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DOI:
10.1113/JP275021

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On behalf of 'MEND', an international consortium focused on '**M**echanisms of **E**xercise **N**europrotection against **D**isease'.

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Running title: Exercise-induced neuroprotection

Keywords: Cognition; dementia; cerebrovascular function; high-intensity interval training; neuroprotection

This is an Accepted Article that has been peer-reviewed and approved for publication in the The Journal of Physiology, but has yet to undergo copy-editing and proof correction. Please cite this article as an 'Accepted Article'; doi: 10.1113/JP275021.

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Abstract

The increasing number of older adults has seen a corresponding growth in those affected by neurovascular diseases, including stroke and dementia. Since cures are currently unavailable, major efforts in improving brain health need to focus on prevention, with emphasis on modifiable risk factors such as promoting physical activity. Moderate-intensity continuous training (MICT) paradigms have been shown to confer vascular benefits translating into improved musculoskeletal, cardiopulmonary and cerebrovascular function. However, the time-commitment associated with MICT is a potential barrier to participation, and high-intensity interval training (HIIT) has since emerged as a more time-efficient mode of exercise that can promote similar if not indeed superior improvements in cardiorespiratory fitness for a given training volume and further promote vascular adaptation. However, randomised control trials (RCTs) investigating the impact of HIIT on the brain are surprisingly limited. The present review outlines how the HIIT paradigm has evolved from a historical perspective and describes the established physiological changes including its mechanistic bases. Given the dearth of RCTs, the vascular benefits of MICT are discussed with a focus on the translational neuroprotective benefits including their mechanistic bases that could be further potentiated through HIIT. Safety implications are highlighted and components of an optimal HIIT intervention are discussed including practical recommendations. Finally, statistical effect sizes have been calculated to allow prospective research to be appropriately powered and optimise the potential for detecting treatment effects. Future RCTs that focus on the potential clinical benefits of HIIT are encouraged given the prevalence of cognitive decline in an ever-ageing population.

Context

Cognitive decline and dementia have emerged as one of the greatest health threats of the 21st century affecting the way an older adult thinks, make decisions, uses language, learns and remembers information (Bishop *et al.*, 2010). The most recent estimates indicate that ~47 million people were living with dementia in 2015 at an annual cost of US$ 818 billion (~£ 623 billion). Incidence is set to almost treble by 2050 (Prince *et al.*, 2015) in tandem with the rising number of older adults and healthcare expenditures are projected to surpass those for all other health conditions by as early as 2060 (Wimo *et al.*, 2013). Since no curative treatments are available, major efforts need to focus on prevention with emphasis directed towards modifiable risk factors that include the promotion of physical activity. Indeed, physical inactivity was shown to contribute to 13% of all diagnoses of Alzheimer's Disease (AD) worldwide (accounting for ~4.3 million cases) and reducing inactivity by as little as 10-25% could potentially translate into a staggering 380,000-1,000,000 fewer cases of AD globally (Barnes & Yaffe, 2011).

Unfortunately, dementia is not the only brain disease causing significant strain on society today, stroke also carries a burden. Broadly defined as a focal neurological deficit caused by an infarction or haemorrhage that can lead to disability or death, there are over 80 million individuals globally who have survived a stroke and 13.7 million new cases annually (Sacco *et al.*, 2013; Lindsay *et al.*, 2019). In the United States of America alone the associated cost of stroke was over US$ 71 billion (~£ 57 billion) in 2012 and is projected to rise to US$ 184 billion (~£ 148 billion) by 2030 (Ovbiagele *et al.*, 2013). The health implications in stroke survivors are multifaceted and vary between individuals, with some making a recovery and others living with permanent disabilities. As a result, preventative measures should be

advocated, including physical activity, that can reduce the risk of stroke by up to 64% (Lee *et al.*, 2003).

It is well established that moderate-intensity continuous training (MICT) can improve cardiorespiratory fitness (CRF), that associates with reduced risk of cardiovascular disease and all-cause mortality across the human ageing continuum (Garber *et al.*, 2011). Accumulating evidence also attests to neuroprotective benefit given its capacity to improve cognitive function in older adults ranging from those with healthy cognition, subjective memory complaints, mild cognitive impairment, dementia and stroke (Quaney *et al.*, 2009; Erickson *et al.*, 2011; Liu-Ambrose *et al.*, 2016; Cai *et al.*, 2017; Northey *et al.*, 2018). However, the optimal mode, frequency and duration remain a constant source of debate. Furthermore, time demands are deemed a potential barrier to participation (Costello *et al.*, 2011), with the World Health Organisation declaring that 27.5% of the adult population worldwide are not meeting recommended physical activity guidelines (Guthold *et al.*, 2018), although this value has been reported to be greater than 90% in some Western societies (Tucker *et al.*, 2011). Attention has since turned to an alternative paradigm, high-intensity interval training (HIIT), given its capacity to further potentiate metabolic, cardiopulmonary and systemic vascular adaptation with the added attraction of less time spent exercising (Weston *et al.*, 2014).

Knowledge gap

However, the number of studies examining the impact of HIIT on the cerebrovasculature in both healthy and clinical populations is lacking (Drapeau *et al.*, 2019; Northey *et al.*, 2019).

This is surprising and highlights a startling paradox in that despite dementia being one of the leading causes of death, astonishingly few studies have been dedicated to understanding how HIIT could beneficially impact any aspect of cerebrovascular function and thus alter an individual's trajectory towards neurodegenerative disease (Figure 1A/B).

To address this knowledge gap, the current review outlines how the HIIT paradigm has evolved and critiques the underlying mechanisms with a translational focus on molecular-haemodynamic-structural-clinical adaptations with the collective potential to attenuate the inexorable decline in cerebrovascular function often shown to accompany sedentary ageing. Components of an optimised HIIT intervention are presented including practical recommendations focused on safety, outcome measures, and statistical power to help guide and inform future HIIT research.

What's in a definition; HIIT and MICT

Unlike the continuous steady-state nature of MICT, HIIT although poorly defined, incorporates periods of high exertion separated by recovery intervals of either low-intensity exercise or complete rest (Figure 2A). Contrary to popular opinion, this form of training is neither new nor revolutionary since reports from as early as the 19th century have described protocols incorporating intervals of running and walking (Bloomfield, 1962). Throughout the 20th century, the popularity of HIIT as a means to improve athletic performance burgeoned, with Olympic gold medallist distance runners Emil Zatopek and Sebastian Coe employing it in their training regimes (Billat, 2001; Figure 2B). However, it is only in the last 15 years that focus has turned to the benefits of HIIT within the clinical setting (Gibala *et al.*, 2012; Meyer

et al., 2013), popularised by accumulating evidence of benefits in patients with established cardiovascular disease (Wisløff *et al.*, 2007), contributing to the exponential rise in scientific publications (Figure 2B).

HIIT potentiates cardiovascular adaptation

Studies in healthy participants and patients with established cardiometabolic disease have consistently demonstrated a greater increase in peak oxygen consumption ($\dot{V}O_{2Peak}$) in the order of ~1.7 mL O_2/kg/min following HIIT compared to MICT (Helgerud *et al.*, 2007; Weston *et al.*, 2014; Milanovic *et al.*, 2015). The superior cardiorespiratory benefits are in part attributed to an improvement in the heart's pumping capacity (Wisløff *et al.*, 2007).

Systemic vascular function has also been shown to improve more markedly following HIIT (Ramos *et al.*, 2015), the likely consequence of an 'optimised' blood flow-shear stress phenotype (see later), triggering calcium influx into hyperpolarised endothelial cells (Cooke *et al.*, 1991) that upregulates endothelial nitric oxide synthase (Bolduc *et al.*, 2013). Accordingly, post prandial lipaemia-induced systemic vascular endothelial dysfunction, a metabolic aberration involving a free radical-mediated reduction in the vascular bioavailability of nitric oxide (Marley *et al.*, 2017), is reversed by HIIT but not MICT (Tyldum *et al.*, 2009). Equally, HIIT has been shown to decrease low-density lipoprotein, increase high-density lipoprotein and improve insulin sensitivity more effectively than MICT (Racil *et al.*, 2013; Sogaard *et al.*, 2018). Collectively, these studies demonstrate that despite shorter bouts of activity, albeit performed at higher intensity, HIIT has the capacity to further potentiate physiological adaptation compared to MICT, which lies at the very heart (and potentially brain, the focus of the current review) of its current popularity.

Translational adaptation; from heart to brain

Evidence indicates that regular physical activity and corresponding improvements in CRF can increase cerebral perfusion and vasoreactivity across the human lifespan (Ainslie *et al.*, 2008; Bailey *et al.*, 2013), although this is not a universal finding (Intzandt *et al.*, 2019; Miller *et al.*, 2019). From a clinical perspective, moderate to high levels of CRF are associated with a markedly lower risk of stroke mortality and dementia (Prestgaard *et al.*, 2019; Tari *et al.*, 2019), and improved cognition (Brown *et al.*, 2010), further confirming the translational neuroprotective benefits of physical activity though the underlying mechanisms remain to be established. Several hypotheses have been proposed, however much of the evidence is based almost exclusively on animal research.

The primary mechanisms include, though are not exclusively confined to: accelerated neurogenesis in particular of the hippocampal dentate gyrus that is especially vulnerable to ageing (Marlatt *et al.*, 2012); reduction in *β*-amyloid (Brown *et al.*, 2013) and neuro-oxidative-inflammatory-nitrosative stress (Parachikova *et al.*, 2008); proprioceptive adaptations incurred by movements that require sustained mental effort (Bak, 2011) and finally; increased brain-derived neurotrophic factor (BDNF) that modulates brain plasticity by promoting neuritic outgrowth and synaptic function (Berchtold *et al.*, 2010). Figure 3 provides a visual summary of the leading translational mechanisms suggested to promote exercise-induced neuroprotection.

Despite burgeoning interest in BDNF (over 1,500 articles since 1995), it is important to emphasise that while brain tissue is directly accessible in rodents, methodological constraints dictate that exercise studies in humans are forced to rely on circulating blood-borne concentrations that do not necessarily reflect local BDNF levels in the brain (Bejot *et*

al., 2011). Indeed, BDNF is unlikely to diffuse much at all beyond the presynaptic terminals releasing it; the protein is designed such that it can only act on immediately adjacent postsynaptic structures. Diffusion through the vascular endothelium is considered unlikely given the presence of truncated receptors preventing any long-range diffusion (DM Bailey, personal communication, Professor YA Barde, Cardiff University, UK) though peripheral to central diffusion could potentially occur subsequent to any transient (exercise-induced) increase in blood-brain barrier (BBB) permeability. Despite preliminary evidence for a transient opening of the BBB subsequent to a free radical-mediated impairment in dynamic cerebral autoregulation (dCA) (Bailey *et al.*, 2011) and net trans-cerebral output of BDNF (Rasmussen *et al.*, 2009) during exercise, the tentative link between peripheral BDNF metabolism and exercise-induced neuroprotection warrants additional, arguably more critical examination.

Considering that HIIT has the capacity to further compound metabolic, cardiac and systemic vascular adaptation, it is surprising to note that there are only two published studies (one as a pilot) (Drapeau *et al.*, 2019; Northey *et al.*, 2019) and no published RCTs exploring its impact on the human cerebral circulation. It is reasonable to speculate that the greater improvements in CRF (beyond those incurred through MICT for any given training volume) could simply confer additional neuroprotection through a translational 'dose-response' effect. This is not unreasonable given that research has demonstrated that incidental CRF in the form of elevated maximal oxygen uptake ($\dot{V}O_{2max}$) in more physically active individuals is linearly associated with improved cerebral perfusion and cerebrovascular reactivity disassociating the brain's 'biological' from 'chronological' age, reducing the former by up to as much as a decade (Ainslie *et al.*, 2008; Bailey *et al.*, 2013). This is clinically relevant given

recent evidence that cerebral hypoperfusion likely precedes dementia (Wolters *et al.*, 2017a) implying a central pathogenic role for impaired oxygen (O_2) and glucose delivery during sedentary ageing.

Cerebral mechanisms; from shear stress to cell signalling

But let's not dismiss HIIT's 'direct' potential to stimulate more local (i.e. cerebrovascular) mechanisms that could equally potentiate neuroprotection. Preliminary evidence, albeit confined to the systemic circulation, indicates that repeated exposure to the mechanical forces associated with acute exercise hyperaemia *per se* promotes complex changes in the pattern of pressure-strain-shear stress (Figure 4A) that can induce functional and structural adaptation of the vascular wall via endothelial cell mechanotransduction (Figure 4B). Precisely how the arterial endothelium recognises and transduces endothelial, longitudinal and circumferential stress is under investigation and likely involves multiple intracellular signalling cascades that are transmitted through the cytoskeleton to the intimal region at the basal endothelial surface (Green *et al.*, 2017).

Complex interactions between integrins, actin filaments, caveolae, the glycocalyx, primary cilia, adherence/gap junction proteins, ion channels, G protein-coupled receptors and receptor tyrosine kinases alter expression of genes governing endothelial/smooth muscle cell fate (i.e., proliferation, migration, and/or apoptosis) and release of key mediators regulating neurogenesis, synaptic plasticity and brain angiogenesis (e.g. BDNF, insulin-like growth factor 1, vascular endothelial growth factor (VEGF)). These molecular cascades are subject to 'upstream' redox-regulation, that is their expression/release is governed by 'quantum-fast' changes in free radicals and associated reactive oxygen/nitrogen species (ROS/RNS) formation that exploit extraordinarily short half-lives and thus are best-placed

from a thermodynamic perspective to serve as upstream signal transductants (Bailey, 2019a). Historically considered as toxic, mutagenic 'accidents' of in-vivo chemistry, constrained to cellular oxidative damage and pathophysiology, it is becoming increasingly clear that at physiological, albeit undefined concentrations, free radicals and associated ROS/RNS serve to maintain cerebrovascular O_2 homeostasis (Bailey *et al.*, 2018). Indeed, free radicals can upregulate antioxidant enzymes, BDNF, VEGF and IGF-1 and their 'hormetic' effects are rapidly emerging as a primary mechanism underpinning exercise adaptation (Bailey *et al.*, 2010).

Yet the majority of this work is based on animal research, thus translation to the human brain remains at best, speculative. Future application of more invasive experimental exercise models measuring trans-cerebral gradients concomitantly across the arterial and jugular venous circulation (with an increase in the latter reflecting net cerebral formation and release) in response to targeted antioxidant prophylaxis will help address this knowledge gap.

If the pattern of shear stress is indeed so important, specifically antegrade shear that is considered anti-atherogenic (unlike retrograde that is pro-atherogenic) notwithstanding the optimal rate-of-flow and rate-of-change in flow, to what extent does HIIT influence the (cerebral) blood flow-shear-strain 'phenotype'?

There are no studies, to the best of our knowledge, that have addressed this in the systemic circulation, let alone the cerebral circulation, due in part to the technical difficulties associated with contemporary techniques and constraints imposed by limb (and head) movement. Figure 5 provides experimental, albeit preliminary insight highlighting the more pronounced increases in regional shear stress (internal carotid artery) that can be achieved

through HIIT compared to an equivalent volume of MICT, due to the intermittency of more pronounced sinusoidal elevations in blood flow/velocity/pressure that prevail even in the face of progressive hyperventilation-induced hypocapnia that would typically be associated with cerebral vasoconstriction. Could it simply be that prolonged exposure to the intermittency of this flow-shear-strain differential explains its (potentially) superior neuroprotective benefits? This is not unreasonable since increased frequency of exposure to sinusoidal shear stress upregulates angiogenesis and anti-oxidative/inflammatory-related genes (Zhang & Friedman, 2013) and improves flow-mediated dilation more effectively than MICT.

Regional heterogeneity; not all parts of the brain respond equally

Importantly, cerebral perfusion during exercise is characterised by marked heterogeneity in the regional redistribution of flow between major cerebral arteries involving complex interactions between brain metabolic and neuronal activity, blood pressure, partial pressure of arterial carbon dioxide (CO_2), cardiac output and sympathetic nervous system activity. In support, flow in the internal carotid and middle cerebral arteries increase proportionally with exercise intensity until ~60% $\dot{V}O_{2max}$, before gradually decreasing due to hyperventilation-induced hypocapnic cerebral vasoconstriction (Smith & Ainslie, 2017), although this may be different across varying exercise modalities (Faull *et al.*, 2015).

Furthermore, there is evidence to suggest that the hindbrain, in particular the brainstem, is one of the most primitive neuroanatomical regions of the human brain that has remained highly conserved across vertebrate evolution given that it houses (almost exclusively) all the

major cardiovascular and respiratory control centres essential for the integrated regulation of autonomic nervous control (Northcutt, 2002). With its development placed at ~300 million years ago, it stands testament to the concept that the ability to 'sense' subtle changes in O_2 and mount a defence against metabolic compromise and/or structural damage was one of the first roles of the CNS and probably represented a major driving force in the evolution of the human brain, thus providing a selective advantage (Bailey, 2019b). This provides a teleological basis to help explain the preferential cerebral perfusion/substrate delivery observed in phylogenetically 'older' regions of the brain sub-served by the posterior circulation in response to not only exercise, but other 'O_2-sensitive' challenges including hypoxia (Binks *et al.*, 2008), hypercapnia (Ito *et al.*, 2000) and hypotension (Lewis *et al.*, 2015).

From a clinical perspective, the posterior circulation appears more susceptible to deterioration than its anterior counterpart (Kim *et al.*, 2017), a predilection site for several dementia types including Lewy Bodies and Alzheimer's, that are confined to the posterior parietal cortex and cingulate gyrus (Minoshima *et al.*, 1997; Ruffmann *et al.*, 2016). Thus, by favouring the posterior circulation, HIIT could be considered an exciting prospect, though equally, it could prove a 'double-edged' sword (see below).

Walking the tightrope; risk versus reward

The safety aspects of HIIT, particularly its impact on the cerebrovasculature, are yet to be systematically explored raising concerns that continue to represent a major barrier toward its (more) widespread clinical implementation. The perceived increased risk of HIIT to

patient safety is based on the notion that high-intensity exercise acutely increases the risk of acute myocardial infarction and sudden cardiac death, particularly in habitually sedentary individuals. However, the evidence to date, albeit in patients with coronary artery disease or heart failure, challenges this concern. Indeed, in their most recent meta-analysis, Wewege *et al.* (2018) examined 23 studies involving 1,117 patients and reported 1 adverse event per 3,417 sessions (2,227 training hours) for HIIT protocols that typically incorporated the 'Scandinavian' approach of 4 × 4-minute intervals with 3-minute recovery intervals and/or protocols that ranged in interval duration from 30 seconds to 3 minutes. This compares to MICT protocols that ranged from 30-60 minutes/session that reported 1 adverse event per 7,134 sessions (5,606 training hours) with no risk difference between training modalities. In contrast, the rewards in terms of health gains and potential cost savings conferred by HIIT over MICT are compelling with meta-analyses consistently reporting more marked improvements in CRF ranging from 1.2-1.8 mL O_2/kg/min, significant given that an improvement in CRF of 3.5 mL O_2/kg/min (1 metabolic equivalent) associates with a 15% lower risk in all-cause and cardiovascular-related mortality (Kodama *et al.*, 2009).

However, it is important to emphasise that these data are based on studies in patients exercising in the cardiac rehabilitation setting supported by 12-lead electrocardiography to screen for cardiovascular abnormalities. Surprisingly, equivalent screening does not exist for the cerebrovasculature, hence the need for continued caution. Perhaps the most pressing cause for concern relates to the rapid increase in systemic blood pressure and hyperventilation induced vasoconstriction once HIIT commences. Unless these actions are countered by the 'shock-absorbing' effects of increased sympathetic activation or CA, constrained by temporal delays of ~5 s, HIIT could potentially increase the risk of cerebral

hyperperfusion injury predisposing to stroke or blood-brain barrier (BBB) disruption. Resultantly, those with ineffective/inefficient dCA or reduced cerebrovascular reactivity to CO_2 may be at a greater risk of cerebrovascular events during exercise.

Barrier disruption can cause extracellular vasogenic oedema and is further compounded by exercise-induced free radical formation resulting in a regional O_2 diffusion limitation with the potential to adversely affect cerebral bioenergetics and cognition (Bailey *et al.*, 2011). This is especially relevant for patients already suffering from impaired CA/autonomic dysfunction including the older adults, notwithstanding patients diagnosed with diabetes, hypertension, stroke and AD. While potentially benefitting from elevated flow and shear, posterior regions of the brain such as the midbrain and cerebellum may equally prove more prone to HIIT-induced autoregulatory breakthrough given that compared to the anterior circulation supplied by the internal carotid arteries, the vertebral arteries are characterised by blunted reactivity to CO_2 and lower CA. It is precisely for these reasons that we have previously recommended a conservative approach that includes a gradual increase in exercise intensity to 'prime-and-prepare' the cerebrovasculature during the first 10 s of the high-intensity period(s) (Lucas *et al.*, 2015). If these potential risks are circumvented, the neuroprotective benefits conferred have the potential to be pronounced, as the observed improvements in cognition and preservation of brain structure/function following lifelong exercise and/or in masters athletes stand testament to (Ainslie *et al.*, 2008; Erickson *et al.*, 2009; Bailey *et al.*, 2013; Tseng *et al.*, 2013).

Practical recommendations; towards the optimal intervention

Given that cardiovascular risks align closely with cognitive impairment and dementia, the potentiating effects of HIIT on CRF have the capacity to further optimise brain health in adults and contribute to current health promotion and disease prevention strategies (Gorelick *et al.*, 2017). However, defining the optimal HIIT paradigm is challenging given the marked lack of published data combined with the fact that dosage involves the complex interaction between duration, frequency, intensity and mode of exercise. Specifically, the term HIIT is often employed to describe protocols that incorporate high-intensity periods at 80-100% HR_{MAX} for 60-240 s. However, another term is regularly used to further define HIIT; sprint interval training (SIT), which incorporates short 'all out' high-intensity periods (Keating *et al.*, 2017). While both paradigms have been associated with superior elevations in CRF compared to MICT (Esfarjani & Laursen, 2007; Wisløff *et al.*, 2007), findings from two meta-analyses evaluating HIIT in populations characterised by vascular endothelial dysfunction indicate that HIIT performed at a higher intensity equivalent to ~85-95% of peak heart rate (HR_{PEAK}) for 4 × 4 minute intervals separated by active recovery periods at an intensity of ~50-70% HR_{PEAK} for 3 minutes (Weston *et al.*, 2014; Ramos *et al.*, 2015) may provide the optimal stimulus.

These findings are noteworthy given that vascular endothelial dysfunction is associated with increased cardiovascular risk and often a precursor of ischaemic events including stroke, cognitive impairment and dementia (see Gorelick *et al.*, 2011). However, the HIIT protocol described was designed to match energy expenditure of traditional MICT training at ~70% $\dot{V}O_{2max}$ (Weston *et al.*, 2014) with comparable time-demands (HIIT; 38 minutes vs MICT; 46 minutes) that could threaten compliance. This has stimulated researchers to explore

alternative (low-volume) HIIT paradigms that incorporate, for example, ten intervals that each last for 60 seconds at 90% HR_{PEAK} with 60 seconds of recovery at low-intensity exercise or rest (Hood *et al.*, 2011). However, it remains unclear whether low-volume HIIT is as effective as high-volume HIIT.

The beneficial effects of HIIT have been documented in a variety of chronic diseases including stroke, hypertension, diabetes and cancer (Molmen-Hansen *et al.*, 2012; Askim *et al.*, 2014; Støa *et al.*, 2017; Rose *et al.*, 2020). Furthermore, exercise prehabilitation with HIIT has the potential to be especially beneficial for the surgical patient given that poor CRF (that falls below multiple 'threshold' metrics) is associated with an increased risk of adverse peri-operative outcomes including major morbidity, mortality, increased length of stay in hospital and reduced health-related quality of life (Davies *et al.*, 2018; Rose *et al.*, 2018a; Rose *et al.*, 2018b). In support, HIIT was recently shown to be a feasible, safe and highly effective intervention with the potential to optimise peri-operative outcome in the 'at-risk' surgical patient defined by multiple co-morbidities (Rose *et al.*, 2020). In contrast, the evidence for benefit in dementia patients remains equivocal, although trials conducted to date have focused on moderate to high-intensity interventions and not HIIT (Hoffmann *et al.*, 2016; Lamb *et al.*, 2018). Though more research is encouraged, HIIT is likely to be more effective as a preventative rather than a post-diagnosis treatment for dementia patients.

However, in order to identify the optimal intervention, it is important that studies include measurement techniques/biomarkers that fully establish the efficacy of HIIT. The integrated assessment of CBF using a variety of established biometrics (Willie *et al.*, 2011; Willie *et al.*, 2014b; Tymko *et al.*, 2018) is eminently justified given the relationship between hypoperfusion and dementia (Wolters *et al.*, 2017b). However, perfusion alone fails to

reveal the full extent of adaptation, given that impaired cerebrovascular reactivity (CVR) is also observed in dementia patients and those at a greater risk of stroke (Vicenzini *et al.*, 2007; Reinhard *et al.*, 2014). While CO_2 is often favoured as a stimulus in CVR assessments due to its relative ease of application, there is a general need for more consistent methodological approaches to optimise application (Burley *et al.*, 2020).

Finally, since cognitive impairment is a hallmark feature of dementia with ~30% of stroke patients developing dementia within the first year of the onset of stroke (Henon *et al.*, 2001), any potential HIIT intervention needs to assess cognitive function. While the abundance of assessments currently available can make it difficult for researchers to select the tests that are most appropriate, The National Institute on Aging and the Alzheimer's Association have advocated incorporation of tests that assess memory, executive function, language, visuospatial skills and attention for those at risk of cognitive impairment (Albert *et al.*, 2011) that may also include a more global assessment using the Montreal Cognitive Assessment tool (Nasreddine *et al.*, 2005).

A question of power

The number of participants required to adequately power an RCT investigating the impact of HIIT on the molecular/metabolic, haemodynamic or structural determinants of cerebrovascular function and corresponding implications for cognitive function remains equally unclear. With this in mind, it is important to apply sound rationale when conducting prospective sample size calculations. For example, researchers have traditionally focused on $\dot{V}O_{2Peak}$ as the primary endpoint without statistical justification for the magnitude of change that constitutes the minimal clinically important difference (MCID, smallest change in

treatment outcome considered important), often relying on arbitrary estimates to authenticate a 'genuine' improvement in CRF (McGregor *et al.*, 2016).

We have more accurately defined the MCID of related CRF metrics by determining the critical difference, a concept that accounts for the underlying imprecision associated with analytical (CV_A) and (mostly) biological (CV_B) or natural variation (Rose *et al.*, 2018b). This approach has identified a CD of 13% for $\dot{V}O_{2Peak}$ (CV_A: 2.2%, CV_B: 3.6%) (Rose *et al.*, 2018b) that when applied to published values (24 ± 4 mL/kg/min) in sedentary older male adults (aged 68 ± 5y) (Bailey *et al.*, 2013) indicates that the MCID would be 3.12 mL O_2/kg/min. This translates into a sample size of 15 participants/patients per arm, as illustrated in Figure 6.

Prospective sample size estimates have also been calculated for remaining determinants of molecular/haemodynamic/structural/clinical function to help inform the design of future RCTs (Figure 6). While the CD has not been formally assessed for these metrics, calculations are based on (retrospectively calculated) effect sizes obtained from the albeit limited HIIT studies and in the absence of data, occasional MICT studies. Sample size estimates range between 6-252 participants/patients, excluding loss to follow-up that conservative estimates suggest range between ~20-25% (Lautenschlager *et al.*, 2008; Morris *et al.*, 2009), highlighting the logistic and economic challenges faced by researchers during recruitment.

Conclusions

Physical inactivity continues to be a major cause of morbidity and mortality with overwhelming evidence supporting the musculoskeletal, cardiovascular and cerebrovascular

benefits of regular exercise that are comparable to drug interventions in a number of chronic conditions. However, healthcare professionals face the constant challenge of having to deal with poor adherence and implementation of exercise interventions that lead to more sustained behaviour. The HIIT paradigm has since emerged as a safe and more time-efficient mode of exercise that can promote further improvements in CRF, molecular and vascular function for an equivalent volume of MICT. However, to what extent HIIT can further compound cerebrovascular adaptation and potentiate neuroprotection remains largely unexplored. The current review provides a mechanistic basis justifying clinical implementation of an optimised RCT that includes practical recommendations focused on safety and statistical power to help guide and inform future HIIT research. Establishing these mechanisms more clearly will provide an evidence-base for the prescription and future optimisation of HIIT interventions that have arguably more potential to promote healthy ageing by delaying stroke, cognitive decline and dementia with corresponding benefits for individuals, their families and society in general.

Additional information

Competing interests

The authors declare no competing interests.

Author contributions

DMB was responsible for the concept of the article. DMB and TNC wrote the first draft of the article. All authors contributed to the analysis, interpretation of the data, along with drafting the article or critically revising it for important intellectual content. All authors have read and approved the final version of this manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

Funding

DMB is supported by a Royal Society Wolfson Research Fellowship (#WM170007), Royal Society International Exchanges Award (IES\R2\192137) and Japan Society for the Promotion of Science Research Fellowship (#JSPS/OF317). MR is supported by a FRQS salary award (Junior I). PNA is supported by the Natural Sciences and Engineering Research Council of Canada and a Canada Research Chair. UW is supported by the KG Jebsen Foundation, the Norwegian Research Council, the Liaison Committee between the Central Norway Regional Health Authority and the Norwegian University of Science and Technology.

Acknowledgements

The authors extend their sincere appreciation to the many participants and patients for their dedication and participation in the experimental studies that form much of the basis of this review.

Abstract figure legend

Summary of the integrated mechanisms and functional adaptations underpinning high-intensity interval training-induced neuroprotection.

High-intensity interval training (HIIT) represents a more time-efficient mode of exercise that can potentiate cardiorespiratory fitness and further enhance neuroprotection compared to more traditional moderate-intensity continuous training paradigms. While the precise mechanisms remain unclear, prolonged exposure to the mechanical forces associated with the intermittency of HIIT-induced sinusoidal hyperaemia can promote complex changes in the cerebral pressure-strain-shear stress phenotype to induce functional-structural adaptation of the vascular wall subsequent to endothelial cell mechanotransduction. Redox-activation of complex intracellular signalling cascades can translate into molecular, haemodynamic and structural adaptations that ultimately enhance neuroprotection. Establishing these mechanisms more clearly will provide an evidence-base for the prescription and future optimisation of HIIT interventions that have arguably more potential to promote healthy ageing by delaying stroke, cognitive decline and dementia. Digits below each of the integrated functionally adaptive benefits proposed (bottom of figure) highlight sample size estimates (number of participants/patients required to achieve adequate statistical power) to inform the design of future randomised control trials.

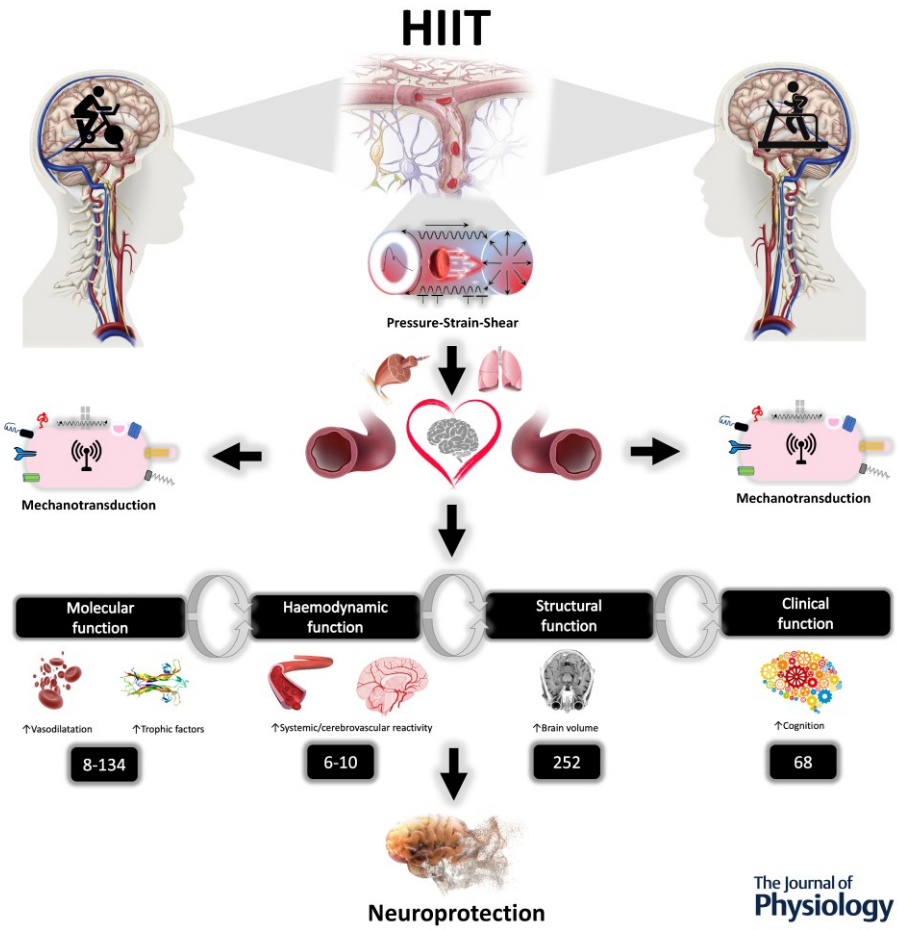

Figure 1. Leading causes of death in the UK and globally (A) and number of published articles focused on high-intensity interval training categorised by clinical subspeciality (B).

UK data obtained from the Office for National Statistics (Patel, 2017); global data obtained from the World Health Organization (2019). All searches retrieved from PubMed (10-09-2019). *n* = number; IHD, ischaemic heart disease; COPD, chronic pulmonary disease; LRI, lower respiratory infections; AD, Alzheimer's Disease and other dementias.

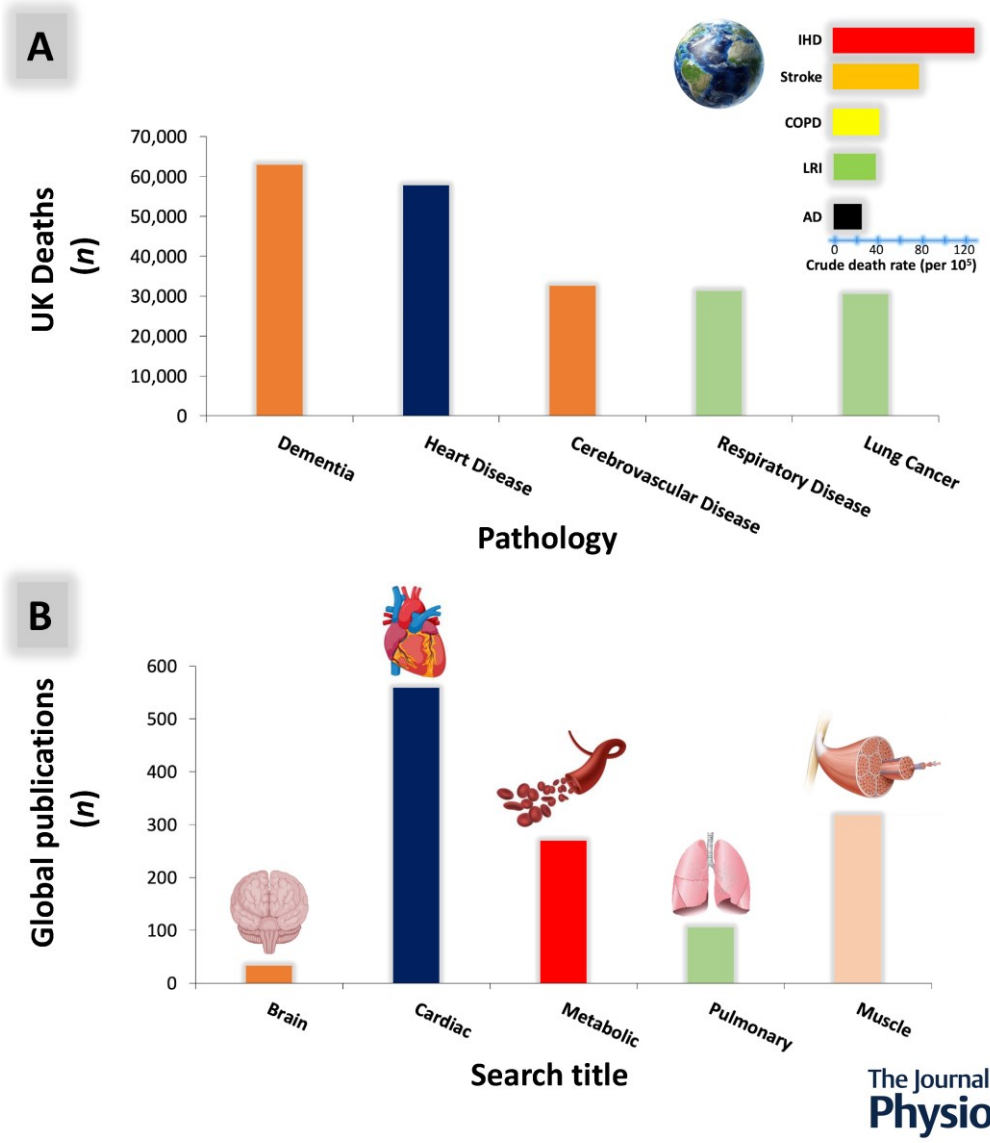

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Figure 2A. Schematic of typical high-intensity interval (HIIT) compared to traditional moderate intensity continuous training (MICT) paradigms recommended by leading health agencies.

Applied paradigm (left panel): Protocol consists of 6 repetitions of 30-second all-out exercise efforts performed at a power output equivalent to 200 % of that achieved at the point of maximal oxygen uptake ($\dot{V}O_{2MAX}$) interspersed by 4 $^{1}/_{2}$ min active recovery at a very low exercise intensity. This protocol is typically performed three times per week, compared to MICT, typically performed at 65 % $\dot{V}O_{2MAX}$ for 60 minutes, five times per week consistent with recommended guidelines (WHO, 2010; Garber *et al.*, 2011). Note that HIIT training volume is ~90% lower and time commitment ~$^{1}/_{3}$ lower compared to MICT. *Clinical paradigm (right panel):* Protocol consists of 4 repetitions of 4 min intervals at 85-95 % $\dot{V}O_{2MAX}$, interspersed by 3 min active recovery at low intensity (adapted from Lucas *et al.* (2015)).

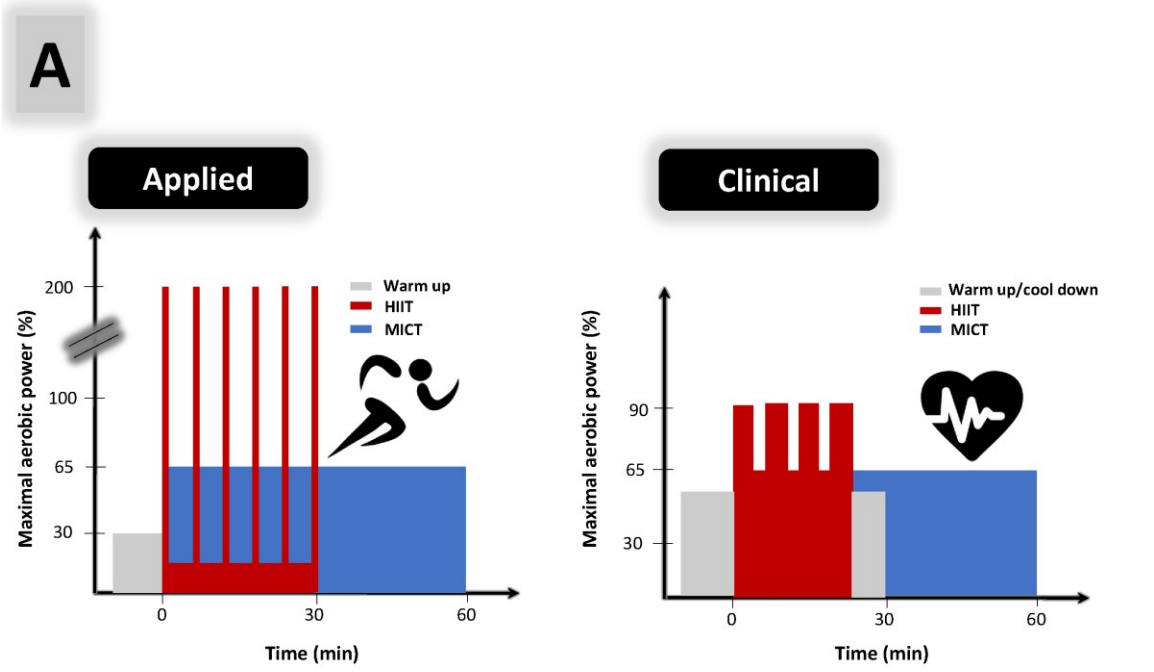

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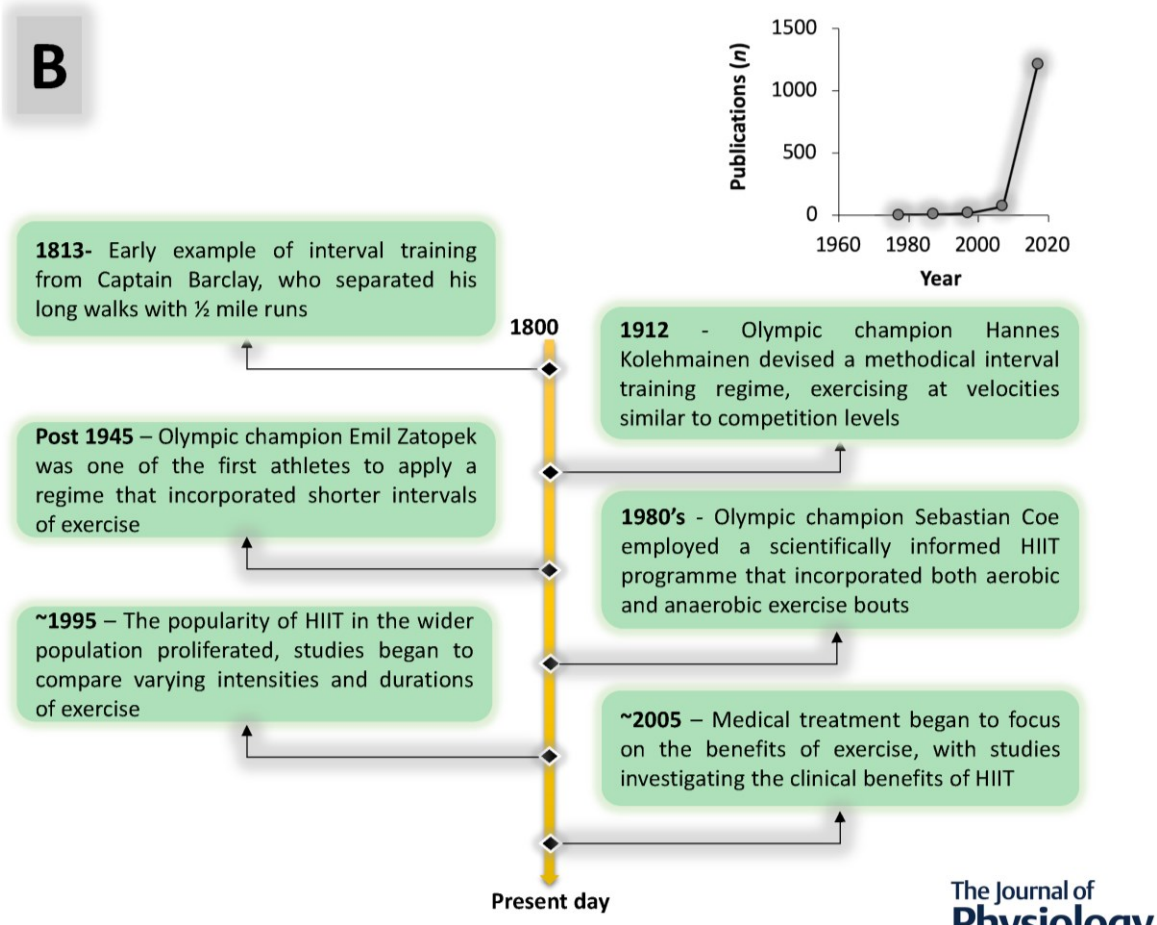
Figure 2B. Historical timeline summarising how high-intensity interval training (HIIT) has developed and exponential increase in publications since the first paper (Lesmes et al., 1978).

All searches retrieved from PubMed (10-04-2020).



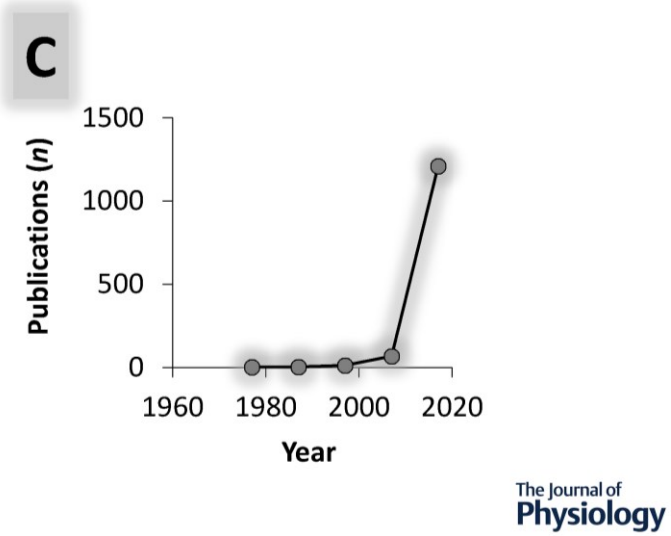


Figure 3. Integrated link between molecular, haemodynamic and structural adaptations underpinning exercise neuroprotection.

Each column summarises the functionally integrated mechanisms/adaptations (connected by dashed lines) common to each of the (four) primary pathways that ultimately converge on a reduction in disease prevalence (highlighted in red). ROS/RNS, reactive oxygen/nitrogen species; NO, nitric oxide; O_2, oxygen.

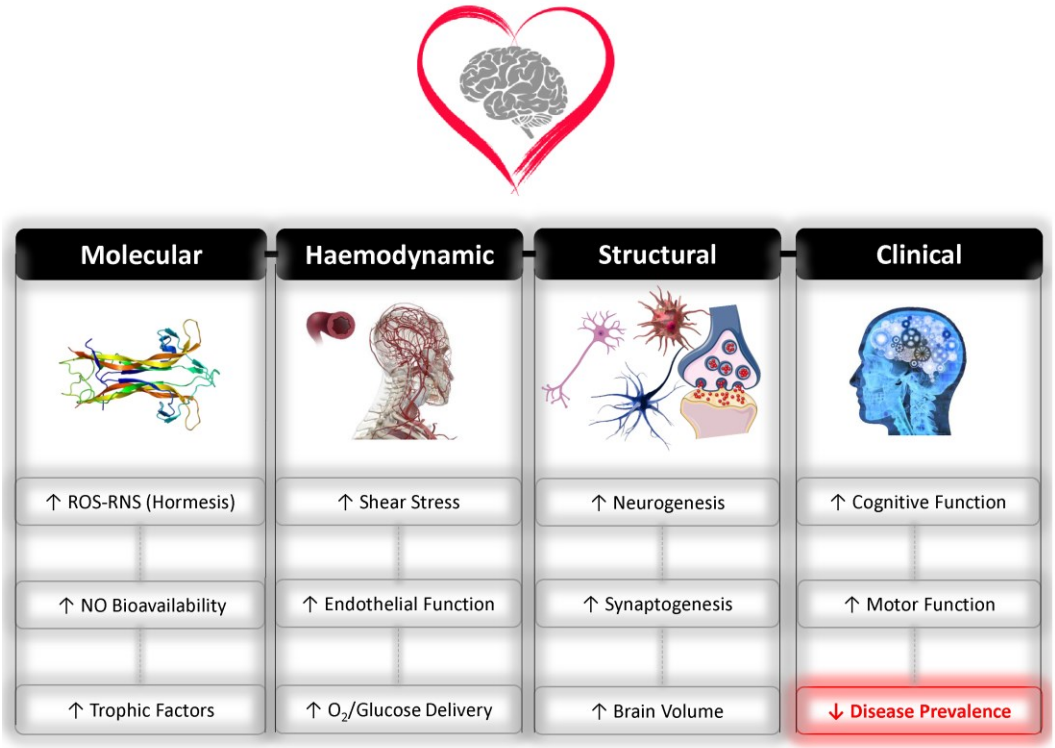


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Figure 4A. Haemodynamic forces acting on the arterial wall during high-intensity interval training that may alter the pressure-strain-shear phenotype.

P_t, tensile pressure; C_s, circumferential stress; W_{ss}, wall shear stress; L_s, longitudinal stress; E_c, external compression; E_{ss}, endothelial shear stress; P_i, intravascular pressure. Brain image is used with permission (Willie *et al.*, 2014a).

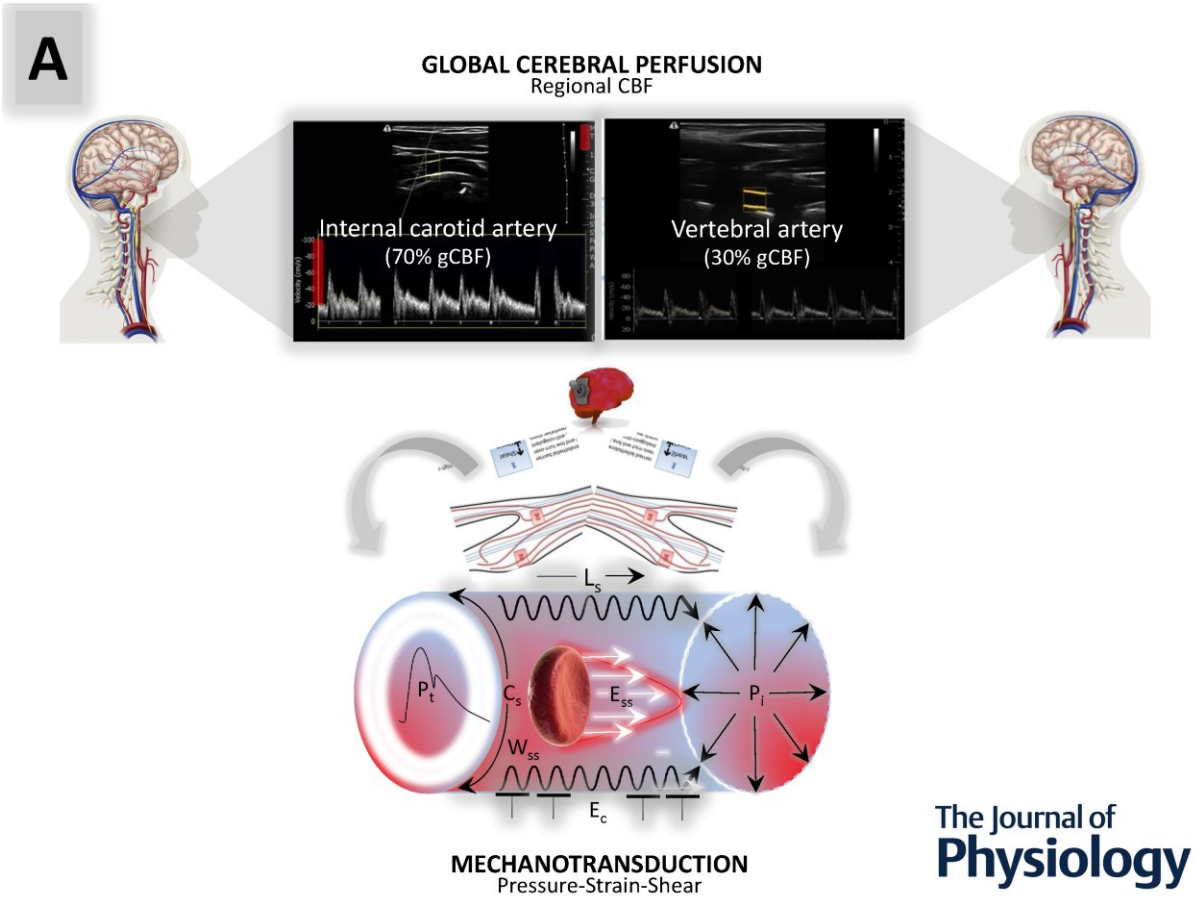

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Figure 4B. Molecular transduction of shear stress to the arterial endothelium is "sensed" by mechanoreceptors activating multiple intracellular signalling pathways involved in neuroprotection.

ROS/RNS, reactive oxygen/nitrogen species; ASK, apoptosis signal-regulating kinase; NF-$\mathcal{K}$B, nuclear factor kappa-light-chain-enhancer of activated B cells; MAPK, mitogen-activated protein kinases; JNK, c-Jun N-terminal kinase; eNOS, endothelial nitric oxide synthase; Nrf, nuclear factor erythroid-related factor; KLF, Krüppel-like Factor; MKP, mitogen-activated protein kinase phosphatase; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; p53, tumor protein p53; RhoA, rat sarcoma homolog gene family, member A; Ca^{2+}, calcium ions; VE, vascular endothelial; VEGFR, vascular endothelial growth factor receptors; PECAM, platelet endothelial cell adhesion molecule. Brain image is used with permission (Willie *et al.*, 2014a).

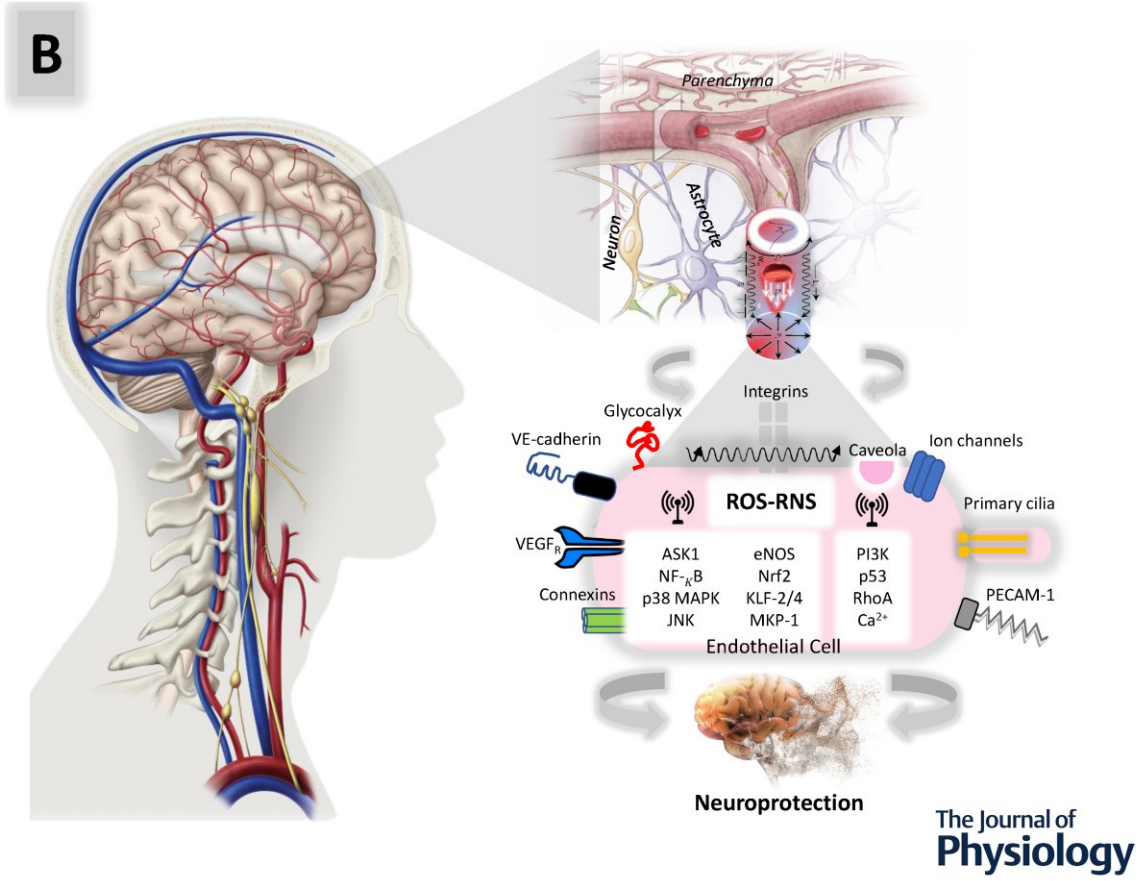

Figure 5. Elevated shear stress response during high-intensity interval (HIIT) compared to moderate-intensity steady-state (MICT) training.

Pilot data obtained from a single healthy male participant. Participant performed HIIT and an identical volume (MICT) of semi-recumbent cycling exercise (as illustrated) during which time blood flow in the (right) internal carotid artery (ICA) was determined 1.5 cm above the carotid bifurcation using duplex ultrasound (Vivid-I; GE Healthcare, Tokyo, Japan) equipped with an 8 MHz linear transducer. Mean ICA diameter was calculated as: $\frac{(\text{Systolic diameter} + \text{Diastolic diameter} \times 2)}{3}$, ICA flow as: Time averaged mean blood flow velocity (BFV) × [π (0.5 × $D_{\bar{X}}$)^2] × 60 (where $D_{\bar{X}}$ refers to mean arterial diameter) and shear rate as: $\frac{4 \times \text{Peak envelope BFV}}{D_{\bar{X}}}$ averaged over the last 4 minutes of each respective intervention (highlighted in red cross-hatches). Note the almost doubling in shear rate [Δ refers to exercise/rest × 100 (%)] during HIIT compared to MICT that was primarily attributable to the (observed) elevation in blood flow/velocity given that arterial diameter changes were comparable. Brain image is used with permission (Willie *et al.*, 2014a).

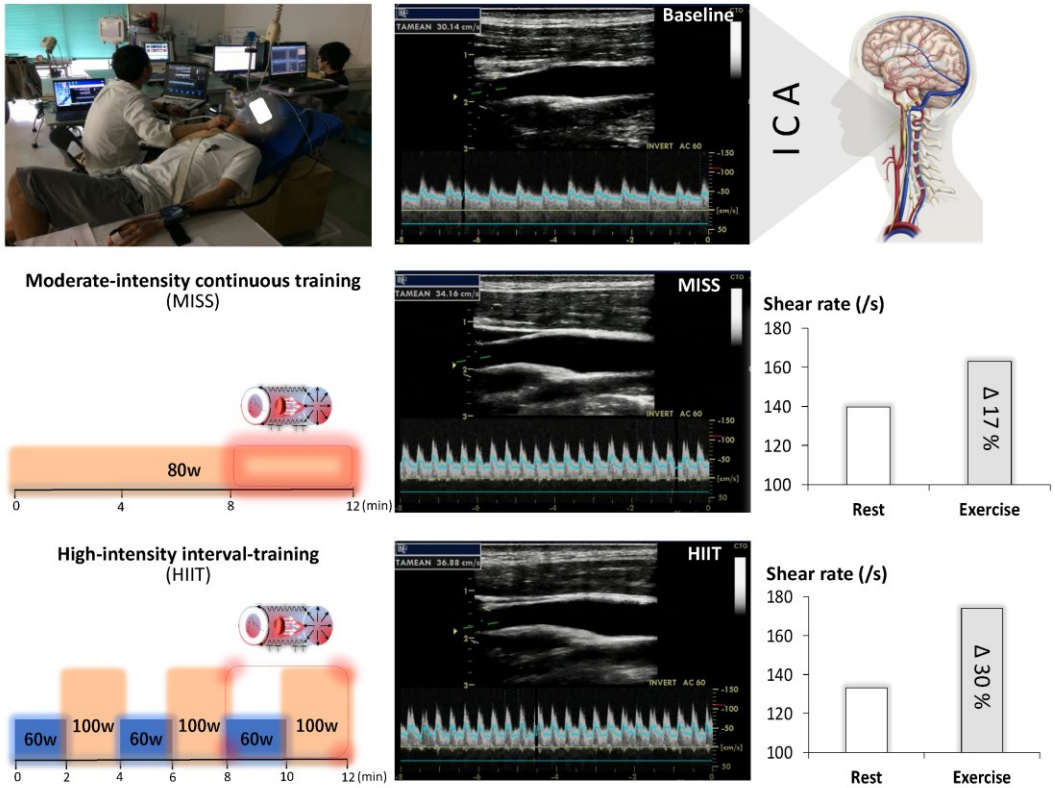

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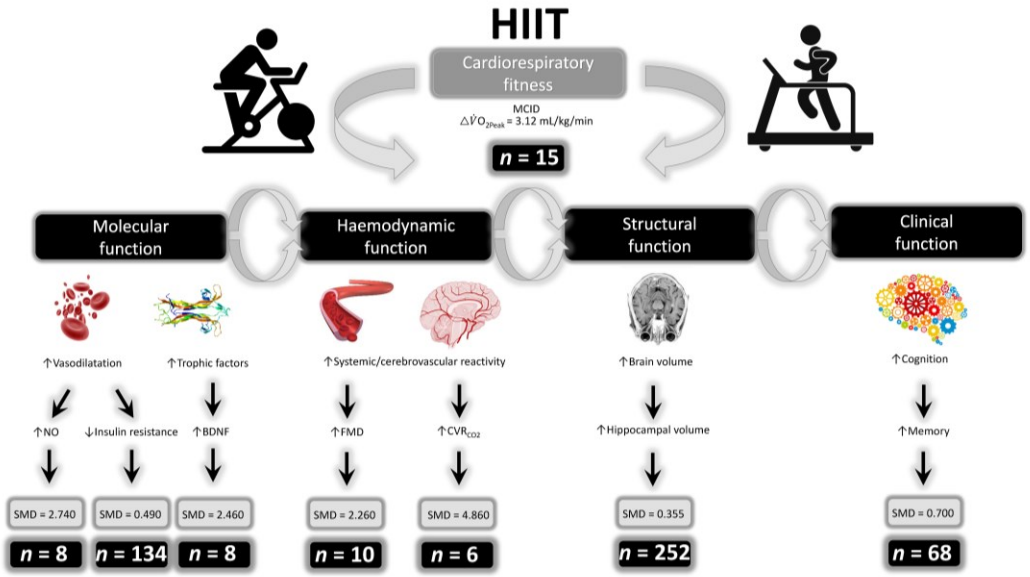
Figure 6. Effect sizes observed and sample sizes required for select components of high-intensity interval training-induced cerebrovascular adaptation.

Top of Figure highlights estimation of the minimal clinically important difference (MCID, smallest change in treatment outcome considered important) for peak oxygen uptake ($\dot{V}O_{2Peak}$). This was based on calculation of the critical difference (CD), a metric that accounts for the underlying imprecision associated with analytical and biological/natural variation (see 'A question of power'). This approach has identified a CD of 13% for $\dot{V}O_{2Peak}$ (CV_A: 2.2%, CV_B: 3.6%) (Rose *et al.*, 2018b) that when applied to published values (24 ± 4 mL/kg/min) in sedentary older male adults (aged 68 ± 5y) (Bailey *et al.*, 2013) indicates that the MCID would be 3.12 mL O_2/kg/min, equating to a sample size of 15 participants/patients per arm (calculated using G* Power, V. 3.1) Critical difference calculations have not been performed for any of the remaining molecular/haemodynamic/structural/clinical metrics that underpin neuroprotection. As an alternative, effect sizes (SMD, standardised mean differences) were calculated based on data outlined in published randomised control trials (RCTs sourced through PubMed and MEDLINE online databases) with prospective calculation of the minimum sample size required to detect a treatment effect (i.e. exercise improvement relative to control intervention) with 0.80 power at $P < 0.05$ using RevMan software (V. 5.3). Note that given the lack of published data, effect sizes for cerebrovascular reactivity to carbon dioxide and hippocampal volume were determined based on moderate-intensity continuous training RCTs and the final sample sizes exclude loss to follow-up with conservative estimates ranging between ~20-25% (Lautenschlager *et al.*, 2008; Morris *et al.*, 2009). NO, nitric oxide; BDNF, brain-derived neurotrophic factor; FMD, flow-mediated dilation; CVR_{CO2}, cerebrovascular reactivity to carbon dioxide. Studies for each outcome measure were obtained from RCTs or previously conducted meta-analyses as follows; nitric oxide (Mitranun *et al.*, 2014; all RCTs; Ghardashi Afousi *et al.*, 2018; Izadi *et al.*, 2018), insulin resistance (Jelleyman *et al.*, 2015; meta-analysis), BDNF (Hebisz *et al.*, 2018; Rentería *et al.*, 2019; RCTs), FMD (Ramos *et al.*, 2015; meta-analysis), CVR_{CO2} (Vicente-Campos *et al.*, 2012; RCT), hippocampal volume (Firth *et al.*, 2018; meta-analysis), memory (Connolly *et al.*, 2017; RCT). Please note, pilot studies, non-human studies and studies that incorporated participants with cerebrovascular disease were excluded from the analyses.



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