility and incentive of exercise in promoting restorative gains against greater or lesser damage to structures at various levels and their related functions.

Pathophysiological Consequences of TBI

The main pathophysiological outcomes of TBI, taking into account several individual difference moderating factors such as general health and conditions, extent of injury and "age-at-injury", include inflammation, ischemia, oxidative stress (which may be integrated with mitochondrial function), alterations in wide-scale networks, e.g., the default mode network, impaired mitochondrial function, altered BBB permeability, and lasting changes in white matter integrity. These outcomes, sited within the brain and CNS, precede, to greater or lesser extent, the plethora of alterations in behavioral performance within cognitive, emotional, sensory and motor domains. The consequences of TBI ought to be viewed at (i) molecular and cellular levels, (ii) at macro levels, including circuitry and regional levels, for instance as exemplified by neuroimaging techniques and functional magnetic resonance imaging (fMRI) networks, and (iii) at the levels of neurobehavioral outcomes and expressions that may offer the initial and preliminary determinants of health status and function. Ancilliary to the notion of TBI levels the moderation by individual difference factors upon outcome implies that exercise may not necessarily present the primary moderator but rather influence and/or be influenced by individual characteristics and predispositions that precede injury. The convergence of adverse factors could result severe clinical outcome. A meta-analysis by Molloy et al. (2011) supports the contention of an increased risk for schizophrenia spectrum disorder following TBI; the authors observed a larger effect in those individuals with a genetic predisposition to psychosis. Thus, the pathological outcomes of TBI take on greater consequence with closer examinations of the affected domains.

TBI is a major cause of death and disability worldwide, according to some sources especially in children and young adults. The causes of TBI include falls, vehicle accidents (highly prevalent), sports injuries, and physical violence. Cerebral inflammation following TBI plays a critical role in the pathophysiology of brain diseases of high prevalence and economic impact, such as major depression, schizophrenia, post-traumatic stress disorder, and Parkinson's and Alzheimer's diseases. The assessment and diagnosis of TBI must take into account a multitude of external and internal (individual) factors that interact at the point-of-confrontation starting from the mechanical forces that induce shearing and compression of neuronal and vascular tissue at the time of impact (Moppett 2007). This is followed by a series of pathological events may then ensue, thereby leading to further brain injury. The presentations of secondary injury may be amenable to intervention but cause deterioration through secondary physiological insults. The presence of various risk factors that lead to poor outcome after TBI may lead to further impairments in tissue integrity. Most of these risk factors are fixed at the time of injury such as age, gender, mechanism of injury, and presenting signs (Glasgow Coma Scale and pupillary signs), but some such as hypotension and hypoxia are potential areas for medical intervention. The diagnosis of TBI and its severity ought to describe cognitive, physical, and psychological domains, with physical deficits include ambulation, balance, coordination, fine motor skills, strength, and endurance. The cognitive deficits ought to include expressions language and communication, information processing,

memory, affective functions, coping behavior, and perceptual skills. Psychological status may be altered all-too-often with the debut of maladaptive behaviors such as substance abuse and problems of impulse control. Not least, adjustment to disability issues and confrontational episodes are frequently encountered by individuals presenting TBI.

At the level of outcome, Kim (2011) has presented a systematic review of patient outcomes in TBI with the following factors associated with unfavorable outcomes: (i) sociodemographic factors, including older age, male gender, lower level of education; (ii) clinical factors, including lower Glasgow Coma Scale score, motor vehicle crash injury, hypotension, hypoxia, increased intracranial pressure, no pupil reaction, hypo- or hyperglycaemia, anemia, coagulophy (clotting and bleeding disorders), hypo- or hyperthermia, abnormal levels of electrolytes, duration of coma; (iii) higher level of computerized tomography classification by Marshall score category [a classification scale of intracranial pathology on head computed axial tomography (CT)]; and (iv) type of intracerebral lesion. Alcohol, another complicating factor, potentiates severity of TBI (Cunningham et al. 2002). Ischemia, the inadequate supply of blood to organ tissues due to blockade, induces poor oxygen supply or cerebral hypoxia thereby leading to the death of brain tissue or cerebral infarction/ischemic stroke and constitutes a particular type of TBI. In cerebral ischemia, excitotoxic cell death results from glutamate release by injured neurons resulting in hyperactive glutamate receptors inducing excessive intracellular Ca^{2+} influx (Zhang et al. 2002). This increase in intracellular Ca^{2+} leads to activation of caspase-3 with eventual apoptotic and necrotic cell death (Raghupathi 2004; Robertson 2004). Free radical production, facilitated by the arachidonic acid cascade in experimentally induced focal ischemia in the rat brain, induces lipid peroxidation in neuronal and glial cell membranes as well as DNA damage in neuronal cells (Djebaili et al. 2005; Lee et al. 2005). Clausen et al. (2011) have shown a close relationship between oxidative stress and excitotoxicity following TBI in humans. fMRI has shown that alterations in the brain resting state default mode network, in the subacute phase of injury, are important in assessing TBI severity and pathophysiology of the disorder (Johnson et al. 2011).

At molecular and cellular levels, TBI induces impaired mitochondrial function, oxidative stress and altered antioxidant activity in the brain and spinal cord (Azbill et al. 1997; Niizuma et al. 2009). Neurons and glial cells in proximity to the damaged region induce apoptotic cell death at the early post-TBI stage (Itoh et al. 2009, 2010), with accompanying cerebral dysfunction (Dressler and Vemuganti 2009). Experimental TBI reliably models the functional deficits, within cognitive, emotional, sensory, and motor domains that are observed in TBI patients (Ekmark-Lewén et al. 2010; Sigurdardottir et al. 2010) thereby providing analyses at all levels of TBI pathophysiology. The notion of 'age-at-injury' poses an important aspect of both clinical and experimental TBI since the immature brain may be particularly vulnerable to injury during critical periods of development (Serra-Grabulosa et al. 2005), whereas considerable evidence indicates that outcomes from TBI are worse in elderly individuals (Marklund et al. 2009; Onyszchuk et al. 2008). Applying a diffuse TBI model in rat pups to exemplify the level of behavioral outcomes, Cernak et al. (2010) showed motor deficits that persisted even after the pups had reached adulthood, as well as reduced cognitive performance 2 weeks after injury. In addition, it was observed that the model induced prominent edema, particularly evident in 7- and 14-day-old animals, as measured by both the wet weight/dry weight method and diffusion-weighted MRI, often seen in pediatric TBI. BBB permeability, as measured by the Evans blue dye technique, peaked at 20 min after trauma in all age groups, with a second peak found only in adult animals at 24 h after injury. The BBB level of cellular pathology presents both global and regional extents of damage with the likelihood that the intervention may take on the role of damage control. BBB disruption in epileptic patients following even mild TBI is not an infrequent observation (Tomkins et al. 2011). Mild TBI induces neuropathological insult ranging from white matter damage to long-lasting neurocognitive deficits (Bazarian et al. 2006; McAllister et al. 2006; Niogi et al. 2008), with or without affective disorder symptoms (Chan et al. 2008; Lanctôt et al. 2010; Rapoport et al. 2008). Zohar et al. (2011), in a mouse model of mild TBI, have observed profound and long-lasting, irreversible cognitive impairments as well as permanent depressive-like behavior. Thus, any understanding of putative interventional efforts ought to present evidence for positive gains at the various levels and loci of injury.

Physical Exercise as Intervention

The common features of activities that may contribute to physical exercise ought to be presented and examined for purposes of determining eventual appropriateness for interventional status. Physical exercise has been described as any and all activity that generates force through muscular activity that disrupts a homeostatic state (McArdle et al. 1978). Although daily physical activity holds benefits for general measures of function, quality-of-life and physical strength, as well as increasing endurance (Dechamps et al. 2010; Marks et al. 2009), much evidence

presents the manifest advantages for cerebral integrity and neurocognition (Kramer et al. 1999; Lustig et al. 2009; Marks et al. 2010). Any bodily activity that enhances or maintains physical fitness implies the involvement of regular and frequent exercise. Morris and Schoo (2004) have defined exercise as a planned, structured physical activity with the purpose of improving one or more aspects physical fitness and functional capacity. It has been characterized on the basis of type, intensity, frequency, and duration, with either endurance or resistance as the training endpoint (Mougios 2010). Endurance exercise develops the capacity to exert oneself over long periods whereas resistance exercise implies the resistance to the force of muscular contraction and elastic or hydraulic resistance, a specific type of strength training that utilizes elastic or hydraulic tension to provide this resistance (Ormsbee et al. 2009). Several molecular agents feature in different aspects within the context of physical exercise and increasingly there is much consideration of how their actions converge to impact the structure and function (e.g., mobility, learning and memory domains) of the brain and CNS (Ang and Gomez-Pinilla 2007). For example, serum brain-derived neurotrophic factor (BDNF) is known to increase with exercise and this increase is believed to originate from the brain and it is suggested that monoamines are involved in BDNF regulation (Maisonpierre et al. 1991).

The nature of physical exercise may vary enormously must needs be tailored to the special requirements of each individual even before proceeding with considerations of cellular, macro-level, outcome-level, and the domains of neurologic/psychiatric condition. The type, intensity, frequency, and duration of exercise determines the extent to which muscle contractions induce generation of reactive oxygen- and nitrogen species (RONS) with strenuous exercise causing oxidation of proteins, lipids, DNA, release of cytosolic enzymes, and other markers of cell damage (Cubrilo et al. 2011; Powers et al. 2011), but only exhaustive (very strenuous) exercise may be detrimental (Gomez-Cabrera et al. 2009). As a general paradigm, running exercise, whether wheel running, treadmill running, running of various other types or fast and strenuous (quadropedal) 'Nordic' walking, is associated with cardiovascular, proprioceptive, metabolic, motor, motivational, and/or general arousal system mobilization with multiple benefits for individuals (Deslandes et al. 2009; Qiu et al. 2010; Zhang et al. 2011). Mitochondrial biogenesis is critical to normal cellular functioning; exercise, particularly aerobic, activates mitochondriogenesis (Eynon et al. 2011). Low mitochondriogenesis is implicated in loss of muscle function in aging and in the development of frailty. Thus, the positive effects of exercise on mitochondriogenesis are limited (Viña et al. 2009), possibly due to depletion of peroxisome proliferator-activated receptor-γ coactivator-1α (Derbré et al. 2011). Physical exercise has been manifested in marked improvements both in function and biomarker integrity (Archer 2011; Archer and Fredriksson 2010; Archer and Kostrzewa 2011; Archer et al. 2010, 2011a, b, Fredriksson et al. 2011). Ang et al. (2003) have indicated that neuroprotection after physical exercise may be the consequence of elevated levels of an endogenous neurotrophic factor/nerve growth factor and the proliferation of its receptive cholinergic neurons.

It is essential to remain aware of the stress-provoking aspect of exercise at both behavioral and biomarker expressions continually. Strenuous, or markedly strenuous, levels of physical exertion, such as during marathons/ultramarathons/triathalons, induce large elevations in plasma cytokine levels (Nieman et al. 2001, 2005; Smetanka et al. 1999). Exercise-induced cytokine release under these conditions may be due to elevation in catecholamines and cortisol, high core body temperature, endotoxemia, etc. (Bosenberg et al. 1988; Camus et al. 1997; Jeukendrup et al. 2000). Notwithstanding these effects of strenuous exercise, physical activity exerts anti-inflammatory effects (Pedersen 2006), and it may be applied as a means to control low-grade systemic inflammation (Mathur and Pedersen 2011). As indicated above and below, it is quite evident that physical exercise presents a form of stress with the exercise–stress–inflammation relationship a model of neuroendocrine interaction. It stimulates the innate immune responses with effects upon inflammatory responses mediated by the sympathetic nervous system and the hypothalamic–pituitary–adrenal axis (HPA), yet subject to the dictates of moderate and long-term necessity (Ortega 2003). Martin-Cordero et al. (2011), using an experimental model of metabolic syndrome, have shown that a physical exercise training schedule on a treadmill (from 25 cm/s for 10 min in the 1st weeks to 35 cm/s in the last month 5 days/week over 14 weeks) produced a reinstatement of the interleukin-6 (Il-6)-noradrenaline (NA) feedback mechanism in response to acute exercise (5 min at 17 cm/s followed by 25-35 min at 35 cm/s with no slope).

The notion of scaffolding provokes the concept of transient measures, *external to the buildings*, that provides for the construction and maintenance of buildings but not the building itself. In this regard, physical exercise regimes, representing environmental mediatory factors or the transient external-locus scaffolding, have provided measureable improvements at both behavioral and biomarker levels under several brain deficit conditions. The notion is analogous to that of parental scaffolding of executive functioning in preschool children (Hammond et al. 2011), presupposing the necessity for some manner of construction, development, maintenance and neuronal repair. Although the notion of "Scaffolding" concerns loss of cognition during aging in the context of a dynamically

adaptive brain and central nervous system, it lends itself plausibly the interventional role of physical exercise in brain disorders. According to Park and Reuter-Lorentz (2009), scaffolding presents a normal process that continues across the lifespan involving the application and development of complementary, alternative neural circuits to achieve a particular cognitive goal; it is protective of cognition in the aging (or disabled) brain and is reinforced by physical exercise and cognitive engagement (which is harnessed during exercise). With regard to the brain afflicted by TBI, the notion of scaffolding offers the viewpoint that exercise buttresses the more or less, dependent upon injury extent, surviving adaptive and compensatory neuroreparative processes. Voss et al. (2010) have shown the scaffolding effect of a 1-year walking exercise intervention that increased the resting functional connectivity and efficiency in higher level cognitive networks that included frontal, temporal, and posterior cortices in the Default Mode Network and Frontal Executive Network. Within the context of TBI situations where long-lasting rehabilitational advantages are sought, physical activity/exercise was shown to provide beneficial outcomes for both stroke and TBI patients: Dejong et al. (2011) showed that two types of physical therapy activities (gait training and community mobility) were both positively associated with discharge motor Functional Independence Measure outcomes across for these patients groups.

Exercise Influence Upon HPA Dysregulation: Stress and Affect Following TBI

Neuroendocrine disturbances are common after TBI, and the detrimental effects of TBI on brain integrity and functioning are markedly potentiated by the effects of stress biomarkers (Griesbach et al. 2011). This situation is hardly surprising since strong correlations were obtained between affective distress and self-discrepancy (Cantor et al. 2005). The initial, protective response to TBI involves acute activation of the HPA axis through promotion of intravascular fluid retention and elevated cortical levels modulating immune/inflammatory responding and elevated metabolic substrate availability (Johnston 2006). Endocrine failure may induce clinically critical consequences during acute and convalescent care after TBI; this condition may be caused by direct injury to the HPA axis, neuroendocrinological effects from catecholamines and cytokines, or from systemic infection/inflammation that produces primary gland failure (Powner et al. 2006). Both acute and chronic dysfunction of the HPA axis expressed through GH, quality-of-life and neurobehavioral deficits, as well as adrenal insufficiency, are observed after mild, moderate and severe TBI (Cohan et al. 2005; Dusick et al. 2008; Kelly et al. 2006). Given the cerebrovascular and anatomical vulnerability exacerbated by the diffuse and variable nature of TBI, HPA complex regulation may be defective to greater or lesser extent, e.g., following head wounds, pituitary damage is not uncommon (Benvenga 2005). The type and duration of pituitary damage varies with TBI characteristics and patient heterogeneity (Tanriverdi et al. 2007, 2010a, b, c). TBI-induced HPA dysregulation due to adrenocorticotropic hormone (ACTH) and/or adrenal insufficiency has been observed in patients with mild to severe TBI (Tanriverdi et al. 2006, 2008a, b). Both among mild TBI patients and in an animal model of TBI, controlled cortical impact injury, severity-dependent disruptions of HPA axis are described (Taylor et al. 2008, 2010). The response of the HPA axis to psychosocial stress and acute exercise is similar although the latter induces a stronger response (Negrao et al. 2000).

There is much evidence that regular physical exercise counteracts some of the effects of stress, although several studies have suggested that prior exercise does not alter the acute HPA axis responses to stress (e.g., Fatouros et al. 2010). Nevertheless, Campeau et al. (2010) have presented results showing that 6 weeks of daily or intermittent, voluntary wheel-running exercise constrains the HPA axis response to mild, but not more intense stressors, and that this regulation may be mediated at a central level beyond the primary sensory input. Regular physical exercise alleviates most of the symptoms associated with stress, affective syndromes from various causes and associated health problems often linked to TBI, such as anxiety. The sympatho-adrenal system with its stress-induced activation and increased release of catecholamines presents a major system involved in the response to stressful events. Exercise training offers as an important modulator of sympatho-adrenal system, adrenal medulla, and stellate ganglia being two components of this system. Gavrilovic et al. (2011) investigated physical exercise-related changes in gene expression of catecholamine biosynthetic enzymes tyrosine hydroxylase, dopamine-β-hydroxylase, and phenylethanolamine *N*-methyltransferase in the adrenal medulla and stellate ganglia of chronically psychosocially stressed adult rats exposed daily to 20-min treadmill exercise for 12 weeks. They observed that treadmill exercise induced decreased gene transcription of catecholamine biosynthetic enzymes in stellate ganglia and an attenuation of cardiac NA production during stressful situations. The reduction of catecholamine synthesis in stellate ganglia may have been linked to the beneficial effects of treadmill exercise on cardiovascular system in stressed animals.

Several studies suggest that physical exercise may alleviate depressive symptoms in clinical/nonclinical populations to greater or lesser extent (Krogh et al. 2010;

Lawlor and Hopker 2001; Rethorst et al. 2009). Takada et al. (2009) examined the links between lifestyle, working environment, depressive symptoms and suicide ideation in 4,118 Japanese business employees (2,834 male and 1,284 female). They found that the factors associated with depressive symptoms were: high levels of job stress, problem drinking, insufficient sleep, lack of social support and absence of stress reduction techniques over both genders, such as lack of physical exercise and sedentary lifestyle. A wide range of studies have shown that regular physical exercise reduces stress symptoms, mood disorder, anxiety and depressiveness (Broman-Fulks and Storey 2008; Janisse et al. 2004; Smith et al. 2007; Tsang et al. 2008; Wang et al. 2010). Acute resistance exercise induced catecholaminergic rather than HPA axis stimulation (Fatouros et al. 2010). Exercise stimulates GH, prolactin and cortisol release (Karkoulias et al. 2008; Weltman et al. 2003) with exercise training, in humans, modulating the neuroendocrine response to challenge (Brooks et al. 2001, 2003), and exerting an antidepressant effect (Mead et al. 2008). Campbell et al. (2009) demonstrated that voluntary wheel running exercise initially caused hyperactivation of the HPA axis, due to enhanced adrenal sensitivity to ACTH, and consequently these alterations in HPA activity were eliminated to give restored normal levels completely by 8 weeks of exercise training.

High rates of depression have been reported in individuals with TBI with estimates ranging from 6 to 77% (Jorge et al. 2004; Kreutzer et al. 2001) and later life-long risk (Dikman et al. 2004). Both cognitive and psychosocial behavior impairments may be observed in the depression following TBI (Chamelian and Feinstein 2006; Fann et al. 1995; Hibbard et al. 2004). Neuropathologically, it appears that an imbalance of left versus right frontal and parietal viable brain volumes is related to the development of depression (Schönberger et al. 2011). Hudak et al. (2011) studied the post-injury atrophy of brain regions of interest in TBI patients with depressive symptoms assessed by the Beck Depression Inventory-II. They found that three regions of interest, left rostral anterior cingulate and bilateral orbitofrontal cortex also relevant to spontaneous depression, were found to be significantly correlated with depressive symptoms. The efficacy of exercise in the treatment of depression has been documented (e.g. Blumenthal et al. 2007; Dunn et al. 2005; Greer and Trivedi 2009). Among TBI survivors presenting depression, physical exercise intervention was highly preferred (Fann et al. 2009), improving several aspects of depressive symptoms including sleep problems, anxiety, fatigue and quality-of-life (Gordon et al. 1998; Lai et al. 2006; Ströhle 2009), as well as cognition (Grealy et al. 1999; Kleim et al. 2003). Schwandt et al. (2011) tested the effect of an aerobic exercise intervention on symptoms of depression among individuals with TBI (more than 11 months previously) using the Hamilton Rating Scale for Depression, aerobic capacity (cycle ergometer, heart rate at reference resistance, perceived exertion), the Rosenberg Self-Esteem Scale and the program perception survey. They have reported that with post-exercise intervention all the participants presented fewer symptoms of depression, improved aerobic capacity and higher self-esteem following the intervention. High levels of satisfaction with the program, improved mood and cardiovascular were reported without any adverse effects. Finally, Hoffman et al. (2010) have reported that TBI patients with higher levels of exercise expressed improved levels of sleep, community participation and overall quality-of-life.

Exercise and Neurocognition Following TBI

With an estimated 10 million individuals affected worldwide annually, the World Health Organization estimates that TBI will surpass other diseases as the major cause of death and disability by the year 2020. The burden of mortality and morbidity that this condition imposes upon individuals, caregivers and society, renders TBI a pressing public health and medical problem. It appears that 40-50% of the afflicted patients express cognitive deficits (Greve et al. 2003). More recently, 33% of adults with TBI were reported to present impaired cognitive function on discharge from hospital, although limited recovery was observed during the 1st year post-injury (Lin et al. 2010). Cognitive impairments associated with TBI, if not permanent, may last decades, including memory deficits, reduced abstract thinking, retarded information processing, poor concentration, information processing and sequencing deficits, slowed reaction time, dysarthia (problems articulating speech), anomia (problems of word/name recollection), impaired auditory comprehension, loss of verbal fluency, deficits in general intelligence and problems in planning and organization (Rimel et al. 1982), which lead to impulse control deficits. Even mTBI causes retarded information processing, poor concentration and memory deficits (Rimel et al. 1981). Adolescents with more severe TBI may underestimate their own degree of executive dysfunction in daily life, particularly aspects of metacognitive abilities (Wilson et al. 2011). Diffusion tensor imaging (DTI) analyses have shown that greater white matter pathology predicted greater cognitive deficits (Kraus et al. 2007). Wilde et al. (2011) assessed the neural correlates with fMRI and DTI of working memory, using the Sternberg Item Recognition Task in 40 children with moderate-to-severe TBI compared to 41 demographically comparable children with orthopedic injury. They observed that diminished white matter integrity of the frontal lobes

and cingulum bundle, as measured by DTI, was associated with longer reaction times on the Sternberg Item Recognition Task. Across modalities, the cingulate emerged as a common structure related to performance after TBI. In view of the marked cognitive deficits and associated neuropathology, the application of physical exercise as an interventional parameter in TBI ought to be of critical importance.

In both human and laboratory animal studies with forced or voluntary exercise, improvements in the cognitive functioning domain (including learning ability and memory capacity) were obtained under conditions of stroke, aging and life-span (McDonnell et al. 2011a; Tseng et al. 2011; Voss et al. 2011). These observations suggest that voluntary exercise programs may be efficacious against cognitive deficits in TBI (e.g., Grealy et al. 1999). For example, older healthy women can improve episodic and working memory through spending time on a challenging physical or mental activity (Evers et al. 2011). Little et al. (2010) have shown that TBI causing diffuse axonal injury that results in damage to the thalamic projection fibers, and physical exercise, rota-rod and treadmill training, contributed to increased expression of synaptophysin in subcortical regions of the ischemic hemisphere including the hippocampus, dentate gyrus, and thalamus (Seo et al. 2010). Synaptophysin is an abundant synaptic vesicle protein without a definite synaptic function. McMorris et al. (2011) concluded that acute, intermediate intensity exercise induced a strong beneficial effect on speed of response in working memory tasks but a low to moderate, detrimental one on accuracy, suggesting that exercise-induced increases in brain concentrations of catecholamines resulted in faster processing whereas increased neural noise may negatively affect accuracy (see also Pontifex et al. 2009). Gosselin et al. (2011) used fMRI and event-related potentials (ERP) to study cerebral dysfunction in 14 mTBI symptomatic patients (5.7 $\pm$ 2.9 months post-injury) compared to 23 healthy controls, during the post-acute phase, using a visual externally ordered working memory task. They observed attenuated blood oxygen level dependent (BOLD) signal changes in the left and right mid-dorsolateral prefrontal cortex (mid-DLPFC), the putamen, the body of the caudate nucleus, and the right thalamus in the mTBI group compared with the controls. Furthermore, symptom severity and BOLD signal changes were correlated: patients with more severe symptoms had lower BOLD signal changes in the right mid-DLPFC. For ERP, a group $\times$ task interaction was observed for N350 amplitude. A larger amplitude for the working memory task than for the control task was found in the controls, but not in mTBI patients, who presented weak amplitudes on both tasks. Figure 1 presents selected neurocognitive deficits with related brain pathology following TBI that were alleviated through exercise intervention together with interrelationships between TBI effects on the brain and cognitive performance, exercise effects on brain and cognition, and the overlap that offers putative treatment possibilities that promote the notion of scaffolding.

Both correlational and regressional studies have demonstrated that healthy (non-clinically debilitated) adults individuals who are generally more active physically are more likely than individuals who are generally inactive to show higher levels of performance on several different cognitive tasks, including executive function and working memory (Ratey and Loehr 2011). Higher levels of self-reported physical activity were associated also with better performance on tasks of selective attention (Hillman et al. 2006), task-switching performance (Kamijo and Takeda 2010), and superior processing speed, memory, mental flexibility and overall cognition (Angevaren et al. 2007). Exercise even improved cognition in older adults who did not present cognitive impairment (Angevaren et al. 2008). The randomized control trial study carried out by McMillan et al. (2002) comparing attentional control training, physical exercise and a control condition in 130 adults presenting TBI, 3 months and 1-year post-TBI and living at home with supervised exercise sessions, is illustrative. Tests of outcome included test of everyday attention, the Adult Memory of Information Processing Battery, Paced Auditory Serial Addition test, Trail Making test, Sunderland Memory questionnaire, and Cognitive Failures Questionnaire, incorporated aspects of both executive function and working memory with recording sessions at baseline, 6 months, and 12 months, with an addition questionnaire at 12 months. Their evidence suggested the aerobic exercise improved performance in speed of information processing, global cognition, attention and cognitive flexibility. Nevertheless, the prevailing constraint being the complexity and inherent inconsistencies of cognition and its expression remains a continual straight-jack to undue optimism (McDonnell et al. 2011b).

Many of the benefits from physical activity augmenting neurocognition appear to be mediated by growth factors, neurotrophins and other biomarkers for the development of greater brain tissue integrity (Berchtold et al. 2010). The benefits of physical exercise for a variety of factors that influence cognitive performance, as well as measures of cognition are well-documented, including neuronal protection (Stummer et al. 1994), enhanced neurogenesis (Kannangara et al. 2010; Van Praag et al. 1999), growth factors, besides BDNF, like IGF1 and VEGF, acting synergistically to benefit neural integrity and function (Carro et al. 2001; Cotman et al. 2007) and cognitive ability (Fordyce and Wehner 1992; Samorajski et al. 1985). BDNF, itself, mediates multiple morphologic alterations at neuronal levels, such as dendritic arborization (Imamura

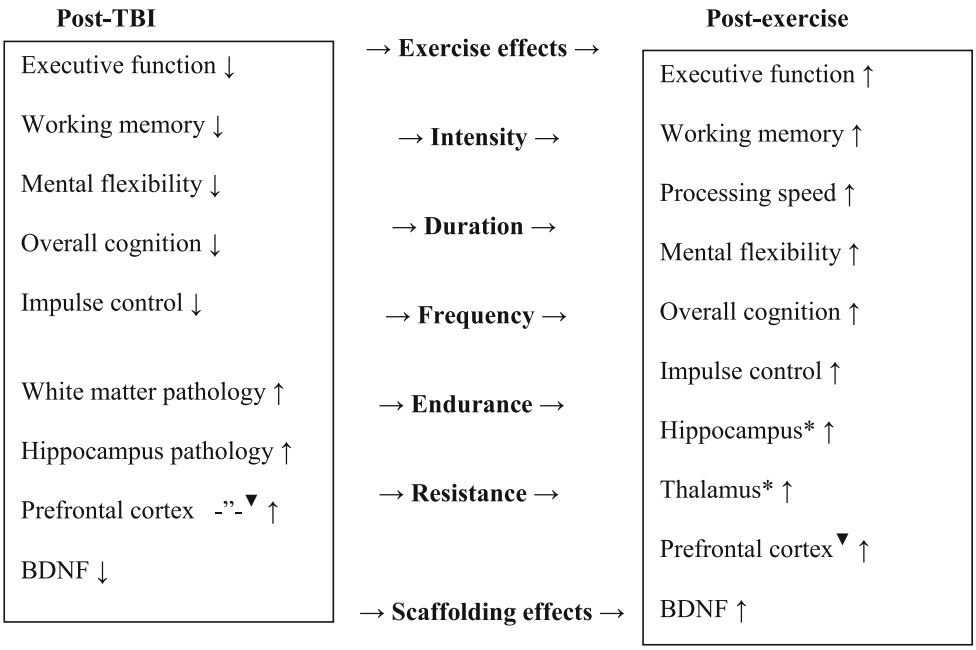

Fig. 1 Selected neurocognitive deficits with related brain pathology following TBI that were alleviated through exercise intervention (see text for descriptions and references). Inter-relationships between TBI effects on the brain and cognitive performance, exercise effects on brain and cognition, and the overlap that offers putative treatment possibilities that promote the notion of scaffolding. *↑, Increased expression of synaptophysin; ▼↓/↑, decreased/increased blood oxygen level dependent (BOLD) signals in right and left mid-dorsolateral prefrontal cortex

and Greer 2009; Zhou et al. 2008), axonal and dendritic remodeling (Yacobian and Lo 2000), synaptogenesis (Lu et al. 2009; Menna et al. 2009), synaptic efficacy (Boulanger and Poo 1999; Sallert et al. 2009) and neural stem cell efficacy (Xuan et al. 2008). Griesbach et al. (2009) have shown that physical exercise counteracted the cognitive deficits associated with the head injury. Western blot analyses demonstrated that exercise elevated the mature form of BDNF, synapsin I and cyclic-AMP response element-binding protein (CREB) in the vehicle treated Sham (intact)-RW (exercised) group whereas only the mature form of BDNF and CREB were increased in the vehicle treated FPI (TBI)-RW group. The blockade of BDNF (through the pre-administration of TrkB-IgG, an immunoadhesin chimera that inactivates BDNF) greatly reduced the molecular effects of exercise in that exercise-induced increases of BDNF, synapsin I and CREB were not observed.

Exercise and Neuroplasticity Following TBI

Neuroplasticity refers to capacity of the brain and central nervous system to remodel itself at several different levels (Hallett 2005): (i) individual neurons and events responsible for remodeling that occur within the cell, (ii) groups of neurons and their functions that can evolve to alter function and daily behavior, (iii) multiple processes that may occur both in parallel and serially. Some of these processes are fast yet transient, other longer lasting but more permanent; it appears that the more persistent the occurrence of early change, the greater its likelihood of its permanence. Exercise impacts brain plasticity by involving the actions of BDNF via an influence upon the expression of select molecular systems related to the effects of BDNF on synaptic plasticity (Ding et al. 2011), but also upon the growth, differentiation and maintenance of neuronal systems (Satomura et al. 2011); in this regard, BDNF, whether induced through exercise or otherwise presents a likely substrate for expressions of scaffolding.

The fastest type of change is a simple effect of BDNF, an essential neurotrophin intimately connected with brain metabolism and homeostasis; the neurotrophic factor induces a cascade of molecular and cellular processes. Kaplan et al. (2010) have suggested treatment approaches that enhance BDNF-related signaling and have the potential to restore neural connectivity. Such treatment approaches could facilitate neuroplastic changes that lead to adaptive neural repair and reverse cognitive and emotional deficits in both TBI and PTSD. In juvenile TBI, molecular responses related to growth, development and metabolism may play a particularly important role in the injury response and the recovery trajectory following developmental TBI (Babikian et al. 2010). Lombardi (2008) has discussed the relative therapeutic effects of psychostimulant drugs co-administered with sensory–motor exercise inventions that have been shown to induce a steady acceleration of motor recovery in TBI laboratory animals; this improvement in turn is considered to exert a facilitation of the neurological recovery process. Griesbach et al. (2007) have demonstrated that an exercise-induced increase in hippocampal BDNF is dependent upon when the exercise schedule is initiated after TBI. They had observed that the introduction of voluntary exercise

2 weeks after TBI-induction with a mild fluid-percussion injury produced an increase in BDNF and an improvement in the behavioral outcome. Adult rats were allowed running wheel access either 0–6, 14–20, or 30–36 days post-injury day showing significant increases in BDNF, synapsin I and CREB. Synapsin I is a neuron-specific phosphoprotein, a substrate for cAMP-dependent and Ca/calmodulin-dependent protein kinases, and is implicated in synaptogenesis and the modulation of neurotransmitter release. CREB (cAMP response element-binding) is a cellular transcription factor with an essential role in neuronal plasticity and long-term memory formation.

According to the analysis of exercise-induced effects of BDNF release in humans (Knaepen et al. 2010), 69% of studies in healthy volunteers and in patients presenting chronic disease/damage displayed only transient increases in serum or plasma BDNF levels after an acute aerobic exercise, with endurance (aerobic) exercise more effective than resistance. It is likely that physical exercise/training elevates basal BDNF only temporarily concurrent with an up-regulation of the cellular processing of BDNF (i.e., synthesis, release, absorption, and degradation). Prolonged physical exercise, rather than limited or discrete periods, ought then to produce higher and more continuous release of the neurotrophin into blood circulation, and in turn through more efficient absorption to peripheral and central tissue, contribute to a cascade of neuroplastic and neuroprotective effects. The particular timing of exercise intervention seems of vital importance since the up-regulation of plasticity-related proteins after TBI (administered as FPI) was compromised by premature voluntary wheel-running exercise (Griesbach et al. 2004a). Contrastingly, it was seen that voluntary exercise endogenously up-regulated BDNF and enhance recovery when it was delayed after TBI (Griesbach et al. 2004b). Finally, Goldshtrom et al. (2010) have reported the case of a 24-year-old female patient, 9-year post hemispherectomy following TBI that caused right hemiparesis. The patient was trained to perform Rhythmic Exercises with Auditory Cues (REAC) with gait pattern, functional assessment, cognitive, and psychological pre- and post-intervention. It was shown that gait pattern improved with reduced 'hip-hiking' and increased cadence, decreased spasticity in right arm and leg together with regained sensation, and improved cognitive performance.

Anti-Inflammatory and Angiogenic Effects of Exercise: TBI

Physical exercise regimes diminish inflammation (Beavers et al. 2010), and elevate the release of adrenaline, cortisol, growth hormones and neurotrophins, prolactin and other agents equipped with immunomodulatory functions (Handschin and Spiegelman 2008). Exercise and in particular strenuous exercise increases the circulating levels of several cytikines/chemokines (Petersen and Pedersen 2005). Physical exercise induces a rapid increase in peripheral blood lymphocytes (Gleeson 2007; Kruger and Mooren 2007) accompanied by monoaminergic involvement, e.g., adrenergic influence (Kruger et al. 2008). There appears to be a consensus that lymphocytosis is observed during and after exercise, proportional to intensity and duration. Both acute and chronic exercises alter the number and function of circulating cells of the innate immune system. Acute bouts of moderate exercise cause little change in mucosal immunity, but prolonged exercise and intensified training may alter both immune functioning and efficacy of the HPA axis. The prophylactic effects of exercise may be linked to anti-inflammatory actions depending upon which aspect of exercise characteristics present the most efficacious levels of protection (Walsh et al. 2011). Exercise training decreased chronic low-level systemic inflammation associated with obesity and a sedentary lifestyle (Kizaki et al. 2011). Given the post-traumatic cerebral inflammation following severe head injury, any eventual anti-inflammatory effects linked to exercise, post-TBI, ought to offer prospects for restorative scaffolding. Infarct size following forebrain ischemia was shown to present altered inflammatory status by profile performing exercise before brain trauma with prophylactic effects on brain damage (Endres et al. 2003; see also Ding et al. 2006). Pre-TBI physical training was found to induce interleukin-10 increase per se and protected against cerebral interleukin-1β and tumor necrosis factor-α increases and fluid perfusion induced brain damage decrements in interleukin-10 (Mota et al. 2011).

Given the sharp increase in TBI since 2001 following US involvement in Afghanistan and Iraq (Martin et al. 2008; Warden 2006) with ca., 5% of a huge military personnel (1.5 million) suffering head injury accompanied by loss of consciousness (Hoge et al. 2008), the utilty of non-invasive interventions is undeniable. Several studies indicate that while stress exacerbates neuropathological changes associated with brain disorder, exercise reduces these changes (Dishman et al. 1998). In this regard, Nation et al. (2011) have presented a neurovascular pathway of neurodegenerative disorder that underlines exercise as an intervention against vascular risk factors that include hypertension, diabetes, and aortic rigidity as well as direct changes in cerebrovasculature that involve changes in cerebral blood flow, angiogenesis and vascular disease improvement. Mota et al. (2011) have shown that exercise preconditioning reduced cerebral inflammation and protected against TBI-induced toxicity; cardiovascular adaptation to physical exercise (Scheuer and Tipton 1977)

offers a necessary adjunct to cerebrovascular integrity. Aerobic exercise reduces mortality in cardiovascular disorder (Taylor et al. 2004), benefits mood (Blumenthal et al. 1999), decreased impulsiveness in ADHD children (Medina et al. 2010), diminishes anxiety and depression (Lewin et al. 1992), and improves cognition (Colcombe and Kramer 2003; Gunstad et al. 2005). In older individuals, physical exercise induced a decrease in cerebral vascular conductance during moderate intensity cycling, compared to younger subjects (Fisher et al. 2008), whereas mean arterial pressure was increased in older subjects (Ogoh et al. 2011). Exercise increased also critical closing pressure (CCP) in young healthy subjects (Ogoh et al. 2010). In the context of TBI, Body Weight-Supported Treadmill Training (BWSTT) on a treadmill with rhythmic passive/active activation over 2-weeks (60 h) total training (de Bode et al. 2007) has been shown beneficial, not least as confirmed by neuroimaging techniques (Horenstein et al. 2009; Luft et al. 2004; Richards et al. 2008; Stewart et al. 2006; Thaut et al. 2007).

The positive benefits of exercise for TBI-induced inflammation and vascular pathology offer a non-invasive form of intervention, tailored to individual requirements and propensities that focuses of general aspects of health and physiology that form the foundations of brain integrity and function.

Conclusion: Exercise as Scaffolding to Alleviate TBI

The localization and severity of mild, moderate, or severe TBI causes both structural and functional destruction that, in addition to presenting symptoms, includes BBB breakdown, apoptosis and excitotoxicity, cerebral vascular pathophysiology, edema, and cerebral inflammation. Other disruptive influences pertain to emotional, neurocognitive and behavioral domains whereby hyperreactivity to stressors, HPA dysregulations and affective conditions, cognitive dysfunctions and loss of neuroplasticity exacerbate further the gravity of the TBI situation. Physical exercise facilitates improvements in debilities due to stress, affect and HPA dysregulation following TBI, augments neuroplasticity, and either reverses or attenuates the cognitive performance impairments due to TBI. It ought to be noted that the complete scope of physical exercise applications in TBI remains apparent rather than real. Chen et al. (2011) have shown that there is an increased risk of stroke among individuals who have sustained a TBI suggesting the need for more intensive medical monitoring and wider health education programs following TBI, especially during the first few months and years. It is likely that exercise models of recovery from stroke may contribute to a further understanding of TBI-exercise interventions, not least with relevance for determining exact parameters regard treatment introduction. As argued by Greisbach (2011), the premature application of post-concussive exercise may potentiate, rather than ameliorate, deficits by exacerbating post-concussive symptomatology and disrupting restorative processes. Nevertheless, it may be concluded that physical exercise/activity offers the critical factor mediating the increased BDNF levels and brain regional and cellular gains (Kobilo et al. 2011).

According to the modified notion of scaffolding (above), physical exercise reinforces the adaptive processes of the TBI brain in facilitating development of networks, albeit less efficient than pre-TBI, that compensate for those lost through cerebral damage. The essential aspect is that of an adaptive brain that through the scaffolding process is ensured optimal aging over an individual's lifespan. It is important to distinguish between what constitutes scaffolding and what constitutes the building itself (Petrik et al. 2012), whereas exercise regimes have been shown to induce neurogenesis, neurorepair, and damage control that buttress the brain against neurodegenerative processes it is the molecular, cellular, circuitry and regional levels, the 'steel and concrete' that form the brain construction within the affected domains. Whether this metaphor facilitates the notion of scaffolding to elucidate the role of exercise in TBI-afflicted individuals depends on the extent to the restorative actions of physical are investigated with this end in view; it ought to be noted that scaffolding has been applied from a perspective affective and anxiety disorders (Petrik et al. 2012). Nevertheless, it is essential that the major differences in brain responses to chronic neurodegenerative aging and the eventual recovery from sudden impact damage not be neglected. Whether or not the aging brain undergoes a qualitative shift of activation to induce complementary or alternative brain networks remains an issue (Gratton et al. 2009; Peltz et al. 2011; Schneider-Garces et al. 2010). According to Voss et al. (2010), the facilitation of the shift of brain networks in the direction of young adults instead of toward alternative network formation among older adults was observed with the implementation of aerobic exercise regimes (see also Voss et al. 2012). Scaffolding hypothesis posits that qualitatively different networks emerge during aging to support/compensate for age-related brain dysfunction. Contrastingly, from the context of TBI given that impacted brain injury may actually impair function completely in certain regions, it is feasible that qualitatively different patterns of activation and/or networks may emerge, under the 'scaffolding' of exercise regimes that compensate for specific loss in specific cases. Under the conditions of disease/disorder following TBI, deficits in cognitive, motor, emotional or neuroimmune functioning that express the critical disturbance in adaptive capacity may be buttressed by the

scaffolding that is provided by explicit physical exercise and activity. Possibly, the scaffolding process will be less effectively generated in the aged brain and in the very young. Despite this, much evidence indicates the physical exercise induces functional plasticity in large-scale brain systems not only in the TBI brain but brains affected by the ravages of time.

If indeed the notion of scaffolding following physical exercise presents a useful conceptualization for the observed evidence of restored structure and function, the question of which biological substrates (the steel and concrete) are available for consideration arises. Most likely, the widespread contributions of BDNF and other neurotrophins to neurogenesis, dendritic plasticity/arborization and neuronal repair present a primary target for further observation and further targeting of conditions influencing BDNF concentrations whether systemic or in regions of the brain. Thus, a reliable prospect for future application of the scaffolding notion to design cohesive studies appears readily available. Finally, the importance of general high level of physical condition in case of TBI affliction in order to enjoy the most advantageous prognosis has been shown to be an essential prerequisite from laboratory, clinical and retrospective studies (cf. Hassett et al. 2011). Suffice it to say that for this reason alone individuals ought to adhere routinely to physical exercise schedules to ensure their own health conditions.

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