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**Symposium Review**

# Brain train to combat brain drain; focus on exercise strategies that optimise neuroprotection

Claire V. Burley[1], Damian M. Bailey[2], Christopher J. Marley[2] and Samuel J.E. Lucas[1]*

[1]*School of Sport, Exercise and Rehabilitation Sciences, University of Birmingham, UK*
[2]*Neurovascular Research Laboratory, Faculty of Life Sciences and Education, University of South Wales, UK*

* Corresponding author: Dr Sam Lucas
School of Sport, Exercise and Rehabiliation Sciences
University of Birmingham
Birmingham, B15 2TT
UK
Email: s.j.e.lucas@bham.ac.uk
Phone: +44 (0)121 414 7272
Fax: +44 (0)121 414 4121

**Author profile**

Claire Burley and Dr Sam Lucas are based at the University of Birmingham and are investigating measures of brain health and novel exercise strategies for interventions. Dr Lucas is an integrative physiologist and Lecturer in exercise and environmental physiology. Dr Lucas supervises a number of PhD students, including Claire. Professor Damian Bailey and Chris Marley are both based at the University of South Wales. Professor Bailey is Chair of Physiology & Biochemistry and Director of the Research Institute of Health and Wellbeing where he leads the Neurovascular Research Laboratory. Chris Marley is a Lecturer in exercise physiology. Collectively, they are interested in better understanding the mechanisms underlying neurodegenerative diseases and the neuroprotective bases of novel exercise interventions.

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**Author contributions**

SL presented at the symposium which was organised and chaired by DB. CB and SL drafted the review. All authors critically revised and approved the final version.

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**New Findings**

The topic of this review is to consider innovative exercise strategies that optimise neuroprotection in order to combat cognitive decline and neurodegenerative disease in older age. The review summarises current understanding around exercise mode, duration, frequency and intensity, and then highlights adaptive roles of select stressors that have equal if not indeed greater capacity than exercise *per se* to induce health-related adaptation in the brain. These stressors include, though are not exclusively limited to, hydrostatic and thermal stress, hypoxia, nutritional supplementation and cognitive loading, and are effective by targeting specific pathways that collectively contribute towards improved brain structure and function.

**Abstract**

The prevalence of cognitive decline and neurodegenerative diseases (e.g. stroke and dementia) is increasing. Numerous studies show that regular exercise has beneficial effects on brain health in clinical and non-clinical populations, yet adherence to public health exercise guidelines is notoriously poor. Recently, novel exercise strategies have been investigated to allow for more individualised and prescriptive approaches that target the key mechanistic pathways that allow exercise to mediate adaptation. This work exploring alternative approaches to the traditional model of exercise training has demonstrated exciting potential for positive health-related adaptations (especially for metabolic, muscle and cardiovascular function). However, few studies to date have focused on brain adaptations. The aim of this review is to summarise new and innovative interventions that have the potential to optimise exercise for improved brain health (i.e., brain structure and function). First, we will briefly summarise current understanding of the nature whereby positive effects of exercise deliver their influence on the brain (i.e., underlying mechanisms and factors affecting its delivery). We will then introduce the effects of exercise training on cognition and give examples of studies showing the beneficial effects of exercise in clinical populations. Finally, we will explore the adaptive roles of individual stressors that may induce greater health-related adaptations in the brain than exercise alone, including environmental stressors (hydrostatic stress, thermal stress and hypoxia), nutritional supplementation and cognitive loading. In summary, optimised interventions that target key mechanistic pathways linked to improved brain structure and function could ultimately protect against and/or ameliorate cognitive decline and neurodegenerative diseases.

**Introduction**

Regular exercise can reduce the risk of cerebrovascular and neurodegenerative diseases (e.g. stroke and dementia), and has been associated with extended longevity (Lautenschlager, Cox & Cyarto 2012). Despite these known effects, the underlying mechanisms that ultimately result in improved brain health are poorly understood (Lucas *et al*. 2015). Further, the "*how"* and "*which form works best"* questions are debated and results remain equivocal. Individuals may therefore be less motivated to engage in exercise and professionals are less able to prescribe it systematically in accordance with detailed guidelines (in contrast to the pharmaceutical industry). Further, given evidence demonstrating the comparable effectiveness of exercise relative to drug treatment (Naci & Loannidis, 2013), as well as the cost-effectiveness and wide ranging effects of exercise on health and well being, research is required to establish optimal exercise strategies that can be delivered in a prescriptive and individualised nature. While a wealth of data from animal models does support some basic mechanisms for the exercise-induced beneficial effects on brain structure and function (for example, brain plasticity) (Voss *et al*. 2013), these findings need translating to human populations for knowledge of dosing, influence of modality and individualised prescriptions. Consequently, we need to develop strategies and perform randomised controlled trials (RCTs) to demonstrate exactly what the treatment effects are - both at the mechanistic level and on population health. Improving health and wellbeing in the general population is vital, particularly considering our ageing and increasingly sedentary population – both of which elevate risk for cerebrovascular and neurodegenerative diseases (Deary *et al.* 2009).

**Exercise and Brain Health: Underlying mechanisms and training effects**

Strenuous exercise induces physiological stress on cells, tissues and organs within the body, facilitating stimulus-strain responses that mediate adaptation and, mostly, an optimisation in function. The benefits of exercise for the human brain are becoming increasingly evident (e.g., improved cerebral blood flow/volume (Colcombe *et al.* 2006), cerebrovascular reactivity (Brown *et al.* 2010; Murrell *et al.* 2013), angiogenesis, neuroplasticity (Voss *et al.* 2013), and cognitive functioning (Kramer *et al*. 1999). However, the underlying mechanisms leading to these adaptations in the human brain remain poorly understood. We (Lucas *et al.* 2015) and others (Davenport *et al.* 2012; Lautenschlager, Cox & Cyarto, 2012; Voss *et al.* 2013; Jackson *et al.* 2016) have recently reviewed the possible mechanistic candidates that may mediate such exercise-induced adaptation in the brain. Briefly summarised here (see Figure 1.), proposed mediators of adaptation include humoral, metabolic and molecular factors that can directly affect brain structure and function via their release within the brain or from systemic tissues and cells (e.g., skeletal muscle, liver, adipose tissue, pancreas and lymphocytes). Further, given established beneficial effects of exercise throughout the body, changes in cardiovascular and immune function also have indirect benefits on brain structure and function, for example improved glycaemic control and reduced inflammation (see Lucas *et al*. (2015) for further details). Therefore, it is crucial we improve understanding of these mechanisms and their relative contributions to help develop exercise strategies that optimise the exercise stimulus-response interaction. Specifically, how exercise mode, duration, frequency and intensity stimulate adaptive responses and ultimately protect against deteriorations in brain and cognitive health.

Studies have shown that aerobic-based exercise interventions lasting between 3 and 12 months involving gym-based circuit training (Colcombe *et al.* 2006; Murrell *et al.* 2013) or walking (Kramer, *et al.* 1999) can improve markers of brain structure and function (e.g., brain volume, cerebrovascular reactivity and neurocognition). Further, smaller individual bouts of exercise or 'exercise snacks' (e.g., 3 bouts ('snacks') of exercise spread across the day consisting of 6x1 minute intense incline walking intervals) in prediabetic participants revealed immediate health improvements through improved glycaemic control (Francois *et al.* 2014). In addition, simply being less sedentary can improve 'health' in older adults (Sjogren *et al.* 2014) and young girls (McManus *et al.* 2015). While caution should be taken when generalising findings across such studies covering different populations, methodological approaches and markers of health, one key message here is that there may be many approaches to optimising exercise strategies, and even simply being less sedentary may be enough to promote improvements in brain structure and function.

Another barrier to people engaging in exercise may be the heterogeneity in the cardiorespiratory fitness response (Ross, de Lannoy & Stotz, 2015), with 'non-responders' losing motivation to continue with exercise. Related to this, Ross and colleagues adjusted intensity and volume of exercise on inter-individual cardiorespiratory fitness and found that increasing the intensity of exercise eliminated the non-response in a dose-dependent manner. Whether these beneficial effects carry over to the brain requires further exploring.

Numerous cross-sectional studies and supervised aerobic-based training studies have shown evidence of the effectiveness of traditional exercise training (e.g., 30 min of moderate intensity exercise, 5 days per week), where higher physical activity levels are associated with improved brain structure and function (Kramer *et al.* 1999; Killgore, Olson & Weber, 2013; Smith *et al.* 2014). However, there is also well-documented poor adherence to regular engagement in exercise (Lee *et al*. 2012). Therefore, alternative strategies are required to encourage participation and adherence. Considering the community level where 'lack of time' is often a barrier to engaging in physical activity, exercise strategies that can achieve similar benefits for less time commitment may offer an attractive solution.

High-intensity interval exercise training (HIIT) is emerging as an effective alternative to current health-related exercise guidelines due to its more time-efficient and superior metabolic, cardiac and systemic vascular adaptations (Weston, Wisloff & Coombes, 2014). However, use of HIIT is controversial and debated, particularly in patients with pre-existing disease (Holloway and Spriet, 2015; Wisløff, Coombes & Rognmo, 2015). Regardless, the reported positive effects and potential of HIIT to provide greater access to the health benefits that exercise provides is exciting; although the lack of evidence to date examining how HIIT affects the brain raises concerns about its global promotion at this stage (Lucas *et al.* 2015). Moreover, given the unique regulation of the cerebral vasculature, determining the specific effects of HIIT on the brain is required since short bursts (10-60 s) of all-out exercise, one form of HIIT, will likely elicit large and rapid increases in blood pressure that may increase risk of an adverse event (as discussed in Lucas *et al.* (2015)). One other consideration is the profile of cerebral blood flow (CBF) across the range of exercise intensities, typically described as returning towards resting values when intensity increases above ~60%$VO_2$max

(Brugniaux *et al.* 2014). This profile is seemingly at odds with the potential for HIIT to mediate greater cerebrovascular adaptation via exercise-induced shear-stress mediated endothelial adaptation (Bolduc, Thorin-Trescases & Thorin, 2013). However, this pattern of blood flow is typically reported from cycling-based studies, and an alternative profile may exist for other exercise modalities; supported by the different CBF profiles recently reported with rowing (Faull, Cotter & Lucas, 2014) and running (Lyngeraa *et al.* 2013). Further, adjunct therapies (e.g., water-based treadmills) may mitigate such an effect across the range of exercise intensities. This highlights the potential for differences in exercise mode and exercise intensity-mode interactions for brain-related adaptation.

**Cognition and the role of exercise in clinical populations**

Interventions involving physical *and* cognitive activity (e.g., motor tasks requiring sustained attention and concentration) have been investigated in humans. A randomised controlled trial in older women found a 16-week multimodal exercise programme lead to improvements in cognition (working memory, inhibition, shifting, verbal fluency and reaction times) and physical function (six-minute walk test and timed up and go) (Vaughan *et al.* 2014). This exercise programme utilised a multimodal intervention of exercise including cardiovascular, strength conditioning and motor fitness training. Similarly, Barcelos and colleagues examined a combination of stressors by observing the effects of physical exercise (cycling) whilst undertaking cognitive tasks of varying loads (virtual bike tour and video gaming) (Barcelos *et al.* 2015). They found that everyday function improved in both conditions though those in the high cognitive demand group performed better than those in the low cognitive demand condition, providing support to further 'stressing' the system by using multiple approaches and the additive benefits that can occur in a dose-dependent manner. Such findings are consistent with observations from cross-sectional studies. For example, Eskes *et al* (2010) demonstrated that the diversity of cognitively stimulating activities was an independent predictor of cognitive fucntion in older (female) adults, and that there was an additive effect on neuropsychological performance with the combination of fitness, cerebrovascular reserve and cognitive stimulation. Research should further explore the underlying mechanisms driving these adaptations with additional cognitive loading, as well as focusing on particular brain areas affected through neurodegenerative disease.

The beneficial role of exercise for brain health in clinical populations and older adults has been demonstrated in numerous studies. For example, physically active dementia patients may deteriorate at a slower rate than their sedentary counterparts (Buchner, 2007; Zschucke, Gaudlitz & Ströhle, 2013). Moreover, in older adults with genetic risk for sporadic Alzheimer's disease (i.e., in individuals who express Apolipoprotein-E 4 (APOE-4)), exercise attenuates the age-related reduction in gray matter hippocampal volume involved in the formation of episodic memory (Smith *et al.* 2014). Gray matter hippocampal volume and performance on memory tasks has also been positively correlated with physical exercise in healthy adult human populations and those at risk for dementia (Erickson *et al.* 2011; Killgore, Olson & Weber, 2013). While such findings suggest that exercise improves markers of brain health (e.g., brain volume and memory performance), many tend to use self-report questionnaires to assess levels of exercise. Further, they do not reveal the specific nature of activity or the fundamental mechanisms that drive these improvements. More research is

needed, particularly in the form of RCTs to improve our understanding of these treatment effects and the mediating mechanisms driving them.

**Exploring novel targeted approaches**

Recent focus has been on alternative conditioning strategies that have potential to selectively target the brain (see Jackson *et al.* 2016; Lucas *et al.* 2015). These have included supplementing exercise with environmental stressors (e.g., hydrostatic pressure via water immersion, thermal stress and hypoxia), nutritional supplements (e.g., antioxidants, dietary nitrate) as well as cognitive challenges included with the physical training, as previously mentioned. The rationale for using such approaches centres on targeting a proposed mechanistic pathway for neurovascular adaption and are discussed in more detail below and illustrated in Figure 1.

*Hydrostatic stress*

Exercising in water has recently been promoted as a method by which to enhance shear-stress mediated vascular adaptation in the brain (Pugh *et al.* 2014). Pugh and colleagues demonstrated greater increases in CBF velocity (by ~10%) during water-based activity compared to matched intensity land-based activity. They proposed that a summative relationship may exist where increases in mean arterial pressure and partial pressure of carbon dioxide ($PCO_2$) in the blood may contribute to increases in CBF velocity. The potential for such enhanced stimulus-response adaptation and therefore improved vascular function serve as additives to other advantages for water-based activities, particularly in populations whereby mobility has been compromised through injury or disease.

*Thermal stress*

Heat stress combined with exercise can provide a strong cardiovascular challenge to humans (Rowell, 1986), but also mediates enhanced stimulus-response adaptation. For example, we observed that a single bout of hot yoga whilst hypohydrated led to higher heart rate and blood pressure responses, along with greater (compared to control) post-exercise hypotension and subsequent expansion of plasma volume following the exercise (Akerman, Lucas & Cotter, 2015). Further, studies utilising thermal stress have indicated that the consequential shear stress stimulates vascular adaptation, particularly related to the endothelium and nitric oxide (NO) mediated vasodilation (Green *et al.* 2010). Similar to hydro-based approaches, thermal approaches could be administered to patients with limited mobility (e.g., peripheral arterial disease) and therefore provide an alternative or adjunct strategy to improve access to exercise-related adpaptation.

*Hypoxia*

Remote ischaemic preconditioning also provides an excellent means of altering flow and creating shear stress in a sinusoidal fashion. Recently, studies have looked at hypoxia as a conditioning strategy, similar to heat and water therapy (Verges *et al.* 2015). These studies indicate that hypoxia may be an effective non-pharmacological therapeutic intervention that can enhance physiological functions (e.g., by enhancing neurogenesis to preserve spatial learning and memory).

Collectively, these studies suggest that combining exercise with heat and/or water and/or hypoxia may provide a greater neurovascular-signalling stimulus for brain adaptation than exercise alone, and *may* eliminate the non-response phenomenon mentioned previously and so encourage participation. Whether short-term changes translate into long-term benefits is less clear, and further research is needed to explore these additive stimuli in long-term exercise training studies to confirm whether they are indeed more beneficial than exercise alone.

We should also consider the potential for additional stress to cause maladaptations if not administered at a correct dosage/pattern and monitored appropriately, particularly in patient populations where function is already compromised. We should also consider efficient approaches in studying these mechanisms, both in isolation and combination. We need to ascertain a sufficient basic understanding or proof-of-concept from which we can progress onto considering advanced applications of combination strategies.

*Nutritional supplementation*

Nutritional supplementation and its potential for improving markers of brain health has also received recent attention. For example, antioxidants such as flavanol have a role in lowering excessive reactive oxygen species (ROS), increasing NO and thereby improving cerebrovascular function. The most robust biomarkers affected by flavanol include endothelial function, blood pressure and cholesterol levels. Flavanol also affects NO synthesis and breakdown of the substrate arginine (Ellam & Williamson, 2013). Sorond and colleagues observed that both cognition and neurovascular coupling can be improved with regular flavanol (i.e. cocoa) consumption in older adults (Sorond *et al.* 2013) and others suggest flavanol may improve CBF regulation (Secher, 2015). Despite these promising observations, calorie and sugar content of chocolate (a rich source of flavanol) and its contribution to the total diet should also be considered. Therefore, dietary nitrate (e.g. beetroot juice) may be preferable and has been linked with improved CBF regulation and cognitive performance (Wightman *et al.* 2015). Taken together these studies suggest nutritional supplementation may serve as an attractive optimisation strategy to compliment exercise and provide additive benefits, but requires further research.

**Conclusion**

When considering the health of the general population, a change in societal attitudes towards exercise is required to encourage participation and adherence. Insights highlighting the benefits of different exercise intensities, duration, modes and timing across the day may encourage people to exercise more, particularly if educational information is disseminated regarding improvements in cognitive health and the neuroprotective role of exercise leading to reduced risk for disease including dementia and stroke. Alternative approaches used in conjunction with exercise such as heat, water, hypoxia, cognitive loading and nutritional supplementation may lead to similar or additive benefits, and pave the way for exciting and innovative strategies that need to be developed and studied in more detail. Research so far indicates that a more multifaceted approach would be beneficial for a number of populations, particularly if they can be delivered in a prescriptive and individualised nature. Further studies are required to examine the impact of optimised exercise strategies that target the brain, and consider how these mechanisms translate to patient health and

well-being. Optimised interventions that target key mechanistic pathways linked to improved brain structure and function could ultimately protect against and/or ameliorate cognitive decline and neurodegenerative diseases, projected to cost the UK and Europe billions in the years to come (Wimo *et al.* 2013).

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**Figure 1.**

A mind-body dualism approach illustrating potential mechanistic pathways through which the components of optimised intervention strategies may lead to beneficial brain adaptations of structure and function, and ultimately, improve brain and cognitive health. Strategies can occur concurrently to create multi-modal and individualised interventions. They include: physical activity; cognitive activity; nutritional supplementation; hydrostatic stress; thermal stress, and hypoxia. Such strategies induce physiological stress on cells, tissues and organs that facilitate stimulus-strain responses within the brain and systemic organs, tissues and cells and involve a number of mediators that can be adaptive or maladaptive depending on their concentrations. Thus, emphasising the potential hormesis effect for dose-response requirements to avoid toxicity (which may lead to dysfunction) and optimise physical and cognitive health. Mediators include: NO (nitric oxide); eNOS (endothelial nitric oxide synthase 3); BDNF (brain-derived neurotrophic factor); free radicals; ROS (reactive oxygen species); IGF-1 (insulin-like growth factor) and antioxidants.