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CRITICAL REVIEW

Be Fit, Be Sharp, Be Well: The Case for Exercise as a Treatment for Cognitive Impairment in Late-life Depression

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Abstract

Objective: To lay out the argument that exercise impacts neurobiological targets common to both mood and cognitive functioning, and thus more research should be conducted on its use as an alternative or adjunctive treatment for cognitive impairment in late-life depression (LLD). **Method:** This narrative review summarizes the literature on cognitive impairment in LLD, describes the structural and functional brain changes and neurochemical changes that are linked to both cognitive impairment and mood disruption, and explains how exercise targets these same neurobiological changes and can thus provide an alternative or adjunctive treatment for cognitive impairment in LLD. **Results:** Cognitive impairment is common in LLD and predicts recurrence of depression, poor response to antidepressant treatment, and overall disability. Traditional depression treatment with medication, psychotherapy, or both, is not effective in fully reversing cognitive impairment for most depressed older adults. Physical exercise is an ideal treatment candidate based on evidence that it 1) is an effective treatment for depression, 2) enhances cognitive functioning in normal aging and in other patient populations, and 3) targets many of the neurobiological mechanisms that underlie mood and cognitive functioning. Results of the limited existing clinical trials of exercise for cognitive impairment in depression are mixed but overall support this contention. **Conclusions:** Although limited, existing evidence suggests exercise may be a viable alternative or adjunctive treatment to address cognitive impairment in LLD, and thus more research in this area is warranted. Moving forward, additional research is needed in large, diverse samples to translate the growing research findings into clinical practice.

Keywords: Physical activity, Geriatric depression, Cognition, Mood, Antidepressant, Brain, Depression, Exercise

Depression is one of the leading causes of disability and can be particularly pernicious in older adults (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018; Vaughan, Corbin, & Goveas, 2015). A meta-analysis estimated the prevalence of current clinical depression in adults aged 50 and older to be 3.29%, with a higher rate of 19.47% for depressive symptoms (Volkert, Schulz, Harter, Wlodarczyk, & Andreas, 2013). Depression, especially in older adults, is associated with functional decline, decreased quality of life, higher healthcare utilization, increased economic burden, and increased mortality (Menchetti, Cevenini, De Ronchi, Quartesan, & Berardi, 2006). The impact of late-life depression (LLD) on daily functioning, quality of life, and other outcomes is attributable at least in part to cognitive impairment (Alexopoulos et al., 2005). Unfortunately, traditional depression treatments—pharmacotherapy and psychotherapy—are generally ineffective in resolving the cognitive impairment that often accompanies mood disorders (Butters et al., 2008; Reppermund, Ising, Lucae, & Zihl, 2009). As such, there is increasing focus on alternative interventions that might better target the underlying brain changes in LLD, thereby benefiting both mood and cognitive functioning (Morimoto & Alexopoulos, 2013). Physical exercise is a prime candidate for such an intervention. We will argue that research in this area is an important focus for the field to improve outcomes in depressed older adults.

In this narrative review, we will 1) briefly summarize the literature on cognitive impairment in LLD, 2) describe the structural and functional brain changes and neurochemical changes that are linked to both cognitive impairment and mood disruption, 3) explain how exercise targets these brain changes and can thus provide an alternative or adjunctive

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treatment for cognitive impairment in LLD, and 4) summarize the existing literature on exercise for cognitive impairment in depression, including LLD.

COGNITIVE FUNCTIONING IN LATE-LIFE DEPRESSION

Depression is a heterogeneous disorder characterized by affective, somatic, interpersonal, and cognitive symptoms. Attention, memory, and other cognitive complaints are not required for diagnosis but are nonetheless common in depressed individuals (Srisurapanont et al., 2018). Despite the discrepancy that can occur between subjective cognitive complaints and objective performance in depression, there is a large body of literature documenting objective cognitive deficits in this population (Zlatar, Moore, Palmer, Thompson, & Jeste, 2014; Zlatar, Muniz, Galasko, & Salmon, 2018). Depressed adults most often show signs of cognitive weaknesses or impairment in the domains of attention, executive functioning, learning and memory, and psychomotor speed (Koenig, Bhalla, & Butters, 2014; Morimoto & Alexopoulos, 2013).

A number of studies report a relationship between subclinical depressive symptoms and cognitive dysfunction, particularly in the area of executive or cognitive control (Dotson, Resnick, & Zonderman, 2008; Elderkin-Thompson, Mintz, Haroon, Lavretsky, & Kumar, 2006; Shimada et al., 2014). A recent meta-analysis (Dotson et al., 2020) examined cognitive control deficits in both clinical and subclinical depression across the lifespan. Across 73 studies, a total of 16,806 participants between the ages of seven and 97 were included. The meta-analysis showed that both major depression and subclinical depressive symptoms were associated with cognitive control deficits, though the relationship was weaker in subthreshold depression. The study also found that the relationship was stronger in later stages of the lifespan. In fact, effect sizes were not significant in studies that only included child, adolescent, or young adult (age ≤ 25 years) samples. The finding that older adults are more vulnerable to depression-related changes in cognitive functioning is supported by other studies as well (Dotson et al., 2008; Dotson et al., 2014; Lockwood, Alexopoulos, & van Gorp, 2002).

Cognitive dysfunction in LLD predicts both short-term and long-term adverse consequences. Studies have shown that the combination of cognitive impairment and depression in older adults is associated with an increased relapse relate, a poorer response to antidepressant treatment, and greater overall disability (Alexopoulos et al., 2000; Sneed et al., 2007). Executive dysfunction, in particular, increases the risk for functional disability in LLD (Gansler, Suvak, Arean, & Alexopoulos, 2015). Considering that normal aging is associated with declines in executive functioning, this suggests that the combination of age and depression makes depressed older adults especially vulnerable to functional decline.

PROGNOSIS OF COGNITIVE IMPAIRMENT IN LATE-LIFE DEPRESSION

The prognosis of LLD with cognitive impairment varies. One possible outcome is the development of dementia. Depression in older adults confers a nearly twofold increase in dementia risk relative to nondepressed seniors (Cherbuin, Kim, & Anstey, 2015; Diniz, Butters, Albert, Dew, & Reynolds, 2013; Ownby, Crocco, Acevedo, John, & Loewenstein, 2006). Moreover, in a longitudinal study that followed adults age 55 and older for up to 20 years, each episode of depression was associated with a 14% increase in risk for all-cause dementia (Dotson, Beydoun, & Zonderman, 2010). The link between depression and subsequent dementia is generally explained in one of three ways: Depression is a prodrome of dementia, depression lowers the threshold at which dementia is manifested, or depression-related brain changes contribute to the development of dementia (Jorm, 2001; Ownby et al., 2006). There is evidence for each of these hypotheses.

Another possible outcome is that cognitive impairment resolves with the remission of LLD. This is sometimes referred to as "pseudodementia" since the cognitive difficulties can be mistaken for a neurodegenerative disease (Connors, Quinto, & Brodaty, 2018). A recent study found that 29% of older adults with remitted depression showed signs of cognitive improvement at follow-up (Siddarth, Funes, Laird, Ercoli, & Lavretsky, 2020). However, these patients still have a high risk for developing irreversible dementia in the future (Alexopoulos, Meyers, Young, Mattis, & Kakuma, 1993; Connors et al., 2018).

The most common outcome of LLD with cognitive impairment is persistent cognitive problems after affective symptoms have remitted (Lee, Potter, Wagner, Welsh-Bohmer, & Steffens, 2007; Majer et al., 2004; Murphy & Alexopoulos, 2004; Nebes et al., 2003; Semkovska et al., 2019). Meta-analysis has shown that deficits in selective attention, working memory, and long-term memory persist in remission from a major depressive episode and worsen with repeated episodes (Semkovska et al., 2019). Cognitive impairment persists for as long as four years in longitudinal studies (Kohler, Thomas, Barnett, & O'Brien, 2010). One study (Bhalla et al., 2006) found that in remitted LLD, a staggering 94% of the patients who were cognitively impaired at baseline remained impaired one year later. More recently, analysis of data from two clinical trials revealed that less than a third of patients showed cognitive improvement after their mood remitted (Siddarth et al., 2020). Reports of persistent executive dysfunction (Koenig et al., 2015; Nakano et al., 2008) are particularly troubling in light of the aforementioned relationship between executive deficits and functional disability. Indeed, there is evidence that persistent cognitive deficits in remitted depression predicts disability, even in younger adults (Woo, Rosenblat, Kakar, Bahk, & McIntyre, 2016).

Risk factors such as lower baseline cognitive function, older age, later age of depression onset, and greater vascular

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burden are associated with worse cognitive outcomes in depression (Barch et al., 2012; Koenig et al., 2014). Conversely, lower baseline depression severity, depression onset prior to age 60, and better social functioning are associated with cognitive improvement after depression remission (Siddarth et al., 2020). The large proportion of older adults whose cognitive impairment persists after depression remission points to the need for depression treatments that address both affective and cognitive symptoms. Neurobiological contributors common to mood disruption and cognitive decline are potential treatment targets.

OVERLAPPING NEUROBIOLOGICAL CONTRIBUTORS IN DEPRESSION AND COGNITIVE IMPAIRMENT

Several recent reviews provide excellent summaries of our current understanding of neurobiological mechanisms underlying LLD (Rutherford, Taylor, Brown, Sneed, & Roose, 2017; Weisenbach & Kumar, 2014). Cognitive impairment and mood disturbance in LLD may be caused by common neurobiological contributors. Indeed, converging evidence from affective neuroscience studies show disruptions in distributed but integrated neural circuits that underlie both emotional and cognitive functioning in LLD (Butters et al., 2008; Linnemann & Lang, 2020).

Structural and functional alterations associated with depressive symptoms have been identified within the frontolimbic network, including the prefrontal and cingulate cortices, medial temporal lobes, and limbic regions (Drevets, Price, & Furey, 2008; Du et al., 2014). Specifically, the orbitofrontal cortex, dorsolateral prefrontal cortex (PFC), anterior cingulate, hippocampus, putamen, and caudate are frequently implicated in the depression literature and in many cases are disproportionately impacted at older ages (Ballmaier et al., 2004; Dotson, Davatzikos, Kraut, & Resnick, 2009; Naismith, Norrie, Mowszowski, & Hickie, 2012). These regions are highly interconnected and interact to form the neural circuitry that govern both emotional and cognitive functioning (Aziz & Steffens, 2017; Crocco, Castro, & Loewenstein, 2010; Kempton et al., 2011; Pandya, Altinay, Malone, & Anand, 2012), including memory, executive functions, attention, and processing speed. For example, hippocampal atrophy, a hallmark of memory dysfunction, is a common finding in depression (Sexton, Mackay, & Ebmeier, 2013). In fact, an ENIGMA Consortium meta-analysis found that hippocampal volume reduction in depression was the most robust finding across a number of brain regions (Schmaal et al., 2016). Stress-related glucocorticoid overproduction (hypercortisolemia), via dysregulation of the hypothalamic–pituitary–adrenal axis, promotes hippocampal cell injury and death and subsequent memory deficits in depression (Herbert & Lucassen, 2016; Keller et al., 2017).

Mood and cognitive dysfunction relate not just to changes to frontolimbic areas of the brain but also to disruption of structural and functional networks made up of these distinct brain regions (Price & Drevets, 2010). Neuroimaging studies have identified altered structural and functional connectivity in frontal-executive and corticolimbic pathways in LLD (Rashidi-Ranjbar, Miranda, Butters, Mulsant, & Voineskos, 2020). Reduced white matter integrity disrupts communication, particularly along frontolimbic circuits, resulting in a "disconnection" between cortical and subcortical brain regions (Liao et al., 2013), thereby yielding mood and executive dysregulation. Negative affectivity in LLD is associated with resting state activity differences in the dorsomedial and ventromedial PFC, as well as changes in the connections of these regions to the amygdala and the posterior cingulate cortex (Steffens, Wang, Manning, & Pearlson, 2017). Aberrant connectivity is also observed in the executive control, default mode, and salience network that mediate internally oriented and self-referential thought and cognitive functions such as attention and cognitive control (Kaiser, Andrews-Hanna, Wager, & Pizzagalli, 2015; W. Li et al., 2017).

Neurovascular changes have also been linked to both cognitive impairment and mood disorders. The importance of vascular pathology in LLD has long been recognized. The "vascular depression" hypothesis was introduced by Alexopoulos and colleagues (1997) over 20 years ago, bringing into focus the role of cerebrovascular disease in predisposing, precipitating, and perpetuating depression in older adults. Neuroimaging evidence is consistent with this hypothesis. White matter hyperintensities, which are typically associated with ischemic damage (Lin, Wang, Lan, & Fan, 2017), occur more often in depressed compared to nondepressed older adults (Greenstein et al., 2010; Joel R. Sneed, Rindskopf, Steffens, Krishnan, & Roose, 2008) and are associated with subthreshold depressive symptoms as well (Dotson, Zonderman, Kraut, & Resnick, 2013; Kirton, Resnick, Davatzikos, Kraut, & Dotson, 2014). Diffusion tensor imaging studies reveal altered white matter connectivity in depression. LLD is also associated with impaired arterial function and abnormal wall structure (Greenstein et al., 2010). These white matter changes in LLD are associated with slower processing speed and executive dysfunction (Respino et al., 2019; Ye et al., 2017).

Overlapping neuromolecular changes also occur in depression and cognitive impairment. The inflammatory immune response, if prolonged, causes a number of adverse changes to the central nervous system. According to the "inflammaging" hypothesis, aging is a process of chronic inflammation that increases mortality risk in older adults (Franceschi & Campisi, 2014). The release of proinflammatory cytokines impact serotonergic, noradrenergic, and dopaminergic neuronal circuits that mediate both depression and cognitive functions such as processing speed, executive functions, and memory (Miller & Raison, 2016; Ownby, 2010; Rutherford et al., 2017; Teixeira, Barbosa, Diniz, & Kummer, 2010). Additionally, studies have demonstrated differences in the circulation of neurotrophic factors between older adults with LLD and healthy

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controls. For example, significant reductions of brain-derived neurotrophic factor (BDNF) and glial cell-line derived neurotrophic factor levels have been observed in adults with late-onset depression compared to matched controls (Diniz et al., 2010; Teixeira et al., 2010). Polymorphisms in the BDNF gene have also been linked to depression risk and response to antidepressant treatment (Amare, Schubert, & Baune, 2017; Nestor et al., 2019). BDNF has a potent effect on synapses and a strong role in learning and memory (Ownby, 2010).

These neurobiological alterations often interrelate. For example, decreased BDNF expression and signaling result in reduced neuroplasticity associated with neuronal atrophy and reduced synaptic plasticity, particularly in the medial PFC and hippocampus (Diniz et al., 2014; Duman & Aghajanian, 2012). Changes in proinflammatory processes and neurotrophic function contribute to hippocampal volume reduction in depression (Audet & Anisman, 2013; Frodl et al., 2007). Moreover, prolonged hypercortisolemia and vascular pathology have both been linked to proinflammatory changes associated with functional changes in brain networks (Butters et al., 2008; Maier, Makwana, & Hare, 2015).

In sum, several neurobiological mechanisms appear to work in concert to mediate mood and cognitive function. Studies suggest that stress-related, neurodegenerative, inflammatory, and vascular processes contribute to dysregulation in multiple parallel and synergistic neural circuits that underlie cognitive impairment in LLD. The overlapping neural underpinnings of mood and cognitive functioning are natural treatment targets for LLD with cognitive impairment.

EXERCISE AND NEUROBIOLOGICAL CHANGES IN LATE-LIFE DEPRESSION

Exercise may be an ideal treatment for LLD with cognitive impairment because of its impact on neurobiological mechanisms that are important for both mood and cognitive functioning. Over the past few decades, exercise has come to be recognized as an effective treatment for mood symptoms in depression equivalent to psychological and pharmacological treatments. The literature on the mood benefits of exercise has been summarized in a number of reviews and meta-analyses (Kvam, Kleppe, Nordhus, & Hovland, 2016; Md Zemberi, Ismail, & Abdullah, 2020; Zhang, Xiang, Li, & Pan, 2021) and will not be repeated here, rather, we highlight the neurobiological mechanisms that might underlie these benefits. It should be noted that the literature not only supports the benefits of exercise—planned, structured physical activity that is intended to improve or maintain physical fitness—but also physical activity in general, that is, any intentional movement that expends energy.

Exercise is a particularly powerful treatment because it improves mood symptoms while also providing protection from age-related brain atrophy (Colcombe et al., 2003), contributing to neuroplasticity in the hippocampus, PFC, and anterior cingulate (Kandola, Ashdown-Franks, Hendrikse, Sabiston, & Stubbs, 2019), and inducing volumetric increases in both gray and white matter regions that overlap with depression-related volume reductions (Gujral, Aizenstein, Reynolds, Butters, & Erickson, 2017). For example, in contrast to hippocampal volume reduction in depression (Sexton et al., 2013), high cardiorespiratory fitness, the ability of the heart, lungs, and vascular system to supply the muscles with oxygen during sustained physical activity, is associated with larger hippocampal volumes among older adults (Erickson, Leckie, & Weinstein, 2014; Gujral et al., 2017; Kvam et al., 2016). Even low-intensity exercise such as training in coordination and balance has been shown to increase hippocampal volume over time (Niemann, Godde, & Voelcker-Rehage, 2014). Increased hippocampal tissue density (Kleemeyer et al., 2016) and vascular plasticity (Maass et al., 2015) driven by exercise may underlie these macro-level volume changes.

While depression is generally associated with volume reductions in prefrontal regions (Bora, Harrison, Davey, Yucel, & Pantelis, 2012), a recent meta-analysis of randomized controlled trials revealed that, compared to control interventions, exercise interventions significantly increase gray matter volume bilaterally in the medial and superior frontal gyri, as well as the inferior frontal gyrus, left cingulate gyrus, and right anterior cingulate (Zheng et al., 2019). Aerobic exercise has also been linked to larger dorsolateral PFC (Jonasson et al., 2017) and superior frontal volumes among older adults (Bugg & Head, 2011). Thus, exercise appears to promote structural brain integrity across the hippocampus and regions of the PFC relevant to depression.

Both structured exercise and everyday physical activity also counteract white matter damage in depression (Reppermund et al., 2014; Respino et al., 2019), preserving white matter integrity across a number of frontolimbic white matter tracts important for emotion regulation, including the corpus callosum and uncinate fasciculus (Loprinzi, Harper, & Ikuta, 2020; Strommer et al., 2020). A systematic review of studies examining physical fitness or physical activity concluded that overall, higher physical fitness and higher physical activity levels are associated with better white matter structure in older adults, including greater white matter volumes, reduced volume and severity of white matter lesions, and improved measures of white matter microstructure (Sexton et al., 2016).

Exercise promotes functional connectivity in the brain, which is important in light of the disrupted functional connectivity reported in LLD (Tadayonnejad & Ajilore, 2014). For example, a systematic review examining the effects of aerobic exercise on structure and functioning within the default mode network reported that aerobic exercise interventions increased functional connectivity between the hippocampus, cingulate cortex, and other medial temporal areas of the default mode network (Li et al., 2017). Nonaerobic exercise including stretching, toning, and yoga has also been found to improve functional connectivity in the default mode network (Gothe, Khan, Hayes, Erlenbach, & Damoiseaux, 2019; Voss et al., 2010).

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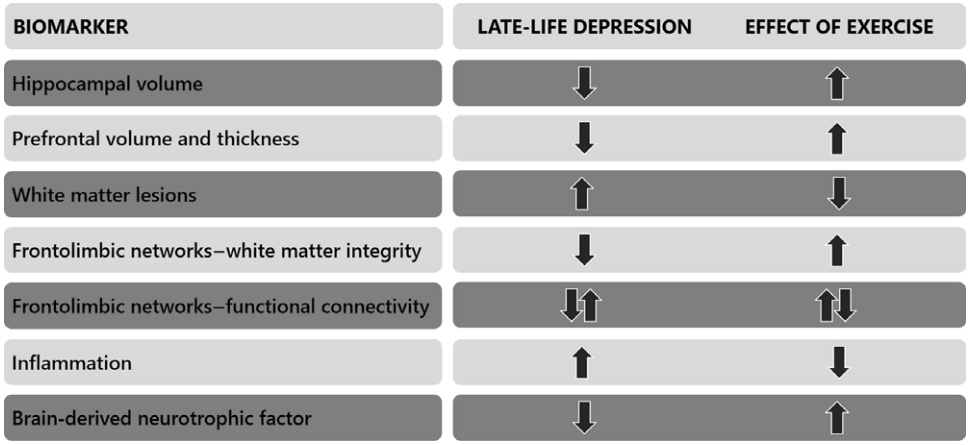

Fig. 1. Summary of neurobiological changes in late-life depression that may be reversed by physical exercise.

Exercise appears to counteract reductions in BDNF that are reported in depression. Aerobic exercise, and potentially strength training, facilitates BDNF expression (Szuhany, Bugatti, & Otto, 2015). The effect is observable after a single exercise session, but is greater in long-term exercise interventions (Szuhany et al., 2015). It should be noted that while animal studies consistently show that exercise can elevate BDNF in the brain (Voss, Vivar, Kramer, & van Praag, 2013), meta-analyses of human studies have produced mixed results when examining whether exercise increases serum or plasma BDNF levels in depression. There is evidence that polymorphisms in the BDNF gene moderate the antidepressant effect of exercise (Dotson et al., 2016).

Overall, the widespread benefits of exercise on the aging brain, particularly in areas negatively impacted by depression (Figure 1), point toward the importance of continuing to study exercise interventions for LLD. Most research focuses on aerobic exercise, which requires more energy expenditure that leads to vascular changes and higher oxygen and glucose consumption (Stimpson, Davison, & Javadi, 2018), but other exercise modalities have brain benefits as well.

EXERCISE EFFECTS ON COGNITIVE FUNCTIONING

Despite the longstanding use of exercise to improve mood in depression, less focus has been put on prescribing exercise for cognitive impairment in LLD. Exercise, especially aerobic exercise, has been shown to improve cognitive function in healthy individuals across the lifespan and among different patient populations (Berwid & Halperin, 2012). Physical activity and long-term exercise have been shown to improve cognitive functioning, preserve cognitive functioning over time, and even prevent or delay dementia in older adults (Sofi et al., 2011). A meta-analysis of 39 randomized controlled trials found that in people over the age of 50, physical exercise improved cognitive functioning, including executive function, memory, and working memory (Northey, Cherbuin, Pumpa, Smee, & Rattray, 2018). Aerobic exercise, resistance training, multicomponent training, and tai chi were all found to be effective. Interventions that included 45- to 60-minute sessions of moderate or vigorous aerobic or resistance activities showed the strongest effects. Other studies have shown that resistance training improves spatial learning and memory, associative memory, cognitive control, and selective attention in older adults (Cassilhas et al., 2007; Liu-Ambrose, Nagamatsu, Voss, Khan, & Handy, 2012). It has been suggested that multicomponent training, involving aerobic and resistance training, may be more beneficial for global cognition than aerobic training alone (Saez de Asteasu, Martinez-Velilla, Zambom-Ferraresi, Casas-Herrero, & Izquierdo, 2017).

The body of literature examining the cognitive benefits of exercise for depression is relatively small and characterized by mixed findings. Although this is a narrative review, we systematically searched the literature in February 2021 using PubMed and PsycInfo to identify studies with this focus. Briefly, the PubMed search terms were "exercise AND cogn* AND depress*[Title] AND Humans[Mesh] NOT "review"[Publication Type] NOT meta-analysis[Title]". The PsycInfo search terms were "exercise AND cogn* AND TI depress*", and for Methodology we excluded literature review, meta-analysis, and systematic review. We then repeated each search substituting "cogn*" with "memory," "executive," "speed," "attention," "language," and "visu*". We will summarize the relevant studies that this systematic search identified.

A recent study (Olson, Brush, Ehmann, & Alderman, 2017) randomized depressed outpatients to an eight-week intervention involving three 45-minute sessions per week of either aerobic exercise or light-intensity stretching. Participants in the aerobic exercise group demonstrated significant improvements in cognitive control, as measured by reduced reaction time on a flanker task, which consists of a set of response inhibition tasks that require selective attention and inhibitory control. The aerobic exercise group also showed an increase in the amplitude of the event-related potential N2 component on incongruent trials. These findings suggest enhanced conflict monitoring and cognitive

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control—an aspect of executive functioning—after engaging in regular aerobic exercise. In a longer 12-week exercise intervention, Greer, Grannemann, Chansard, Karim, and Trivedi (2015) showed that aerobic exercise improved performance across several cognitive domains in depressed individuals, including psychomotor speed, visuospatial memory, and executive function. For individuals who exercised the most, improvements were also noted in spatial working memory. Similarly, aerobic exercise interventions led to greater improvement in cognitive functions including processing speed, working memory, and visual memory compared to control interventions in other studies (Krogh, Videbech, Thomsen, Gluud, & Nordentoft, 2012; Oertel-Knöchel et al., 2014), including a study that examined the acute effects of 30 minutes of aerobic exercise (Kubesch et al., 2003). Moreover, Buschert et al. (2019) found significant improvements in reaction time and immediate memory in depressed inpatients who participated in an average of ten 30-minute aerobic exercise sessions compared to the active controls who underwent occupational therapy. No differences in executive function were noted post-intervention. In a large sample of 3,658 participants with either subsyndromal or clinical depression, self-reported physical activity was positively associated with processing speed and verbal fluency in men (Joutsenniemi et al., 2013). Another study of self-reported physical activity found lower physical activity levels were associated with worse global cognitive functioning (Sanchez-Carro et al., 2021).

Despite these positive findings, other studies have failed to find an effect. For example, a four-month study comparing aerobic exercise, strength training, and relaxation training did not find an effect of either exercise intervention on cognitive functioning (Krogh, Saltin, Gluud, & Nordentoft, 2009). A recent meta-analysis in this area (Sun, Lanctot, Herrmann, & Gallagher, 2018) included 9 studies and, consistent with a previous meta-analysis (Brondino et al., 2017), failed to find a significant benefit of exercise for cognition in major depression in the overall analysis. However, positive findings were found when (a) exercise was combined with cognitive training and (b) in lower-intensity interventions, presumably due to the significantly better treatment adherence that was also found in the meta-analysis. Importantly, the authors noted several limitations to their findings. First, the mean dosage of exercise used in the included studies (131 minutes) was below the World Health Organization guidelines of 150 minutes of moderate intensity exercise per week (World Health Organization, 2019). In addition, cognitive impairment was not an inclusion criterion for any study in the meta-analysis, resulting in a general lack of cognitive impairment at baseline. This left little room for improvement (i.e., a ceiling effect), and research suggests that those with greater cognitive impairment may benefit more from exercise interventions (Smith et al., 2010). Overall, the lack of scientifically rigorous studies in this field suggests these results should be interpreted with discretion.

Even less research has addressed the impact of exercise on cognition in depressed older adults in particular. In an intervention study, Neviani et al. (2017) randomly assigned 121 depressed older adults to an (a) antidepressant medication group, (b) antidepressant plus nonaerobic exercise group, or (c) antidepressant plus progressive aerobic exercise group. After the six-month intervention, older adults in the antidepressant plus progressive aerobic exercise group showed significant improvements in Montreal Cognitive Assessment total scores as well as visuospatial/executive and language subdomains. Of note, disability scores improved after the intervention as well. Participants in the nonaerobic exercise group did not show significant cognitive differences compared with the control group. Benefits of exercise have been shown in shorter interventions as well. Depressed middle-aged to older adults who spent four months in an aerobic exercise intervention showed greater improvements in memory and executive functions than their peers who received antidepressant medication (Khatri et al., 2001). Another study found that 12 weeks of exergames improved cognitive functioning in older adults with subsyndromal depression (Rosenberg et al., 2010). In contrast, a small pilot study that compared six older depressed inpatients who completed a 4-week exercise program involving aerobic, strength, and coordination exercises to six who received relaxation training did not find any changes in cognitive functioning (Heissel et al., 2015). The small sample size, short time frame, or the severity of depression in the inpatient sample might all contribute to the null results. It should be noted that at least one study suggests an acute benefit of aerobic exercise on inhibitory control but not on immediate memory or working memory (Vasques, Moraes, Silveira, Deslandes, & Laks, 2011).

Studies that examine self-report of physical activity provide supporting evidence that exercise might benefit cognitive functioning in LLD. In a recent cross-sectional study examining data from 2,604 adults aged 60 and older from the National Health and Nutrition Examination Survey (Hu, Smith, Imm, Jackson, & Yang, 2019), verbal fluency and processing speed were preserved even in moderately to severely depressed older adults who maintained a sufficient level of physical activity (≥ 150 min/week moderate-to-vigorous physical activity). Similarly, two studies with middle aged or older samples with depression found positive relationships between higher self-reported exercise frequency and cognitive functioning (Pitts et al., 2020; Yuan, Fu, Liu, & Fang, 2020).

Overall, the research in this area is limited, but the emerging evidence supporting the procognitive effects of exercise in LLD is promising.

FUTURE DIRECTIONS

Physical exercise has the potential to be an accessible and effective treatment for cognitive impairment in LLD. Overall, there is a strong body of literature supporting

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the benefits of exercise as a treatment for affective symptoms in depression and as a positive modifier of cognitive and brain aging in nondepressed older adults (Chen et al., 2020; Kvam et al., 2016; Md Zemberi et al., 2020; Quigley, MacKay-Lyons, & Eskes, 2020; Zhang et al., 2021). Studies specifically examining the impact of exercise on cognitive impairment in LLD are more limited, but emerging studies are encouraging. Much more work is needed in this area in order to translate the growing research findings into clinical practice. Clinical translation will need to address issues of motivation and adherence, since depressed mood and related symptoms, such as loss of interest and energy, fatigue, and low self-worth, are common barriers to participation in exercise (Firth et al., 2016; Knapen, Vancampfort, Morien, & Marchal, 2015).

Large randomized clinical trials are needed, focused on the impact of different forms of exercise on impairment in different cognitive functions in LLD. Although aerobic exercise interventions are most common, studies have shown that other forms of exercise can benefit mood, cognitive functioning, and brain health, including resistance training, yoga, and tai chi (Gordon et al., 2018; Gothe et al., 2019; Wayne et al., 2014). Future studies should seek to determine which forms of exercise, or combination of forms, is most effective for ameliorating cognitive impairment in LLD. Similarly, there is evidence that exercise can benefit a variety of cognitive functions (Northey et al., 2018), but more research is needed to understand whether different forms of exercise are differentially beneficial for specific cognitive deficits in LLD. Executive dysfunction is particularly important to target since executive abilities are affected in normal aging as well as depression and are predictive of functional decline (Gansler et al., 2015).

It is important for future studies to consider the demographic and clinical heterogeneity within the population of depressed older adults. Clinically, there is growing evidence that cognitive and brain changes, response to treatment, and clinical outcomes differ depending on the severity of specific dimensions of depressive symptoms, such as affective, somatic, and cognitive symptoms (Lugtenburg, Zuidersma, Oude Voshaar, & Schoevers, 2016; Majd, Saunders, & Engeland, 2020; McLaren et al., 2017; Schouten et al., 2019). There is also preliminary evidence that the antidepressant effect of exercise varies across symptom dimension in older adults (Dotson et al., 2016; Murri et al., 2018). Thus, future studies should seek to determine whether there are subtypes of LLD based on clinical presentation that are more responsive to the mood and cognitive enhancing effects of exercise.

Also important is the impact of sex, race/ethnicity, socioeconomic status, and other aspects of diversity on both the efficacy and the feasibility of implementing exercise as an intervention for cognitive impairment in LLD. Demographic factors have been shown to impact risk for and outcomes of depression, trajectories of cognitive and brain aging, as well as access to and participation in structured exercise (Komulainen et al., 2008; Vyas et al., 2020). In order for this area of research to be relevant to the increasingly diverse population of older adults, it is critical for studies to consider aspects of diversity in their design and analysis (Dotson & Duarte, 2020).

Neuroimaging studies will be helpful in identifying the neurobiological mechanisms underlying exercise-related improvements in cognitive functioning in LLD. Although a systematic review concluded that exercise produces changes in cortical activity, endocrine response, and oxidative stress in depression (Schuch et al., 2016), and there is evidence that cardiorespiratory fitness is associated with cortical thickness in LLD (Gujral et al., 2019), it is still unclear whether these changes mediate the relationship between exercise and cognitive functioning. Alternatively, or perhaps in conjunction, it is possible that exercise-related reductions in depression lead to improved cognitive functioning. For example, in a sample of older adults, some with mild cognitive impairment, Vance et al. (2016) used structural equation modeling to show a path from higher self-reported physical activity to lower depressive symptoms, which in turn related to better cognitive ability. Clarifying the mechanism underlying any cognitive enhancing effects is important, as it will aid in identifying other treatments for cognitive impairment in LLD that can target those mechanisms.

Finally, future studies should examine the benefits of combined interventions for cognitive impairment in LLD. For example, there is evidence suggesting that the combination of cognitive and exercise training is more beneficial than either intervention alone (Karssemeijer et al., 2017). Such interventions can involve either simultaneous cognitive challenge and physical exercise (such as performing a cognitive feat while walking) or a program that includes both cognitive training and physical exercise activities performed asynchronously. In addition, omega-3 fatty acids, antioxidants such as Vitamin E, and polyphenols have been shown to enhance the effects of exercise on cognition and BDNF-related synaptic plasticity in nonhuman animal subjects (Gomez-Pinilla & Nguyen, 2012; Sakr, Abbas, & El Samanoudy, 2015; Wu, Ying, & Gomez-Pinilla, 2008), though limited studies have been conducted in humans (Bischoff-Ferrari et al., 2020; Schattin et al., 2019).

CONCLUSION

Depression in older adults is a risk factor for a number of negative outcomes, in part due to comorbid cognitive impairment that is common in this population. Traditional treatments often result in improved mood yet lingering cognitive and brain changes that put depressed older adults at risk for recurrence of depression, functional decline, and dementia. Treatments are needed that target the underlying neurobiological changes that contribute to both cognitive impairment and mood disruption. Exercise appears to have potential as an alternative or adjunctive treatment given its known impact on depression, on cognitive functioning in older adults and in other patient populations, and on many of the neurobiological mechanisms linked to depression

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and cognitive functioning. Additional research in this area in large, diverse samples has the potential to tremendously impact the health and well-being of the growing population of older adults.

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CONFLICT OF INTEREST

VMD is owner of CerebroFit LLC.

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