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Review

Towards an understanding of the physical activity-BDNF-cognition triumvirate: A review of associations and dosage



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ABSTRACT

Physical activity has received substantial research attention due to its beneficial impact on cognition in ageing, particularly via the action of brain-derived neurotrophic factor (BDNF). It is well established that physical activity can elevate circulating levels of BDNF, and that BDNF has neurotrophic, neuroprotective and cognitively beneficial properties. Yet, practical implementation of this knowledge is limited by a lack of clarity on context and dose-effect. Against a shifting backdrop of gradually diminishing physical and cognitive capacity in normal ageing, the type, intensity, and duration of physical activity required to elicit elevations in BDNF, and more importantly, the magnitude of BDNF elevation required for detectable neuroprotection remains poorly characterised. The purpose of this review is to provide an overview of the association between physical activity, BDNF, and cognition, with a focus on clarifying the magnitude of these effects in the context of normative ageing. We discuss the implications of the available evidence for the design of physical activity interventions intended to promote healthy cognitive ageing.

1. Introduction

There is an urgent need to better understand brain ageing, in order to identify mechanisms amenable to modification and which may be targeted to enhance brain ageing from childhood through to old age. The number of individuals aged 65 years and over are projected to make up 16 % of the population by 2050 (Population Reference Bureau, 2018), and the health of this growing segment of the population has profound implications for the burden of age-related diseases (Chang et al., 2019). Brain-Derived Neurotrophic Factor (BDNF) is heavily implicated in the development of neuronal cells and some of their key functional parts (dendrites, spines, synapses), and has profound impacts on the structure and function of the brain (Binder and Scharfman, 2004; Koshimizu et al., 2009).

Physical activity, defined as any voluntary bodily movement produced by skeletal muscles that requires energy expenditure, is one of the most potent lifestyle factors impacting BDNF levels in the body and brain (Bechara et al., 2014; Szuhany et al., 2015). BDNF is thought to contribute to the established benefits of chronic physical activity on cognition (Colcombe and Kramer, 2003; Northey et al., 2018) through activity-related increases in BDNF (Dinoff et al., 2017). Yet, specifics relating to the type, intensity and duration of physical activity required, the degree and dose of BDNF elevation, and the size of the consequent impact on the ageing brain remain unclear. As Erickson et al. suggest, an improved understanding of dose-response parameters and their underlying mechanisms is required to produce evidence-based guidelines aimed at specific target populations (Erickson et al., 2019). This review utilises available evidence as well as theoretical mechanisms underpinning a dose response between physical activity and circulating BDNF, to synthesise available evidence to inform the design of physical activity interventions intended to promote healthy cognitive ageing.

2. BDNF

BDNF is a neurotrophic protein found both centrally (within the brain), and peripherally (primarily measured in blood) (Binder and Scharfman, 2004). The relationship between BDNF, the body, and the brain is summarised in Fig. 1. Peripherally, it is expressed within muscle cells (particularly skeletal (Matthews et al., 2009)), adipose tissue (Nakagomi et al., 2015), and in endothelial cells (Helan et al., 2014), and stored primarily bound to platelets in the blood, liver, and spleen (Yang et al., 2017). While BDNF dynamics in different structures within the brain, brainstem, spinal cord and skeletal muscle are an important topic (covered in detail elsewhere, e.g. (Bathina and Das,

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Fig. 1. Schematic overview of the relationship between BDNF, the body and brain. *Note.* BDNF structure obtained from the RCSB PDB Protein Databank, 1B8M Asymmetric Unit assembly, with minor author post-processing for visual clarity.

2015; Yarrow et al., 2010)) this review will relate to the more readily measured pools of circulating BDNF, that are found in the cerebrospinal fluid (either within the brain or spine) and the blood (whole blood, plasma, and serum).

BDNF permeates somewhat across the blood-brain-barrier (Pan et al., 1998) with animal data showing clear associations between peripheral and central concentrations ($r^2 = 0.44$, p = 0.025 and $r^2 = 0.41$, p = 0.025 in rats and pigs respectively) (Klein et al., 2011). In serum, the BDNF concentration is approximately 100-fold higher than in plasma and platelets, though at rest all measures are positively correlated: when measured in the same individuals (n = 140), median BDNF was 92.7 pg per 10⁶ platelets, 92.5 pg/ml in plasma, and 22.6 ng/ml in serum (Lommatzsch et al., 2005).

BDNF can be measured by several techniques, historically immunohistochemical visualization in Western Blot (e.g. (Dugich-Djordjevic et al., 1995)). The most common method isenzymelinked immunosorbent assay (ELISA) which marks BDNF with antibodies and has high accuracy but relies on comparatively large sample volumes. The most recent method is Single Molecule Array (SIMOA), a single-molecule immunoassay, have shown improvement in sensitivity relative to other methods by a factor between 10-100 (Naegelin et al., 2018; Polacchini et al., 2015). As with all biological assays, there is measurement error in BDNF with common assay sensitivity on the order of 5-20 pg/ml, a range of 8-1000 pg/ml, intra-assay coefficients of variation from 12 to 20% for the same blood samples (Polacchini et al., 2015), though newer assays (such as SIMOA) are improving upon this.

BDNF levels change across the lifespan. In infancy, basal serum BDNF averages 9230 pg/ml (SD = 6410 pg/ml; n = 108 infants aged 0–4 years, (Morichi et al., 2012)). This falls in childhood prior to adolescence (mean 504.0 pg/ml, SD = 301.6 pg/ml, n = 59 pre-pubescent children), and again during puberty (mean 413.8 pg/ml, SD = 288.8 n = 51). BDNF levels are higher in childhood than adulthood, but when focussing only on adults central measures indicate that BDNF is highest in early adulthood (Webster et al., 2006), and soon begins to decline further. Lommatzch et al. (2005) stratified median plasma BDNF into age groups of young adulthood ~100 pg/ml (n = 45 aged 20–33), mid-life ~80 pg/ml (n = 59 aged 34–47), and later life ~50 pg/ml (n = 36, aged 48–60). This decreasing trend continues into later life, with a large study of serum BDNF in 5104 adults aged 65–97 finding an average 21 ng/ml (SD = 5.4 ng/ml), which decreases by approximately 0.1 ng/ml per year of age (Shimada et al., 2014).

Alongside physical activity, which is discussed in detail in the

following sections, BDNF is modulated by several factors, including acute responses to passive environmental heat exposure (Kojima et al., 2018), intravenous tetrahydrocannabinol administration (D'Souza et al., 2009), hypoxic stress (Helan et al., 2014), electroconvulsive therapy (Salehi et al., 2016) and long-term factors such as exposure to sunlight and time of year (Molendijk, Haffmans, et al., 2012a,b), environmental enrichment (Falkenberg et al., 1992; Ickes et al., 2000) and schizophrenia (Palomino et al., 2006). Caloric restriction significantly increases serum BDNF after one month (Guimaraes et al., 2008), with a $25\ \%$ caloric reduction associated with an increase of serum BDNF from 3.97 \pm 0.87 to 6.75 \pm 1.62 ng/ml after three months in a sample (n = 17) aged 24-48 years (Araya et al., 2008). Fasting can be distinguished from caloric restriction in that its health benefits in humans and animals appear to arise from the duration between meals, rather than the total calories consumed (Paoli et al., 2019). Intermittant fasting can positively impact ageing brain health (Mattson, 2015) and has been observed to upregulate BDNF expression by up to three times (Walsh, Scribbans, et al., 2015a,b). While it is unclear whether intermittent fasting or caloric restriction provides superior BDNF release, but fasting for a clear block of time rather than consistent caloric restriction appears to be more achieveable for human subjects(Anton and Leeuwenburgh, 2013). Long term fasting (8+ hours), stringent caloric restriction, or restriction to a ketogenic diet (high protein and fat, low carbohydrate foods) can induce ketosis, a state in which the liver converts fats into ketones, and which is linked with BDNF upregulation in humans and animals (Maalouf et al., 2009). A ketogenic diet protocol is associated with a significant, yet transient increase of serum BDNF from 78 pg/ml to 92 pg/ml after two weeks in a sample (n = 35, aged 30-45 (Mohorko et al., 2019)).

Patterns of macronutrient intake, notably adherence to the Mediterranean diet (Sanchez-Villegas et al., 2011) and the ketogenic diet (in obese individuals) (Mohorko et al., 2019) are also associated with higher circulating BDNF. Numerous associations between dietary supplementation and increased peripheral BDNF have been reported (e.g. Chung et al., 2012; Sandberg et al., 2018; Solati et al., 2015), such as omega-3 polyunsaturated fatty acids (3-PUFA; found in foods such as fish and flaxseed oil), with reported increases of plasma BDNF from 0.80 pg/ml to 1.04 pg/ml and 0.89–1.10 pg/ml in adult females and males, respectively (Hadjighassem et al., 2015).

Together, these studies highlight the need to interpret BDNF levels in light of measurement error (up to 20 %), sample age range and characteristics. Broadly, in any given healthy adult sample, basal serum BDNF is expected to fall somewhere in the range of 20-30 ng/ml. In the absence of disease, the age-associated decline in BDNF is at least in the order of 0.5 %–5 % per year.

3. Brain ageing

In this section we will briefly review some of the main contributors to biological ageing, to provide context for understanding the link between physical activity and BDNF in ageing.

3.1. Ageing mechanisms

Although ageing mechanisms are very complex, they can be broadly grouped into four categories.

3.1.1. Promotion of cellular and DNA damage

Oxidative stress (OS) refers to the excess production of reactive oxygen species (i.e. oxidants) relative to the production of endogenous and intake of exogenous (dietary) anti-oxidants which buffer their corrosive actions. OS damages DNA, degrades cell structures, and progressively impairs cellular function. Consequently it leads to increased apoptosis, inflammation, cellular senescence, tissue and organ damage, and decreased neurogenesis. **Inflammation** is an essential immune response to pathogens and trauma which contributes to combat infections and initiate tissue repair. Persistent low-grade systemic or central inflammation also develops in chronic conditions such as obesity, type 2 diabetes, cardiovascular disease and depression. This leads to increased oxidative stress, DNA and cellular damage, impaired tissue repair, insulin resistance, and decreased neurogenesis (Perry, 2004).

3.1.2. Accumulation of waste products

Protein mis-folding occurs all the time but defective proteins are mostly recycled or removed from tissues through intra- or extra-cellular mechanisms (Klaips et al., 2018). Dysfunction in recycling processes occuring increasingly with age promotes the accumulation of waste products intra-cellularly or in tissues and leads to the formation of aggregates, often toxic (e.g. amyloid plaque in Alzheimer's disease) or which impair cellular (e.g. neurofibrillary tangles) or organ (e.g. atherosclerosis) function (Sweeney et al., 2017). Waste product accumulation is exacerbated by reduction in the telomere length of Leukocytes (white blood cells) (Mons et al., 2017), and disruption of a healthy level of autophagy (Lipinski et al., 2010).

3.1.3. Impairment of cellular metabolism

Glucose and oxygen metabolism impairment occurs at the cellular level due to damage to cell structures (e.g. mitochondria) or impaired transport across the cell membrane; or at the extra-cellular level due to defective transport mechanisms associated with obstruction (e.g. atherosclerosis, stroke), diffusion, and circulation through the body (e.g. cardio-vascular and pulmonary disease). Impaired metabolism leads to insufficient availability of energy to cells, and fosters increased oxidative stress, cellular senescence, apoptosis and decreased neurogenesis (Gandhi and Abramov, 2012).

3.1.4. Down-regulation of the formation of new cells and tissue repair

Neurogenesis refers to the formation of new neurons. It has only been demonstrated in the hippocampus and the sub-ventricular zone in human adults and contributes to healthy memory function (Farzanehfar, 2016). Neurogenesis is very sensitive to environmental factors and is depressed in the context of oxidative stress, inflammation, and other environmental stressors as well as in several chronic conditions such as depression, diabetes, and cardiovascular disease.

3.2. Ageing & neurodegeneration

hallmarks of early damage are already observable in children or young adults. Oxidative stress and inflammation, signs of cellular and DNA damage have been seen in children (Buxton et al., 2011; Reinehr and Roth, 2018; Tran et al., 2012). Higher levels of plasma amyloid- β 42 (the main protein in Alzheimer's disease plaques) have been detected in children with obesity, and consequent intracellular accumulation in the basal forebrain has been found to be already widespread in young to middle-adulthood (Baker-Nigh et al., 2015). Brain shrinkage becomes detectable from around 25 years onwards (Fotenos et al., 2005; Luders et al., 2015). By age 40, the hippocampus of generally healthy individuals has lost approximately 2%, and this increases to about 8% by age 60, and 20 % by age 80 (Fraser et al., 2015). While the hippocampus is one of the structures most affected in typical ageing, total brain volume shrinks at about half these rates, indicating that no brain region is completely spared by these processes.

to neurodegeneration, producing cumulative damage across the life-

span starting in childhood. At a macroscopic level, their effects only become easily detectable later in life, but at a microscopic level, the

3.3. Ageing & cognitive decline

Ageing processes lead to important and progressive impairment of thinking abilities. Decline in cognition is subtle, but there is substantial evidence that most mental functions decrease almost linearly from about 20–40 years of age (depending on the cognitive domain and the population studied) and into old age in the normal population (Salthouse, 2009), with acceleration in those affected by dementia or other neurocognitive disorders. Significant differences in brain and cognitive ageing are observed between individuals, and accumulating evidence indicates that this is attributable to life choices and environmental variables (Gow et al., 2012; Kramer et al., 2004). It is, therefore, critical to understand how modifiable factors influence ageing trajectories.

4. BDNF and the ageing brain

BDNF is involved in a wide variety of processes throughout the body, including energy homeostasis, appetite and weight regulation (Yeo and Heisler, 2012), and sleep (Schmitt et al., 2016). Importantly, BDNF is a neurotrophin. Although vital for physiological neuronal formation and function, imbalances in BDNF production, uptake, and clearance are notable in disorders such as epilepsy, anxiety, depression and schizophrenia (Binder et al., 2001; Brunoni et al., 2008; Palomino et al., 2006). In this section, we will briefly review the pathways through which BDNF likely impacts the brain, both structurally and functionally.

4.1. BDNF and ageing mechanisms

BDNF mechanistically related to all four of the major aspects of biological brain ageing. There is animal evidence that BDNF is protective against cellular and DNA damage by down-regulating oxidative stress (Hachem et al., 2015; Hacioglu et al., 2016; Jiang et al., 2015), having anti-inflammatory properties (Han et al., 2019; Jin et al., 2019; Xu et al., 2017), and preserving telomere length (Vasconcelos-Moreno et al., 2017). Evidence relating BDNF to accumulation of waste products is limited, with some suggestion that its neuroproliferative effects may serve to increase the accumulation of abnormal cellular protein isoforms (prions) in specific animal models (Nordström et al., 2005). BDNF is implicated in healthy glucose metabolism in the brain (Nakagawa et al., 2002), and as the following sections outline, is heavily implicated in cellular formation and tissue repair.

4.2. Neurogenesis

All the mechanisms reviewed above impact cerebral health and lead

BDNF modulates neurogenesis in adult humans, specifically in the

hippocampal dentate gyrus (Brown et al., 2003). Transgenic mice without the BDNF TrkB receptors in neural progenitor cells showed impaired neurogenesis (Liu and Nusslock, 2018). Direct infusion of BDNF into adult rat hippocampi over two weeks substantially increased the number of granule cells (over twice more cells relative to controls) (Scharfman et al., 2005). In vitro studies on cerebellar granule neurons demonstrate increased cell survival in the presence of BDNF, in the order of 40 % more surviving cells than controls (Koshimizu et al., 2009). Similar results are seen when BDNF is infused during in vitro cultivation of adult human stem cells (Yu et al., 2014).

4.3. Neuronal morphology

BDNF promotes both axonal and dendritic growth, essentially speeding up neuronal maturation (Gonçalves et al., 2016). Adult transgenic mice with the BDNF receptor TrkB deleted have shorter, less branched, and overall less complex neurons formed during adulthood in the dentate gyrus of the hippocampus than their wild type counterparts (Bergami et al., 2008). Conversely, adult mice with BDNF over-expression induced by retroviral injection at birth have longer dendrites (on average 42 % longer) and more dendritic branching (33 % more branches) compared with sedentary wild type controls (Wang et al., 2015). Addition of BDNF in solution of adult rat dentate gyrus neurons produced a dose-dependent increase in axonal branching in just eight days, with a 36 % increase when 10 ng/ml BDNF was infused, and a 48 % increase when 100 ng/ml BDNF was infused (Patel and McNamara, 1995).

4.4. Synaptic plasticity and function

BDNF modulates synaptic plasticity, the capacity for strengthening and weakening of neural connections over time, which underlies cognitive processes such as memory formation and recall (Zenke et al., 2015). In vitro, the introduction of 50 ng/ml of BDNF to rat hippocampal neurons doubles their firing rate within just three minutes (Levine et al., 1995). This is likely due to postsynaptic action, as in vitro introduction of BDNF is associated with increased glutamate release (Jovanovic et al., 2000). Removal of BDNF or inhibition of its TrkB receptor downregulates the postsynaptic dispersion of GABA (a neuroplasticity inhibitor) and downregulates multiple synaptogenic pathways (CREB, synapsin I and N-methyl-Daspartate (NMDA) receptors (Brady et al., 2018; Vaynman et al., 2004; Yoshii and Constantine-Paton, 2007)).

4.5. Brain volume

Together, the neuroproliferative, morphological, and synaptogenic action of BDNF within the hippocampus results in detectable positive associations between serum BDNF and volume in animal and human brains (Lee et al., 2002; Voss, Vivar, et al., 2013). Val66Met is a genetic substitution in the gene for BDNF, which occurs in approximately a quarter of Caucasians (Voss, Vivar, et al., 2013). The size of the effect of Val66Met on the brain varies widely in the literature, likely due to underpowered individual studies (Molendijk, Haffmans, et al., 2012a,b), though large meta analysis indicate carriers have a trend of lower hippocampal volume than non-carriers, experience significantly less hippocampal activation during cognitive tasks, and perform significantly worse on declarative memory tasks (Kambeitz et al., 2012). Older human Met carriers have approximately 11 % lower hippocampal volume than non-carriers (Bueller et al., 2006), with animal evidence suggesting this is likely due to impaired survival of new neurons in the dentate gyrus, rather than impaired neurogenesis (Bath et al., 2012).

4.6. Cognition

There is growing evidence that some aspects of cognition are reliant

on the magnitude of neurogenesis and neuroprotection linked to BDNF. Greater cell proliferation and survival in the dorsal ganglion has been associated with non-impaired cognitive performance in rats (Drapeau et al., 2003). Conversely, animals with inhibited neurogenesis following irradiation to the hippocampus show spatial learning deficits and longterm memory loss (Raber et al., 2004; Snyder et al., 2005). In humans, a methionine rather than valine-specifying allele at amino acid 66 of the BDNF gene, the Val66Met genotype, is associated with cognitive deficits, namely in attention and working memory performance (Erickson et al., 2013). One study noted up to a 50 % reduction in participants' with the Val66Met polymorphism performance on a skilled task involving several aspects of cognition, such as memory and attention (Sanchez et al., 2011). This section highlights that understanding the factors which underly BDNF expression is key to the development of interventions intended to promote healthy brain ageing across the lifespan.

5. BDNF and physical activity

Physical activity has been associated with increased circulating levels of BDNF. In particular, systematic reviews (Huang et al., 2014; Knaepen et al., 2010) and meta-analyses (Dinoff et al., 2017; Szuhany et al., 2015) have concluded that an acute bout of physical activity transiently increases peripheral BDNF. Similarly, there is consistent evidence showing chronic interventions involving physical activity can improve cognitive function (Colcombe and Kramer, 2003; Erickson et al., 2019; Northey et al., 2018). These improvements are likely to be mediated by repeated, exercise-induced transient increases in circulating BDNF.

Currently, a major hurdle to optimising the BDNF response to acute physical activity is our lack of understanding of their dose-response relationship. Based on current evidence, strength training appears to be mostly ineffective (Huang et al., 2014; Knaepen et al., 2010), whereas aerobic training has been shown to successfully elevate circulating BDNF (Cassilhas et al., 2012). The magnitude of the effect may be intensity- (Huang et al., 2014) and duration- dependent (Dinoff et al., 2017). Furthermore, chronic physical activity was found to increase the BDNF response to an acute bout of physical activity (Szuhany et al., 2015). In recent meta-regression analyses including 55 studies, Dinoff et al. (2017) found no difference between aerobic and resistance training, but did observe an effect of duration, with physical activity lasting longer than 30 minutes leading to higher BDNF levels. Only a trend was observed between higher intensity and increase in circulating BDNF. However, meta-analyses are constrained in their capacity to answer specific dosage questions, particularly where the relationship may not be linear, and often do not include the interaction between variables. In order to address these limitations, it is vital to ensure empirical evidence around physical activity dose and BDNF is supported by underlying mechanisms.

Different types of movement place different homeostatic stresses on the body, leading to different acute responses, and subsequent adaptation. As highlighted by Walsh and Tschakovsky (2018) the major pathways through which physical activity is implicated in BDNF release are increases in both cerebral (Monnier et al., 2017) and peripheral (Prigent-Tessier et al., 2013) blood flow, splenic platelet release (Brunelli et al., 2012), hypoxia (Helan et al., 2014) and perhaps increased body temperature (Goekint et al., 2011; Kojima et al., 2018). In addition, physical activity dose will differentially influence these mechanisms.

While the literature debates the relative contribution of central and peripheral sources of circulating BDNF levels (Walsh and Tschakovsky, 2018), depending on the source, there may be differences in the optimal dose for physical activity dependent BDNF responses. For example, in the periphery, blood flow peaks at high intensity (Jones et al., 2012), whereas in the brain blood flow is higher at moderate intensity (Ogoh and Ainslie, 2009). In addition, circulating BDNF is mostly bound to

platelets (99 %) which are stored in the spleen for later release. Platelet bound BDNF represents a stored form, not necessarily cellular sources of de novo BDNF, which is unable to bind with its neural receptors until it is released into plasma where it exists in a bioactive form. Whilst platelet related increases in BDNF may not represent an overall increase in the total BDNF pool, exercise-induced increases of this pool may offer strategic benefits. For instance, a physical activity bout or activity to increase the splenic release of platelets prior to a memory dependent task that requires BDNF mediated long-term potentiation may be advantageous, though the temporal relationship between these activities is not clear.

5.1. Physical activity related BDNF link to neurocognition

5.1.1. Chronic effects

Exercise-training interventions increase basal BDNF (Dinoff et al., 2017) and BDNF has been long-implicated in both cognition (Leckie et al., 2014) and structural benefits (Erickson et al., 2011). Training-induced changes in BDNF have also been found to mediate improvements in cognitive performance in both animal (Vaynman et al., 2004) and human models (Leckie et al., 2014) via both hippocampal and peripheral levels.

However, the relationship between BDNF and chronic exercise interventions is complicated. Two meta-analytical studies to date have found small effects of exercise training on resting BDNF levels (Szuhany et al., 2015: Hedge's g = 0.27; and Dinoff et al., 2017: SMD = 0.39). Although Dinoff et al. (2017) found an overall effect of training, only nine of the twenty-nine studies that met the inclusion criteria reported a significant increase in resting peripheral BDNF. Whilst differences in dose parameters may account for this variability (e.g., aerobic, but not resistance exercise was implicated in higher resting BDNF levels in the Dinoff paper), the interaction between these dose parameters and the participant characteristics could also contribute.

Studies investigating exercise interventions and BDNF tend to include more sedentary populations in which there is a higher likelihood that overall health outcomes would improve and thus elevate BDNF levels. Exercise training is associated with improvements in endothelial function, insulin resistance, metabolic function, and cerebral blood flow. Endothelial function is related to cardiovascular risk factors and peripheral vascular reactivity both of which are associated with exercise-induced increases in basal BDNF (Lemos et al., 2015; Zembron-Lacny et al., 2016). Although the link between higher cerebral blood flow and elevations in circulating BDNF is not conclusive, it may offer a further mechanism linking physical activity and BDNF. Cerebral blood flow decreases with age and sedentary behaviours, a process that can be reversed with exercise training (Witte et al., 2019).

Another important counfounding factor in assessing BDNF responses and action relates to cellular signalling. Cellular signalling may also cloud the interpretation of BDNF responses and action. Chronic exercise training (see Fahimi et al., 2017; Kim et al., 2015) or overexpression of BDNF (LeMaster et al., 1999) in animal models results in upregulation of the TrkB receptor. This receptor upregulation is known to improve the sensitivity of BDNF function in the brain and may lead to lower basal BDNF levels. Indeed it was recently reported that in both middle-aged males (54 \pm 7 years) with 35 \pm 15 years training (5 \pm 3 hours per week), and in younger trained males (20 ± 2 years; 9 ± 4 hours per week) basal serum levels are lower than their sedentary counterparts with a negative correlation observed between these BDNF levels and weekly hours of exercise training (r = -0.32 and r = -0.70 for)the middle-aged and younger males respectively) (De la Rosa et al., 2019). In response to BDNF-TrkB signalling, downstream effects are also influenced by the nature of the BDNF signal, with acute or gradual increases eliciting transient or sustained activation of the receptor respectively (Guo et al., 2018).

5.1.2. Acute effects

In contrast to chonic effects the relationship between the acute BDNF response to physical activity and cognitive function is much more tenuous. Some have argued that the acute positive association between physical activity and cognition (see Piepmeier and Etnier, 2015), and the longer-term link between BDNF and cognition/brain structure are consistent with acute changes in BDNF playing a role in cognition. However, there is no known mechanistic link for this to occur outside those related to memory function. Physical activity produces a number of biological effects independent of the BDNF response that could account for acute cognitive improvements, from increases in blood flow (Ogoh and Ainslie, 2009), to a flood of neurotransmitters (Meeusen and De Meirleir, 1995) or greater connectivity of attentional networks (Chang et al., 2017) and more. More generally it is important to note that in a recent review of seven studies published at that point, only three supported a link between acute physical activity-induced increases in peripheral BDNF and cognitive performance (Piepmeier and Etnier, 2015). All three of these related to learning, whereas no association was observed with any other cognitive activity. Since this review, there have been at least another five studies investigating the acute physical activity-BDNF-cognition relationship, with no relationship observed (Chang et al., 2017; Etnier et al., 2016; Hötting et al., 2016; Slusher et al., 2018; Tsai et al., 2016).

A potential mechanistic underpinning does exist between physical activity-related BDNF and acute memory-related performance since BDNF is known to facilitate long-term potentiation in neurons (Lu et al., 2008). The timing between physical activity and memory may influence this effect given physical activity four hours after encoding images has been shown to lead to superior recall compared to physical activity performed immediately post-encoding (van Dongen et al., 2016). Outside these memory-related tasks there is little support for acute variation in BDNF and enhanced cognition. Nevertheless, the acute BDNF response is important as it appears that the regular transient increases in BDNF serve to nourish the brain in a way that provides capacity for a healthy adaptive brain into the future (e.g. Walsh and Tschakovsky, 2018). In part, this may be due to the effect of other exercise-mediated peripheral factors, such as the muscle secretory factor Cathepsin B, which has been found to potentiate BDNF release following exercise, and consequently measurably enhance cognitive function in mice, Rhesus monkeys and humans (Moon et al., 2016).

5.2. Mode of activity

Although physical activity spans a a broad modality spectrum, BDNF research typically dichotomises activities as being either aerobic or resistance based. The majority of the available research has focussed on aerobic activity (Dinoff et al., 2017), possibly due to the historical focus on this modality in relation to neurocognition (Northey et al., 2018) and early investigations, particularly in animal models, suggesting resistance training was not associated with increases in BDNF (see for example Cassilhas et al., 2012). Acutely, aerobic physical activity increases tissue metabolism, which results in physiological changes including increased cardiac output, vascular shear stresses, and energetic requirements as well as as triggering biological responses to hypoxia. These physiological responses, most notably hypoxia (Helan et al., 2014), and increases in cerebral (Monnier et al., 2017) and peripheral (Prigent-Tessier et al., 2013) blood flow are closely associated with and mechanistically explain the transient increases in BDNF (Dinoff et al., 2017). However, there is substantial variability in the magnitude of the acute BDNF response to aerobic physical activity. This may be due to individual differences and/or to the interaction with dose parameters (Walsh and Tschakovsky, 2018).

Anaerobic physical activity is characterised by short periods of high exertion. Anaerobic physical activity increases lactate formation in muscles, although this increase only becomes detectable in the blood compartment after longer bouts of intense physical activity (Schiffer et al., 2011). The research on resistance training and BDNF suggests physical activity dose and the way in which training is prescribed is particularly important. Resistance training can be undertaken in a variety of ways, but typically uses an external resistance or body weight in order to increase muscular strength, power and endurance through adaptations to the neuromuscular system and muscle properties. Its impact on the body can vary according to the muscle action and type of resistance used, the structure and exercises included in a workout, and the sequence in which those exercises are performed (Paoli, 2012). The acute responses to resistance training that may be relevant to BDNF release likely include stimulation of BDNF release in response to elevated lactate (Schiffer et al., 2011), an increased cardiovascular response, and if the activity is sufficiently intense, elevated sympathetic activity to the point where platelets are released and contribute to the circulating BDNF pool (e.g., Fujimura et al., 2002; Walsh et al., 2017). The literature linking resistance exercise and BDNF is mixed: some studies have found no effect (e.g. Goekint et al., 2010), while others have reported increases (e.g. Yarrow et al., 2010). It would appear that subtle differences in the prescription of resistance training may be an important factor in explaining some of this variation. For example, Marston et al. (2017) compared a "strength" protocol (5 \times 5 repetitions at 5RM (maximal) with 3 min recovery between sets) with a "hypertrophy" protocol (3 \times 10 repetitions at 10RM (maximal) with 1 min recovery between sets). Although both protocols are considered resistance training and were matched for work and volume, serum BDNF increased (13 %) immediately post-activity in the hypertrophy condition only. The hypertrophy protocol also resulted in higher blood lactate levels than the strength protocol, suggesting that metabolically, the hypertrophy protocol was much more demanding and, perhaps, had a greater cardiovascular and sympathetic nervous system response. Although the exact source of BDNF and mechanism of release is unclear, this study highlights the problematic nature of simply dichotomising physical activity into aerobic or resistance-based, and the importance of carefully considering the physiological response to physical activity in research design. What is clear that BDNF can be elevated through multiple mechanisms (cardiovascular changes and lactate release), so possibly a combination of aerobic and anaerobic activity may produce the greatest elevation of BDNF.

5.3. Intensity

The literature commonly claims that physical activity intensity is positively associated with increased circulating levels of BDNF. The majority of this evidence is sourced from aerobic types of physical activity and, mechanistically this linear relationship has a strong basis. Higher physical activity intensities are associated with increasing heat load, hyperthermic and splenic responses (Brunelli et al., 2012; Flamm et al., 1990; Laub et al., 1993; Stewart et al., 2003), along with rising cardiac output (Flamm et al., 1990), increased blood-brain barrier permeability (Roh et al., 2017), and increased hypoxia (e.g., Frances et al., 2008). These responses are, in turn, commonly implicated in BDNF release (e.g., Fujimura et al., 2002; Helan et al., 2014). Although existing meta-analyses have investigated linear relationships between intensity and BDNF release (Dinoff et al., 2017; Szuhany et al., 2015), the original research which predominantly utilised incremental tests to maximal exertion may be contaminated by the preceding submaximal stages. For instance, whilst the hypoxic and peripheral cardiovascular responses can be considered to have a linear relationship with physical activity intensity, other factors may not. Sympathetic nervous system activity tends to show an exponential increase as intensity reaches closer to maximal aerobic capacity, whereas cerebral blood flow tends to show an inverted-U response (Ogoh and Ainslie, 2009). Cerebral blood flow tends to peak at an activity intensity corresponding to ~ 60 % of maximal aerobic capacity before declining towards resting values due to lower P_aCO₂ as exercise intensity exceeds the ventillatory threshold, which is commonly used as a marker to divide moderate from vigorous intensity.

Direct comparisons of intensity in humans are not readily available. However, close examination of the available studies suggests a threshold or non-linear relationship may be present. Aerobic physical activity at an intensity equivalent to ~31 %– 33 % of VO_{2max} uptake does not appear to increase serum BDNF, whereas an intensity of ~ 56 %-67 % does (an increase ~16 % (Nofuji et al., 2012), or ~14 % (Hötting et al., 2016). Schmolesky et al. (2013) showed aerobic physical activity at intensities equivalent to ~64 % and 82 % of VO_{2max} had similar transient increases in serum BDNF (mean ~ 32 % increase from rest, or 45 % higher than controls). When Gilder et al. (2014) exercised individuals at ~78 % of VO_{2max} , they also observed an increase of ~ 48 % in serum BDNF, but these levels decreased when measured immediately after a subsequent maximal exertion trial, although they remained \sim 33 % above baseline. These studies suggest a non-linear relationship between aerobic physical activity intensity and circulating BDNF. Animal research offers further support for this theory. In Wistar rats, acute treadmill running at 15 (m/minute) (Soya et al., 2007) increases hippocampal BDNF but not 20 m/min (Goekint et al., 2010) or 25 m/minute (Szuhany et al., 2015). Normative data for Wistar rats indicates the lactate threshold corresponds to a running speed of 20 m/minute, suggesting that sub-threshold running is preferentially associated with acute increases in BDNF. This finding may be limited by the fact that lactate is one of several meaningful factors in such exercise (e.g. the type and intensity of contraction of motor units is also meaningful), but if taken at face value, the possibility of an inverted-U relationship may also explain why Dinoff et al. (2017) only observed a trend between intensity and BDNF. It also highlights the limitations of using meta-regression models which which typically only test linear relationships. From a mechanistic perspective, physical activity intensity of 56-82 %, as highlighted above, would correspond to the point at which cerebral blood flow peaks in exercising humans and therefore the point at which shear-stress induced BDNF release from the cerebral endothelium may be greatest. Consistent with this, in an animal intervention model, a week of daily 30 min running at 18 m/min was associated with higher cerebral BDNF and greater cerebral pe-NOS^{ser1177}, a marker of blood flow and shear stress, compared to a group which ran at 12 m/min (Pedard et al., 2019). These factors clearly require more investigation and while the idea that higher intensities are associated with greater BDNF release stands, this relationship may not be as simple as is often presented in the literature.

While insufficient data is available to provide exact recommendations on optimal PA intensity, based on the available evidence it would seem that aiming for VO_{2max} around 60 % is most likely to lead to higher BDNF levels. The current inability to clearly define the optimal intensity of physical activity to stimulate transient increases in BDNF is likely due to a tendency for experiments to prioritise physical activity dose parameters over mechanistic explanations. We argue that a more systematic approach whereby research design seeks to understand the optimal physiological response to stimulate particular mechanisms of BDNF release may be the most efficient path forward. This should not be construed as a recommendation to avoid research on physical activity dose, indeed to the contrary, physical activity dose is a means to manipulate and understand mechanistic pathways.

5.4. Duration

In a meta-analysis on optimal physical activity dose, Dinoff et al. (2017) interpreted their analysis as suggesting that a threshold of 30 minutes was necessary to optimise the BDNF response. However, direct comparisons of physical activity duration on BDNF release are rare. Studies spanning Dinoff's duration threshold find no difference comparing exercise of 20 or 40 minutes duration, regardless of whether the activity was at a moderate or high intensity (~64 % and 82 % of VO_{2max} respectively) (Schmolesky et al., 2013), and similarly those comparing shorter durations also find no difference (e.g. ~10 vs 21

minutes in (Cabral-Santos et al., 2016).

Continuous measurement of BDNF throughout a physical activity bout is more informative. Saucedo-Marquez et al. (2015) assessed serum BDNF continuously during a 20 min bout of continuous physical activity which would appear to approximate 70 % of VO2max (Saucedo-Marquez et al., 2015). Although serum BDNF did not significantly increase over time, it appeared to rise early (~six minutes) in the bout and plateau until physical activity ended. An extreme example of this type of research, which is commonly cited in the literature, is from Rasmussen and colleagues (Rasmussen et al., 2009). They evaluated circulating BDNF over four-hours of continuous physical activity. No change in plasma BDNF was observed after two hours of rowing, at a low-moderate intensity, however a two- to three-fold increase was observed after four hours. Whilst the authors concluded that 70-80 % of circulating BDNF originated from cerebral sources, the prolonged length of this intervention may mean that mechanistic sources of the BDNF response are different from more common shorter physical activity interventions, particularly given the likely energy deficit created in this scenario.

It would appear that when intensity is held constant, and a steadystate is achieved, a relatively short period (perhaps as little as six minutes) is required to achieve representative BDNF levels. BDNF action may benefit from increased exposure time, such as longer physaboutical activity duration, but this would require greater structural or functional insight from well-controlled longitudinal studies.

5.5. Work and rest

The ratio of work-to-rest periods within a single session of physical activity impacts BDNF levels in both aerobic and resistance paradigms. This principle of manipulating the periods of work and rest (complete rest or low-intensity physical activity) forms the basis of many training methods, including the popular high-intensity interval training (HIIT) paradigm, where exercise is carried out in short bouts at high intensity (e.g. over 80 % of maximal heart rate (Jiménez-Maldonado et al., 2018)), interspersed with rest periods of lower intensity activity. The principle allows for greater volumes of higher intensity work to be completed, which is thought to provide the stimulus for superior cardiovascular adaptations commonly observed with such training in part due to the activation of other metabolic pathways (e.g. PGC1 alpha).

From a BDNF perspective, this manipulation may also afford greater changes in blood flow, hypoxia and thermal load to evoke larger BDNF responses than continuous efforts. Given the increased ability for very high-intensities of physical activities with intermittent training, the potential for large splenic responses may also be magnified. In an early example of research into intermittent physical activity, Saucedo-Marquez et al. (2015) compared two 20 minute bouts of either continuous activity at 70 % or ten 1 min efforts at 90 %, interspersed with 1 minute rest periods (Saucedo-Marquez et al., 2015). In this comparison, the intermittent protocol resulted in a significant 38 % increase in serum BDNF from baseline, whereas the continuous protocol had a non-significant 24 % increase.

It is unclear if the different BDNF response is related to the intermittent nature of the protocol or differences in the activity intensity. Understanding how the intermittent nature of the physical activity impacts BDNF levels, outside the increased capacity for higher intensity, is complicated by the lack of research into the physiological responses to this type of physical activity. For example, high-intensity intermittent activity may decrease cerebral blood flow, at least after the initial few work periods due to the hypercapnic response (e.g. Simair (2017)), and increased fat oxidation in skeletal muscle (Jiménez-Maldonado et al., 2018). Together, these studies are consistent with a general principle of higher intensities equating to higher BDNF, but it remains unclear how the intermittent nature might influence other mechanistic contributors such as heat load, shear stresses, or even platelet release.

5.6. Prior training and acute response

Prior training is likely to have implications for BDNF response to an acute physical activity bout, though direct evidence is sparse. The animal literature suggests that a decreased noradrenergic response to the acute exercise, following chronic training, may attenuate the acute BDNF response (Venezia et al., 2017). Conversely, in humans, metaanalytical evidence suggests that regular exercise training intensifies the BDNF response to an acute bout of physical activity (Hedge's g =0.58; p = 0.02) (Szuhany et al., 2015). It may take some time for adaptations to facilitate these higher levels as five, but not three weeks of aerobic training augmented the serum BDNF response to an acute bout of maximal exercise (Griffin et al., 2011). It may be that this training benefit extends across exercise modes, but in terms of resistance training, there is evidence both for (Yarrow et al., 2010) and against cross-mode benefit (Goekint et al., 2010). In older adults (mean 66 years), it has also been claimed that this attenuation of the acute BNDF response exists within resistance training (Walsh, Scribbans, et al., 2015a,b) although the effects on serum BDNF appear quite modest (9% increase post-exercise pre-training compared to an 11 % increase post-training). As shown in a meta-analysis (Szuhany et al., 2015), the majority of studies contributing to this literature include aerobic exercise interventions. Given that aerobic interventions typically improve endothelial function, there is a logical mechanism through which aerobic training can facilitate this augmentation of BDNF response to acute exercise.

Rather than record actual training regimens, cross-sectional studies often utilise an individual's VO_{2max} as a surrogate of training to compare training status for the BDNF response. For example, in those with lower fitness levels as defined by VO_{2max}, higher serum BDNF responses are observed in those with lower fitness (Antunes et al., 2019). On the other hand, Tsai et al. (2016) found individuals with higher VO_{2max} had higher BDNF levels following 30 min of moderate-intensity exercise, calibrated to fitness level (~62 % increase versus ~42 %) although this was not significant, and may have been due to the higher absolute intensity in the fitter participants (Tsai et al., 2016). Interpretation and synthesis of these findings can be problematic because fitness alters the absolute intensities, and physiological responses at which the BDNF response is compared. It may be that the cerebral blood flow is lower, and splenic response higher in lesser trained individuals

5.7. Exercise context

As in animal studies, impoverished or enriched environments are implicated in human BDNF response to exercise. In the context of acute exercise, a warm environment can further increase the serum (Goekint et al., 2011), and plasma (see Collins et al., 2017) BDNF levels, possibly via thermoregulatory mechanisms including blood flow changes or plasma shifts. Exposure to novel, socially and cognitively engaging circumstances are associated with preserved cognitive function in late life (Kelly et al., 2017; Park et al., 2014; Staff et al., 2018), and combining cognitive and physical interventions may have added benefits for cognitive functions in older adults (Law et al., 2014; Zhu et al., 2016). It has been established in animal models that combining physical and cognitive loads may be optimal for brain mass (Curlik and Shors, 2013), possibly through the neuroprotective and potentiating effects of BDNF. In humans, acutely higher serum BDNF levels have been reported after a high-cognitive engagement physical training session compared to a low-cognitive engagement physical training session in a military sample (post levels ~30 % higher in high versus low-cognitive engagement condition, 18-40-year-olds, mean age 29 and n = 43: (Hawkes et al., 2017)). This extends to benefits of participation in cognitively and socially enriched forms of physical activity, such as dance, which have the additional benefit of including a variety of different forms of movement. For example, basal plasma BDNF increased almost two-fold on average after a 6-month dancing program compared



Fig. 2. Overview of recomendations for future research.

to an intensity matched conventional fitness training program (combining aerobic, resistance and flexibility training) in older adults (63–80 years) (Rehfeld et al., 2018).

6. The context of ageing for BDNF, physical activity and brain volumes

Recent meta-analyses (Dinoff et al., 2017; Szuhany et al., 2015) have found no effect of age on the acute BDNF response to a bout of exercise. However, there are very few studies that have utilised cohorts above 45 years of age. For example, Dinoff's analysis included 59 studies investigating the acute exercise-induced BDNF response, with only 5 of those studies having a participant group with an average age over 45 years. Similarly, to date, there are no large-scale studies that explore the dynamics of BDNF response to the same (or even comparable) mode, intensity, duration, and regimen of physical activity, and the consequent impact on the brain and cognition, across different age groups. The same types of association found between higher physical activity leading and elevated BDNF, which is in turn is associated with better brain health and cognition have been demonstrated in young adulthood (eg. samples aged 18-30 Chang et al., 2017; Ferris et al., 2007; Winter et al., 2007), the less-studied midlife (e.g. samples aged 30-59 De la Rosa et al., 2019; Kimhy et al., 2015), and the heavily studied in late life (e.g. samples aged 60 and beyond de Melo Coelho et al., 2013; Leckie et al., 2014; Ruscheweyh et al., 2011; Voss, Erickson, et al., 2013a,b). Yet there are important factors that have implications for the development of evidence-based physical activity guidelines.

Younger individuals are physically stronger, so can withstand more vigorous and demanding physical activity regimens (e.g. Muehlbauer et al., 2015). Brain maturation is mostly complete and central BDNF levels are at their peak in the early 20s (Gur, 2005; Webster et al., 2006), so there is comparatively greater scope for detecting large fluctuations in BDNF in younger samples. Conversely, older individuals have had a lifetime accumulation of risk, resulting in greater scope for remediation and improvement of cognitive difficulties and physical brain health. This can be exemplified in the comparison of two studies with aerobic exercise interventions: in a sample with a median age of 22 (previously sedentary) individuals experienced an average elevation of 319.3 pg/ml (75 % of baseline average 974.7 pg/ml) serum BDNF following a single bout of exercise, and after 5 weeks of training experienced moderate improvement in one of several cognitive tasks

(Griffin et al., 2011). In Erickson et al. (2011), a sample with a mean age of 67 experienced an elevation of just 2.5 pg/ml (90 % of baseline average 21.3 ng/ml) serum BDNF. The older participants had lower BDNF levels overall, but exhibited a more marked response and experienced substantially increased spatial memory performance, and 2% hippocampal volume increase, after 7 weeks of training. This is not a clean comparison: samples differed in sampling, physical activity protocol, and measures – but these differences illustrate the need to explore the physical activity-BDNF-cognition triumvirate with a more explicit focus on participant age.

7. Conclusion: implications for exercise interventions to promote healthy cognitive ageing

This review has highlighted the complexity, richness and limitations of knowledge needed to design exercise interventions intended to promote healthy cognitive ageing. While physical activity is clearly implicated in acute BDNF response and consequent positive impacts on cognition and function, the specifics of mode, intensity, duration, work and rest, prior exercise, and context remain mechanistically unclear. To date, this story can only be mapped out through combinations of research spanning animal, human, central and peripheral pools of BDNF: in humans, the normative adult resting peripheral BDNF levels sit around $\sim 20-30$ ng/ml (Shimada et al., 2014), in rats 10 ng/ml infusion of BDNF to dentate gyrus has detectable neuroproliferative benefits (Patel and McNamara, 1995)), in both animals and humans acute bouts of physical activity have been regularly found to elevate BDNF far beyond 10 ng/ml, at least peripherally (Dinoff et al., 2017; Szuhany et al., 2015). Differences in the organism, physical activity paradigm, and measures of both BDNF and brain outcomes in this example and the literature as a whole make it difficult to provide specific guidelines for physical activity intended to promote healthy cognitive ageing

From a practical perspective, high-intensity short-duration activity is likely to be effective in promoting BDNF response and by extension brain health. High-intensity work is typically of short duration, and due to warm-up effects, cerebral blood flow may not be the same throughout the exercise bout leaving uncertainty as to which element (or elements) are the most beneficial. Taken together, the literature reviewed indicates that a > 60 % VO_{2max} combination of aerobic and anaerobic exercise undertaken for 20 minutes or more may be recommended. Yet, this may not be optimal, and in many forms may be impractical to attempt for older adults, who will likely experience the most marked neuroprotective benefits, and are likely to benefit through addressing common age-related diseases (e.g., diabetes, cardiovascular disease) that likely inhibit BDNF release. A particularly interesting but underexamined line of further research is how multicomponent bouts of exercise may influence the BDNF response, and the possible opportunities such an approach might provide for a regimen that evolves as an individual ages. Understanding how the physiological response to exercise is related to the mechanism of release is important, and may yet help distil an optimal and practical physical activity regimen. Accordingly, we call for a substantially more systematic approach to investigating these mechanisms across the human lifespan, to allow a more coherent synthesis of results. In the meantime, we highlight key considerations for future research in Fig. 2, and propose that physical activity be viewed more in the context of its physiological response rather than broad categorisation, and emphasise the clear benefit that repeated physical activity and consequent BDNF release has for the ageing brain.

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