Neuroscience and Biobehavioral Reviews 83 (2017) 11–20

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review article

Combining aerobic exercise and repetitive transcranial magnetic stimulation to improve brain function in health and disease

Joshua Hendrikse[a,*,1], Aaron Kandola[a,b,1], James Coxon[a], Nigel Rogasch[a], Murat Yücel[a,*]

[a] School of Psychological Sciences and Monash Institute of Cognitive and Clinical Neurosciences, Monash University, Australia
[b] Amsterdam Brain and Cognition, University of Amsterdam, Australia

ARTICLE INFO

Keywords:
Cognitive enhancement
Non-pharmacological
TMS
Exercise
Synaptic plasticity
Depression
BDNF
Neurotrophins
Multi-modal intervention
Cognitive dysfunction

ABSTRACT

The aetiology of various psychiatric and neurological disorders may be partially attributable to impairments in neuroplasticity. Developing novel methods of stimulating neuroplasticity is a promising treatment approach to counterbalance these maladaptive influences and alleviate symptomologies. Two non-pharmacological approaches with significant and direct impacts on neuroplasticity are aerobic exercise and repetitive transcranial magnetic stimulation. Aerobic exercise is associated with the promotion of numerous neurotrophic mechanisms at a molecular and cellular level, which have a broad influence on neuroplasticity. Transcranial magnetic stimulation is a form of non-invasive brain stimulation with the capacity to modulate the synaptic efficacy and connectivity of particular brain networks. This review synthesises extant literature to explore the complementary physiological mechanisms targeted by aerobic exercise and repetitive transcranial magnetic stimulation, and to substantiate the hypothesis that the use of these techniques in tandem may result in synergistic impact on neural mechanisms to achieve a more efficacious therapeutic approach for mental disorders.

1. Introduction

A crucial adaptive property of the human brain is its capacity to reorganise and restructure – its *neuroplasticity*. Neuroplasticity refers to the capacity for the nervous system to reorganise itself in accordance with intrinsic and extrinsic influences (Shaw and McEachern, 2001). This can occur through a range of neuroplastic changes such as through the reorganisation or formation of new synaptic connections, strengthening of existing synaptic connections, or the proliferation and integration of adult-born neural cells. The resulting structural and functional changes are necessary to maintain proper functioning and the promotion of neuroplastic changes is essential to facilitate certain processes such as learning and memory. Neuroplasticity can sometimes be disrupted in response to a disease or injury state, which can lead to maladaptive consequences for brain functioning (Cramer et al., 2011). To some extent, the aetiology underlying various neurological and psychiatric disorders may be attributed to impaired neuroplasticity (Kays et al., 2012). For example, the rate of neurogenesis and synaptic plasticity are markedly reduced in patients with major depressive disorder and these impairments are thought to significantly contribute towards the development of cognitive and affective symptoms associated with the disorder (Duman and Aghajanian, 2012; Sahay and Hen, 2007). Finding ways to induce or harness neuroplasticity has emerged as a promising treatment approach to counterbalance maladaptive influences and reduce symptoms across a range of neurological and psychiatric disorders (Krystal et al., 2009).

Patients who are prescribed pharmacological medications are at risk of experiencing a number of adverse side effects that are inherent to these interventions. Common side effects of antidepressants and antipsychotics range in severity from nausea to cardiovascular dysfunction (Anderson et al., 2012; De Hert et al., 2012), and long-term use has even been associated with structural abnormalities in the brain (Fusar-Poli et al., 2013; Ho et al., 2011; Navari and Dazzan, 2009; Rubio et al., 2013; Vernon et al., 2011). Further, treatment responses elicited by some of the most commonly used pharmacological drugs like antidepressants or antipsychotic medications have been inconsistent. In the case of schizophrenia and major depressive disorder (MDD), the proportion of treatment resistant patients is as high as 20–30% (Hasan et al., 2012; Keitner et al., 2006). Even regarding those patients who do respond well to treatment, recent reviews have suggested that the efficacy rates of various widely used antipsychotic or antidepressant medications differ only slightly from that of a placebo (Leucht et al., 2009; Rief et al., 2009). The growing uncertainties regarding just how efficacious certain pharmacological medications are raise the question

* Corresponding authors.
E-mail addresses: joshua.hendrikse@monash.edu (J. Hendrikse), murat.yucel@monash.edu (M. Yücel).
[1] These authors have contributed equally to the manuscript.

http://dx.doi.org/10.1016/j.neubiorev.2017.09.023
Received 31 January 2017; Received in revised form 2 August 2017; Accepted 21 September 2017
Available online 23 September 2017
0149-7634/

of whether patients are being exposed to an unnecessary degree of risk. In cases where symptoms are not effectively reduced, patients are likely to be exposed to multiple different pharmacological medications and longer intervention periods, which may increase the risk of experiencing adverse side effects (Kandola et al., 2016).

The pharmacological approach has undoubtedly benefited modern society. However, there is an increasing awareness that other, non-pharmacological approaches could also be useful in treating brain disorders, as they are typically associated with a lower risk of adverse consequences for the patient (Gartlehner et al., 2015, 2016). The effective promotion of neuroplastic changes may be a promising addition to current therapeutic approaches that could improve treatment outcomes for certain disorders and may be achievable using non-pharmacological interventions.

Two non-pharmacological approaches with significant and direct impacts on neuroplasticity are aerobic exercise and transcranial magnetic stimulation. Aerobic exercise (AE) refers to forms of exercise that elevate ones heart rate and respiration, such as running, cycling or swimming. AE has been extensively associated with the promotion of numerous neuroplastic mechanisms (Cotman et al., 2007; Voss et al., 2013). Transcranial magnetic stimulation (TMS) is a safe and painless form of non-invasive brain stimulation. TMS causes neurons to generate action potentials via electromagnetic induction and, when delivered repetitively, induces effects that outlast stimulation via mechanisms akin to synaptic plasticity, such as long-term potentiation (LTP) or long-term depression (LTD) (Thickbroom, 2007). Importantly, both AE and TMS are relatively low-risk approaches to treatment. If established safety guidelines are followed, TMS is a low risk intervention with few adverse side effects (Rossi et al., 2009) and AE is associated with a range of benefits for the social, physical, and affective well-being of individuals with psychiatric disorders (Fiuza-Luces et al., 2013). In this paper, we will discuss how AE and TMS interact with neuroplasticity, their unique and overlapping mechanistic pathways, and argue that their combination might result in complimentary and additive effects for enhanced therapeutic gain (Fig. 1).

2. Aerobic exercise

The benefits of leading a physically active lifestyle have long been common knowledge and physical exercise is increasingly being recognised as medicinal and even preventative of numerous physical illnesses such as cardiovascular disease (Fiuza-Luces et al., 2013). Over the past two decades, neuroscientific methods have continued to advance exponentially and it has become clear that the benefits of physical exercise are also applicable to the brain.

Exercise is a subcategory of physical activity and refers to any deliberate and repetitive form of movement intended to improve or maintain physical fitness (Caspersen et al., 1985). While other forms of exercise, such as resistance training, also have a positive influence on the brain (e.g. Liu-Ambrose et al., 2010; Suo et al., 2016), the current literature has focussed predominantly on AE. AE involves increases in respiration and heart rate above basal levels to increase delivery of substrates (e.g. oxygen and glucose) to working skeletal muscles. Common consequences of engaging in regular AE include increased maximal oxygen uptake and cardiorespiratory endurance (Voss et al., 2013). A host of longitudinal studies have consistently correlated high levels of aerobic fitness with greater academic achievement and an improved cognitive capacity across the lifespan, and especially in later life (for reviews, see Hillman et al., 2008; Prakash et al., 2015). To determine whether AE engagement causes an improvement in cognitive performance, a number of randomised control trials (RCTs) have been conducted (e.g. Erickson et al., 2011). Meta-analyses of this data have shown that AE interventions improve performance on cognitive tasks, particularly within the domains of executive functioning and memory (Chang et al., 2012; Colcombe and Kramer, 2003; Roig et al., 2013; Smith et al., 2010; Verburgh et al., 2013).

Due to the cognitive benefits associated with AE, there is a growing perception that it may represent a promising therapeutic tool to counteract cognitive decline associated with ageing and dementia (Ahlskog et al., 2011; Duzel et al., 2016). Furthermore, the clinical application of AE may extend beyond remediating cognitive impairment towards the reduction of broader affective or psychotic symptoms

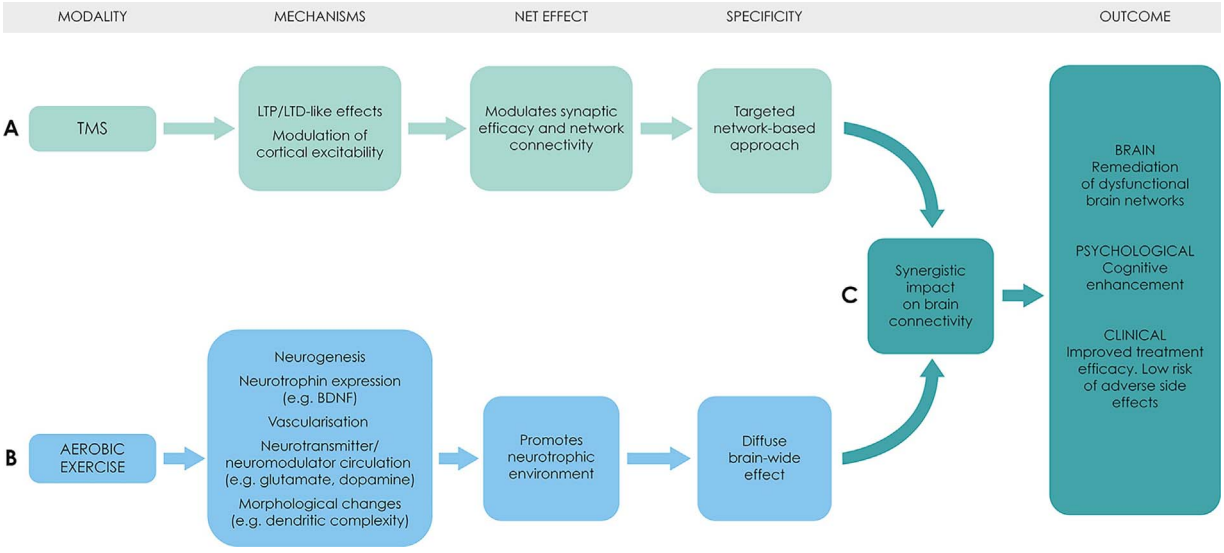

Fig. 1. (A) Repetitive transcranial magnetic stimulation (rTMS) has the capacity to modulate cortical excitability. Through analogous mechanisms to long-term potentiation and long-term depression, rTMS can induce changes to synaptic efficacy that outlast the period of stimulation and influence cognitive functioning. These effects are seen not only in local cortical regions underlying the TMS coil position, but can be induced across distributed neural networks. The application of rTMS, particularly when informed by magnetic resonance imaging, may be an effective technique to manipulate aberrant brain connectivity associated with psychiatric or neurodegenerative disease states. (B) Aerobic exercise (AE) stimulates neurotrophic mechanisms at cellular and molecular levels that are necessary for brain plasticity to occur. Through the upregulated expression of key neurotrophins and growth factors, such as BDNF, VEGF and IGF-1, AE promotes synaptic and vascular plasticity and increases the rate of neurogenesis within the hippocampus. The capacity for AE to influence neuroplasticity at a micro and macro scale across multiple brain regions offers a versatile therapeutic tool, which may be further benefitted by the application of other neuromodulatory techniques. (C) The mechanisms promoted by both rTMS and AE could work in tandem to produce a synergistic effect that leads to greater therapeutic effects with the potential to alleviate cognitive or affective symptoms associated with a number of disorders..