

THE EFFECT OF EXERCISE ON MENTAL HEALTH: A FOCUS ON INFLAMMATORY MECHANISMS

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SUMMARY

A growing body of research suggests that neuropsychiatric disorders are closely associated with a background state of chronic, low-grade inflammation. This insight highlights that these disorders are not just localized to dysfunction within the brain, but also have a systemic aspect, which accounts for the frequent comorbid presentation of chronic inflammatory conditions and metabolic syndromes. It is possible that a treatment resistant subgroup of neuropsychiatric patients may benefit from treatment regimens that target their associated proinflammatory state.

Lifestyle factors such as physical activity (PA) and exercise (i.e. structured PA) are known to influence mental health. In turn, mental disorders may limit health-seeking behaviors - a proposed "bidirectional relationship" that perpetuates psychopathology. PA is renowned for its positive physical, physiological and mental health benefits. Evidence now points to inflammatory pathways as a potential mechanism for PA in improving mental illness. Relevant pathways include modulation of immune-neuroendocrine and neurotransmitter systems, the production of tissue-derived immunological factors that alter the inflammatory milieu and neurotrophins that are critical mediators of neuroplasticity. In this paper, we will focus on the role of PA in positively improving mental health through potential modulation of chronic inflammation, which is often found in individuals with mental disorders. In a related paper by Edirappuli and colleagues (2020), we will focus on the role of nutrition (another significant lifestyle factor) on mental health.

Thus, inflammation appears to be a central process underlying mental illness, which may be mitigated by lifestyle modifications. Lifestyle factors are advantageous as first-line interventions due to their cost efficacy, low side-effect profile, and both preventative and therapeutic attributes. By promoting these lifestyle modifications and addressing their limitations and barriers to their adoption, it is hoped that their preventative and remedial benefits may galvanize therapeutic progress for neuropsychiatric disorders.

Key words: physical activity - exercise - inflammation - neuropsychiatric diseases - mental health

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INTRODUCTION

Expanding research evidence is pointing to neuropsychiatric disorders being intimately associated with a background state of chronic, general low-grade inflammation. This insight highlights that these neuropsychiatric disorders can no longer be considered to be localized within the brain but also have systemic aspect, accounting for the disproportionate comorbid presentation with chronic inflammatory conditions and metabolic syndromes. This may potentially be evolutionarily adaptive in cases of acute illness: concomitant depressive symptoms that promote social withdrawal and preservation of energy resources may limit the spread of infection during the healing process. However, in conditions of chronic inflammation that impact longer-term psychology, the prolonged sickness behavior that ensues is no longer adaptive but rather, debilitating (Rosenblat et al. 2014).

In both animal models and human studies, inflammation has been shown to underlie neuropsychiatric symptoms. Inflammation and oxidative stress can engage in a positive feedback loop: tissue injury (which can be caused by oxidative stress) leads to inflammation, generating chemokines, cytokines and reactive oxygen species that may cause further tissue injury in a locally destructive process. If this process continues

unchecked and is excessive, systemic pathology may manifest such as in neuropsychiatric disease, since the brain is particularly vulnerable (Ng et al. 2008). Larger scale studies and meta-analyses have recently provided both correlative and causative evidence for a critical role of immune-related molecules in psychopathology.

Lifestyle factors such as physical activity (PA) or exercise (i.e. structured PA) are known to influence mental health. This may be bidirectionally perpetuated by the influence of mental disorders in limiting health-seeking behaviors. Exercise has long been advocated for its positive physical, physiological and mental health benefits. Exercise may ameliorate mental disorders through modulation of immuno-neuroendocrine and neurotransmitter systems, production of tissue-derived immunological factors that alter the inflammatory milieu, and neurotrophins that mediate neuroplasticity.

Thus, inflammation is a central underlying driver process influencing mental health, and lifestyle modifications may offer therapeutic benefit through interplaying with inflammatory pathways. By promoting these lifestyle modifications and addressing their limitations and barriers to their adoption, it is hoped that their preventative and remedial benefits may galvanize therapeutic progress for neuropsychiatric disorders.

INFLAMMATION IS A CENTRAL UNDERLYING DRIVER PROCESS FOR PSYCHOPATHOLOGY

Modulating inflammation can influence neuropsychiatric symptoms. Healthy volunteers given a typhoid vaccine which experimentally induces inflammation (IL-6 \uparrow) leads to depressive symptoms. Moreover, neuroimaging in these subjects shows activation of the subgenual anterior cingulate cortex (sgACC), characteristic of depression (Drevets et al. 2008), and reduced cognitive performance (Harrison et al. 2009). In support of a central role for inflammation, anti-inflammatory agents have often shown efficacy as adjunctive treatments for psychopathology. Etanercept (a TNF- α inhibitor) can reduce depressive symptoms and fatigue in psoriatic patients, independent of changes in psoriasis (Tyring et al. 2006). Moreover, a meta-analysis of NSAIDs administered as sole treatment or as an adjunct to antidepressants indicates that they are more effective than placebo in treating depression (Köhler et al. 2014), notably celecoxib. These studies highlight that neuropsychiatric symptoms may arise independently through an underlying inflammatory pathway, which can be effectively targeted.

Chronic inflammatory conditions (such as rheumatoid arthritis and psoriasis) often have co-morbid impairments in mental status. Patients with autoimmune pathology frequently report profound, debilitating fatigue, as concluded by a 2015 survey by the American Autoimmune Related Diseases Association (AARDA). Moreover, inflammation may impede the acquisition and maintenance of an alert state in a visual attention paradigm (Balter et al. 2019). These studies highlight that underlying inflammation may cause significant cognitive impairments to patients that impact their quality of life. The variety and extent to which aspects of brain function are impacted is a subject of active investigation.

Chronic, low-grade systemic inflammation has often been found in patients with treatment resistance to antidepressants and antipsychotics. Around 1 in 3 depressed patients have elevated circulating C-reactive protein (CRP) levels while 1 in 3 are antidepressant resistant, underscoring a potential predictor of poor response to antidepressants (O'Brien et al. 2007). The drug-resistance displayed by psychiatric patients with elevated inflammation markers may be due to failure to correct inflammation-related pathologies. In particular, inflammatory cytokines activate indoleamine 2,3-dioxygenase (IDO), an enzyme that shifts metabolism of tryptophan (a 5HT precursor) towards kynurenine, leading to increased production of neurotoxic and potentially depressogenic metabolites such as 3-hydroxykynurenine (3-HK) and quinolinic acid (an NMDA receptor antagonist). In mice, lipopolysaccharide (LPS) induced systemic inflammation leads to depression-like behavior through activation of IDO, which is prevented by blocking inflammation with the broad-spectrum antibiotic, minocycline (O'Connor et al. 2009). A similar association has been reported in other chronic inflammatory condi-

tions, such as murine models of obesity (Vancassel et al. 2018). The kynurenine pathway has therefore been hypothesized to link peripheral inflammation and CNS alterations by reducing tryptophan availability, and also through production of oxygen radicals and highly potent neurotoxins (Réus et al. 2015). Thus, tryptophan degradation and its role in the availability of serotonin have brought attention to the kynurenine pathway as a potential therapeutic target for alternative treatments for intractable depression (Figure 1).

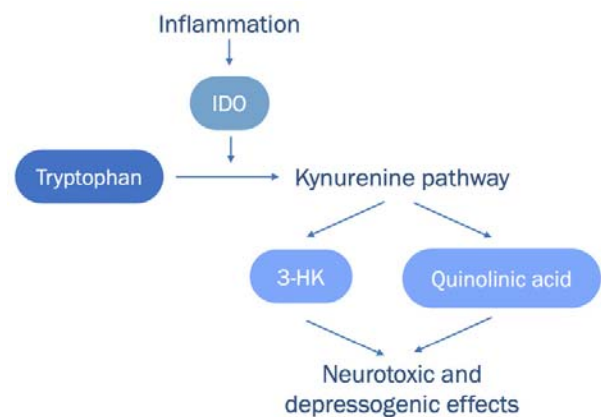


Figure 1. Inflammation shifts the metabolism of tryptophan to the kynurenine pathway which may contribute to neuropsychiatric disorders. Inflammatory cytokines activate indoleamine 2,3-dioxygenase (IDO), an enzyme that diverts metabolism of tryptophan (a 5HT precursor) towards kynurenine, increasing production of neurotoxic and potentially depressogenic metabolites such as 3-hydroxykynurenine (3-HK) and quinolinic acid (an NMDA receptor antagonist). Figure adapted from O'Connor et al. (2009) and Vancassel et al. (2019)

Genetic, imaging and transplantation studies support a role for the immune system in psychopathology. The largest genome-wide association study of schizophrenia to date has shown that schizophrenia is associated with genes involved in adaptive (CD19 and CD20 B-lymphocytes) and innate immunity (complement C4 genes) (Sekar et al. 2016). PET studies in patients with schizophrenia and those with subclinical symptoms have provided evidence for neuroinflammation (microglial activation) (Bloomfield et al. 2016). Novel research transplanting human glial progenitors from schizophrenia patients into mouse brains led to the mice developing abnormalities characteristic of schizophrenia (Windrem et al. 2017). These studies suggest a primary role for glia in the complex disease pathogenesis, potentially through altering neurodevelopment and plasticity.

High quality evidence supports a causal relationship between inflammation and depression. Meta-analyses of cross-sectional studies have confirmed that the levels of circulating proinflammatory cytokines and acute phase proteins are elevated in acutely depressed patients, which are largely normalized after recovery (Goldsmith et al. 2016). Longitudinal studies (e.g. of the ALSPAC

birth cohort) have since demonstrated that elevated cytokine (IL-6) levels preceded and predicted later development of depressive and psychotic symptoms, consistent with a causal function (Khandaker et al. 2014, 2018). Recently, a mendelian randomization approach was used to support an association between a functional IL-6 receptor genetic variant (Asp358Ala) with reduced risk of depression and psychosis via anti-inflammatory effects exerted downstream of IL-6 (Khandaker et al. 2018). The field now awaits the results of the Insight study - a randomized controlled trial of tocilizumab targeting IL-6/IL6R for patients with depression and psychosis, specifically those with evidence of inflammation - to evaluate whether this therapeutic approach offers evidence-based benefits for patient subgroups (Khandaker et al. 2018).

EXERCISE PLAYS AN IMPORTANT ROLE IN PSYCHOPATHOLOGY VIA INFLAMMATORY MECHANISMS

The bidirectional relationship of exercise with mental health conditions

Individuals with mental disorders are typically less physically active. This has been supported by large population-based studies (De Moor et al. 2006), and other evidence linking mental illness with premature mortality (Cuijpers et al. 2014), which is mainly related to comorbid cardiovascular and metabolic disease (Charlson et al. 2013). These findings have been reinforced by evidence that over two-thirds of people with depression failed to comply with the recommendation of 150 minutes of moderate or vigorous PA per week (F. Schuch et al. 2017). Critically, this corresponds to a 50% reduced likelihood of depressed individuals meeting PA recommendations when compared to controls without depression. One theory posits that there is a mismatch between exercise levels and interest levels in these individuals (Roberts & Bailey 2011), which suggests that systematic barriers may exist that limit health promoting behaviors (discussed later). Through targeting these barriers, it may be possible to enhance PA and improve the morbidity of individuals with psychopathology.

Moreover, lower levels of PA increases the risk of mental illness. Based on over 100 population-based observational studies completed since 1995, the 2008 Physical Activity Guidelines Advisory Committee Report (NPAGCR) concluded that inactive people were more likely to have depressive symptoms by as much as 40%. This association is supported by several lines of evidence, ranging from prospective cohort studies (Balboa-Castillo et al. 2011) to cross-sectional analyses (Stubbs et al. 2016) and meta-analyses (Zhai et al. 2015) across a gamut of population groups. Interestingly, interruptions in activity patterns, be it voluntary (e.g. loss of motivation or fear of injury) or involuntary (e.g. hospitalization), can also greatly detriment one's mental health status (Weinstein et al. 2017). Additionally, direct

and indirect associations have been made between PA and self-esteem, perceived physical fitness and body image, which is pertinent given how commonplace low self-esteem features in many psychiatric disorders (Zamani Sani et al. 2016). These findings collectively highlight a bidirectional relationship between physical inactivity and mental health problems, wherein reduced activity may be both a cause and consequence of mental illness. This self-perpetuating cycle therefore highlights a possible reversible target for therapeutic intervention.

Several lines of evidence highlight that PA can improve mental health symptoms and quality of life among people with mental illness. Even a single bout of exercise can offer acute symptomatic benefit for patients with depression, irrespective of absolute intensity levels (Meyer et al. 2016). In the longer term, exercise undertaken thrice weekly for over eight weeks has demonstrated efficacy for treating depression (Stanton & Reaburn 2014), and large effect sizes have been reported in meta-analyses (F. B. Schuch et al. 2016). Aside from self-reports of symptomatic benefit, neuroimaging correlates have also been evidenced, such as reduced brain activity in the sgACC (Ohmatsu et al. 2014).

Given the heightened rates of cardiovascular risk, metabolic dysfunction and chronic inflammation are associated with psychopathology, and the potential for PA to improve these conditions, interventions that increase PA could confer substantial benefits.

The evidence for anti-inflammatory mechanisms of exercise in improving mental health

The therapeutic effect of long-term PA on depression likely includes an immune-mediated optimization of neurotransmitter level and function, hormone regulation, muscle-derived protein (e.g., Pgc-1 α and IL-6), and neurotrophic factors (Phillips & Fahimi 2018).

Immuno-neuroendocrine

Exercise is a physiological stressor that mounts a neuroendocrine response that has immunological consequences. Exposure to psychological and physiological stressors activates the paraventricular nucleus of the hypothalamus, leading to the release of corticotropin-releasing hormone (CRH), which stimulates the release of adrenocorticotrophic hormone (ACTH) from the pituitary that induces cortisol and catecholamine secretion from the adrenals. These stress hormones inhibit excess production of proinflammatory cytokines (e.g., IL-12, TNF- α , and IFN- γ) in healthy individuals with optimal regulatory capacity, while simultaneously increasing production of anti-inflammatory cytokines (e.g., IL-10 and IL-4) (Elenkov & Chrousos 1999). Regulation of the immune response is paramount as failure and dysregulation of the HPA axis leads to persistent hypersecretion of proinflammatory cytokines. This can cause peripheral immune challenge to then induce central neuroinflammation (Lacy & Stow 2011) via active transport mechanisms at the circumventricular

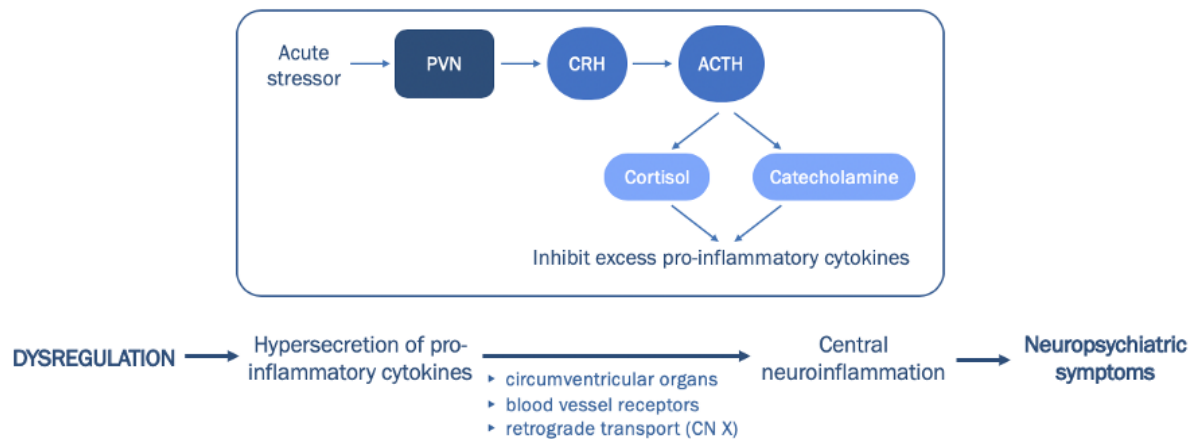


Figure 2. Dysregulation of the HPA axis may contribute to neuropsychiatric symptoms. Exposure to stressors activates the paraventricular nucleus of the hypothalamus, leading to the release of corticotropin-releasing hormone (CRH), which stimulates the release of adrenocorticotropic hormone (ACTH) from the pituitary that induces cortisol and catecholamine secretion from the adrenals. These stress hormones inhibit excess production of proinflammatory cytokines in healthy individuals. However, dysregulation of the HPA axis leads to persistent hypersecretion of proinflammatory cytokines that can then induce central neuroinflammation and neuropsychiatric disease in vulnerable individuals

organs, binding to blood vessel receptors, or by retrograde transport by the vagus nerve (Maier & Watkins 2003), culminating in the activation of resident microglia in the brain (McCusker & Kelley 2013), leading to neuropsychiatric disease in vulnerable individuals (Figure 2).

Neurotransmitter systems

Serotonergic neurons originating in the raphe nucleus are important modulators of mood, appetite, arousal, impulsivity, aggression and the sleep-wake cycle. Pro-inflammatory cytokines contribute to serotonergic dysfunction, reducing firing rates of serotonergic neurons by as much as 50% (Manfridi et al. 2003). Plasma-free tryptophan is increased following PA (Melancon et al. 2012) leading to increased tryptophan availability to the brain and, in turn, enhance serotonin synthesis. Serotonin levels are then maintained by the anti-inflammatory bias of PA, due to both downregulation of IDO activity - which shifts the balance of kynurenine metabolites toward neuroprotective kynurenine acid and away from neurotoxic quinolinic acid - and reduced serotonin uptake by transporters to increase synaptic serotonin availability. Thus, through inflammatory modulation, exercise is able to boost serotonin levels, whilst concomitantly mitigating glutamate excitotoxicity (a feature of neurodegenerative disease), leading to a net improvement in mental health symptoms.

Noradrenergic neurons located in the locus coeruleus (LC) are a vital component of the central stress circuitry that induces “fight or flight” behavior, fear, and anger. Cytokines can contribute to noradrenergic dysfunction, increasing LC firing activity (Borsody & Weiss 2002). Notably, effective antidepressants characteristically reduce LC neuronal activity. Neurochemical investigations have shown that cytokines increase noradrenaline metabolism in multiple brain regions (Dunn 2006), whilst drug that increase noradrenergic action and dura-

tion at the synapse (e.g., noradrenergic reuptake inhibitors) elevate mood and attention, mitigating the effects of stress-mediated noradrenergic depletion. PA leads to a rapid sympathetic response, characterized by intermittent secretion of adrenaline and ACTH in parallel, which leads to anti-inflammatory effects. PA can reduce LC firing following stress (Greenwood et al. 2003). These changes may reduce noradrenaline levels in the amygdala to limit anxiety behavior. Longer term PA has been shown to increase basal NA levels in the hippocampus, which may inhibit the release of pro-inflammatory cytokines by local microglia whilst stimulating astrocytes to release trophic factors (e.g., BDNF) for neuroprotection (Junker et al. 2002). Prospective randomized controlled trials have demonstrated that hippocampal volumes increase following long-term aerobic PA (i.e., 1–2 years) (Rosano et al. 2017).

Dopaminergic neurons originating in the ventral tegmental area (VTA), substantia nigra pars compacta (SNpc) and arcuate nucleus mediate important functions such as working memory, motor execution, and reinforcement learning via their respective pathways. Pro-inflammatory cytokines alter the dopaminergic system by reducing ventral striatal activity to reward cues via depletion of tetrahydrobiopterin (BH4), a cofactor essential for dopamine biosynthesis (Felger et al. 2013). Human volunteers exposed to low-dose polysaccharide exhibited reduced ventral striatal activity to monetary reward cues, a change that correlated with increased depressive symptoms (Eisenberger et al. 2010). This alteration resembles the dopaminergic status seen in depression, explaining their co-occurrence of inflammation in a distinct subset of persons who are clinically depressed. PA can cause a widespread increase in dopamine levels, such as through anti-inflammatory mechanisms that limit iNOS induction thereby reversing BH4 depletion (Kitagami et al. 2003). In rodents, long-term voluntary wheel running is rewarding (rats exhi-

bited conditioned place preference) and produces plasticity in the mesolimbic reward pathway (Greenwood et al. 2011). Such a feed-forward mechanism may contribute to longer term reductions in inflammation and metabolic disease.

Tissue-derived immunological factors

PA promotes the modulation of visceral fat mass, in which reside infiltrates of proinflammatory immune cells that contribute to persistent low-grade inflammation, insulin resistance, and depression (Ouchi et al. 2011). Macrophages within adipose tissue secrete pro-inflammatory cytokines TNF- α , IL-1, IL-6, and monocyte chemoattractant protein-1 (MCP1) (Skurk et al. 2007). Another important example of an adipokine in the pathophysiology of neuropsychiatric disease is adiponectin. Decreased serum adiponectin levels have been reported in patients with major depressive disorders, panic disorders and schizophrenia (Wędrychowski et al. 2014). Reduced adiponectin also plays an important role in depression-related behaviors, such as in promoting withdrawal in a chronic social defeat stress model of depression, which was relieved by intracerebral administration of adiponectin, even in obese diabetic mice (Liu et al. 2012). Notably, a recent meta-analysis has determined that exercise increases adiponectin levels (Becic et al. 2018), which may contribute to how exercise bolsters mental health.

During acute exercise, working muscles generate exponential increases in IL-6, the canonical myokine. To study whether acute exercise induces a true anti-inflammatory response, a model of "low-grade inflammation" was established in which healthy volunteers, were randomized to either rest or exercise prior to endotoxin administration (Starkie et al. 2003). In resting subjects, endotoxin induced a 2- to 3-fold increase in circulating levels of TNF- α , whilst 3 hours of ergometer cycling abrogated the TNF- α response. Moreover, the effect of exercise could be mimicked by infusion of IL-6, suggesting that IL-6 may be involved in mediating the anti-inflammatory effects of exercise. IL-6 effectuates blunting of pro-inflammatory TNF expression, and increases the expression of the soluble TNF receptors, IL-10, and IL-1ra, with increases in CRP up to 10-hours later (Petersen & Pedersen 2005). Upon release into the local and systemic circulation, IL-10 promotes an anti-inflammatory milieu in the periphery. This suggests exercise-related intermittent increases in IL-6 could prevent the aetiology of a pro-inflammatory environment via the blunting of TNF- α and increased IL-10 expression.

At the nexus of PA and immune interactions is a regulator of adaptation: the muscle-derived protein PGC-1 α . PA upregulates skeletal expression of PGC-1 α (Russell et al. 2003), a factor that controls pro-inflammatory gene expression in muscle partly via inhibition of the NF- κ B pathway. Muscle tissue levels of TNF- α and IL-6 negatively correlate with PGC-1 α levels in healthy and glucose-intolerant models (Handschin et al.

2007). PGC-1 α mitigates insulin resistance, upregulates ROS-detoxifying enzymes, AMPK activation and VEGF expression, modulates kynurenine metabolism and reduces depressive symptoms. This has led Phillips and Fahimi to propose that PGC-1 α and its reciprocal interaction with NF- κ B is the "molecular pivot" that determines the inflammatory balances endemic to conditions of health and disease (Phillips & Fahimi 2018).

Neuroplasticity

Neurotrophins are important mediators of neuroplasticity, and accordingly their levels are dysregulated in many neuropsychiatric disorders and modulated by exercise. The neurotrophic hypothesis of depression proposes that stress-related alterations in BDNF levels occur in key limbic structures to contribute to the pathogenic processes in MDD by contributing to neuronal atrophy, synaptic disconnection, and circuit dysfunction (Duman & Monteggia 2006). Evidence for a role of BDNF has garnered genetic support: the Val66Met polymorphism in the BDNF gene is a common single-nucleotide variant predisposing to MDD, which affects intracellular packaging of the pro-BDNF polypeptide and activity-dependent release (Zhao et al. 2018). In depressive individuals, upregulation of BDNF occurs in the amygdala and nucleus accumbens whereas downregulation of BDNF occurs in the hippocampus and medial prefrontal cortex (mPFC), structures in which pathologic volume loss is routinely evidenced (Yu & Chen 2011). Conversely, therapeutic optimization of BDNF levels facilitates synaptic plasticity and remodeling, induction of long-term potentiation (LTP), modulation of gene expression for plasticity, resilience to neuronal insults, and alleviation of depressive symptoms (Phillips 2017). Exercise is associated with increased levels of BDNF (Phillips 2017) which has been shown to trigger neuroplastic mechanisms that counteract the adverse effects of depression in several brain regions such as the hippocampus, prefrontal and anterior cingulate cortices, potentially mitigating pathologic cognitive deficits (Gujral et al. 2017). Interestingly, evidence supports a synergistic effect of aerobic exercise and restricted dietary intake leading to enhanced BDNF upregulation and learning and memory in rodents (Alomari et al. 2016). Thus, it seems plausible that multidomain lifestyle treatments may be particularly beneficial in persons with MDD who exhibit decrements in BDNF levels.

Therapeutic implications, limitations and barriers to adoption

In our review of the literature, we noted significant heterogeneity across studies. This highlights the importance of careful phenotyping of the patients and control subjects, and controlling for variables that influence inflammation, such as smoking, diet, body mass index (BMI), age, sex, somatic co-morbidities, as well as psychiatric and non-psychiatric medication use.

Is there currently enough evidence to support the clinical deployment of exercise to improve mental illness? A meta-analysis of 39 randomized trials reported that aerobic exercise produced effects comparable to treatment by either antidepressants or psychotherapy (Cooney et al. 2013). Another meta-analytic study demonstrated that aerobic PA moderately reduced the signs of depression, with populations over 60 years of age and those with mild depression deriving the greatest response (Silveira et al. 2013).

Which modality of PA is optimal (e.g. aerobic, strengthening, flexibility, or combinations)? Stanton and Reaburn tried to determine optimal parameters for using PA to treat depression (e.g., frequency, intensity, duration, and type of exercise). All five randomized controlled studies meeting inclusion criteria were aerobic in nature (walking on treadmill or outdoors, cycling on a stationary bike, or training on an elliptical machine) (Stanton & Reaburn 2014). Positive evidence was found that aerobic PA of moderate intensity, undertaken 3 times weekly, was effective in treating depression, recommending a minimum of 9 weeks. In one of the largest cross-sectional studies in the USA analysing data from 1.2 million adults, those who exercised had 43% fewer days of poor mental health in the past month compared to those who did not exercise. It was also found that all exercise types were associated with lowered mental health burden. However, largest associations were seen in popular team sports such as cycling and aerobic gym activities. Additionally, exercise for 45 minutes with frequency of 3-5 days per week was more effective (Chekroud et al. 2018). Despite many positive findings, the precise activity parameters that need to be prescribed to mitigate neuropsychiatric symptoms and co-morbid inflammation need to be determined in future work.

Whilst exercise has demonstrable benefit for mental health symptoms, it is not a panacea, and may not be equally effective for all. The Depression Outcomes Study of Exercise found a response rate of about 40% in depressed people free from other treatments (Dunn et al. 2005), which concurs with more recent data from the REGASSA trial, the largest study with exercise and depression, which found a response rate of about 50% (Hallgren et al. 2015). The remission rate (people who no longer meet criteria for MDD diagnosis) was investigated in the Treatment with Exercise Augmentation for Depression (TREAD) study, and found to be 28% (Trivedi et al. 2011). It would therefore be beneficial to be able to identify patients more likely to benefit from prescribed structured PA. To achieve this, further investigation into the potential predictors and moderators of the antidepressant effects of exercise is required.

An adjunctive role for exercise has been supported by many lines of evidence. In a randomized clinical trial, a regimen of pharmacotherapy plus 16 weeks of supervised structured aerobic exercise training program was effective for women with clinical depression (Carneiro et al. 2015). Moreover, an add-on aerobic exercise program significantly decreased the need to increase

doses of sertraline as compared to sertraline monotherapy (Siqueira et al. 2016), and increased the frequency of beneficial treatment responses (Kerling et al. 2015). Another study assessed the effects of a 4-month course of aerobic exercise, sertraline therapy, or a combination of exercise and sertraline in persons with depression, found that remitted persons in the exercise group exhibited significantly lower relapse rates than subjects in the medication group (Babyak et al. 2000). Lastly, we eagerly await the results of the SPeED study (Sport/Exercise Therapy and Psychotherapy - evaluating treatment Effects in Depressive patients), a randomized controlled trial that aims to investigate whether a preceding endurance exercise program will enhance the effect of a subsequent cognitive behavioral therapy, and the associated underlying mechanisms (Heinzel et al. 2018).

Physical, psychological, and socio-ecological motivational factors and barriers to exercise have been identified (Firth et al. 2016). Despite improvement in physical health being the most endorsed reason for exercising, the main physical barrier to exercise was tiredness and other physical co-morbidities. Other barriers include improving overall mental wellbeing, sleep problems, reducing stress, managing mood fluctuations, as well presence of significant mental illness. Lastly, socio-ecological motivations included, the availability of professional and social support, and a lack thereof was a significant barrier. Addressing these barriers may prove significant in optimizing adoption and adherence to exercise regimens.

CONCLUSIONS AND FUTURE DIRECTIONS

Taken together, the overall evidence suggests that exercise is beneficial for individuals suffering from or predisposed to neuropsychiatric disease. However, the evidence base is still equivocal and future studies are warranted. Research should seek to first identify subtypes of neuropsychiatric disorders in which a chronic inflammatory component co-exists, then further characterize relationship between inflammation and neuropsychiatric disorders with larger-scale clinical trials. Following this, identification of biomarkers and molecular targets through genetic and transcriptomic analysis with neuroimaging and behavioral analyses will further permit pathologic and therapeutic characterization.

It is important to identify and address various barriers to the adoption and maintenance of regular and effective physical activity as a part of therapeutic programme and indeed making it a lifestyle measure in those suffering from various neuropsychiatric disorders.

Finally, clinical and economic evaluations of the longitudinal benefits of combination therapies (lifestyle measure, non-pharmacological and pharmacological therapies in various combinations) may eventually be conducive to prescribing personalized exercise regimens for neuropsychiatric disorders.

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Contribution of individual authors:

Ashwin Venkatesh & Shantal Edirappuli carried out literature search and wrote the paper.

Haris Pedersen Zaman reviewed the literature and contributed to the final draft.

Rashid Zaman conceived the idea of the paper, reviewed the literature and wrote the final draft.

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