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Default Mode Functional Connectivity, Aerobic Exercise, and Depressive Symptoms: A Resting-State fMRI Study

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ABSTRACT

Depressive symptoms are common in older adults. Previous studies have shown that aerobic exercise is effective in treating depression and improves brain function. The goal of the current study was to determine the interrelationships between aerobic exercise, default mode network (DMN) functional connectivity, and depressive symptoms in thirty-eight healthy older adults. Results showed that (a) increased connectivity within the DMN and to the sgACC is associated with greater depressive symptoms at baseline, (b) decreases in functional connectivity within the DMN after a 12 week exercise intervention were greater for participants in the aerobic group relative to the control group, and (c) there is a positive association between changes in DMN functional connectivity and changes in depressive symptoms, but a negative association between other regions of the brain. These findings suggest that changes in resting-state functional connectivity are associated with changes in depressive symptoms in older adults with subthreshold depressive symptoms.

INDEX WORDS: Default mode network, Resting-state, Functional connectivity, Exercise, Depression, Aging
DEFAULT MODE FUNCTIONAL CONNECTIVITY, AEROBIC EXERCISE, AND DEPRESSIVE SYMPTOMS: A RESTING-STATE fMRI STUDY

by

ANDREW GRADONE

A Thesis Submitted in Partial Fulfillment of the Requirements for the Degree of Master of Arts in the College of Arts and Sciences

Georgia State University

2020
DEFAULT MODE FUNCTIONAL CONNECTIVITY, AEROBIC EXERCISE, AND DEPRESSIVE SYMPTOMS: A RESTING-STATE fMRI STUDY

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August 2020
DEDICATION

This work is dedicated to my parents, family, and girlfriend. Without their continued support, none of this would have been possible.
ACKNOWLEDGEMENTS

I extend my utmost gratitude to my mentor and committee chair, Dr. Vonetta Dotson, whose guidance, encouragement, and enthusiasm throughout this process was instrumental in its completion. I also thank my committee members—Dr. Keith McGregor, Dr. Sarah Barber, and Dr. Joe Nocera—for their immense support. I am particularly indebted to Dr. McGregor, who spent countless hours of his own time teaching me the imaging methodology I needed to run the analyses for this project. This dataset was collected by Dr. McGregor and Dr. Nocera, and I am extremely grateful to both for sharing it with me. Additionally, I am thankful for the scholarly knowledge, contributions, and critiques provided by Dr. Nocera and Dr. Barber. Finally, I thank the Brains & Behavior Program for their funding and support.
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1 INTRODUCTION

1.1 Subthreshold Depression in Older Adults

1.1.1 Epidemiology

Millions of people worldwide suffer from functional impairment and disability due to depressive symptomology, yet do not meet DSM-5 criteria for major depressive disorder (MDD). Termed subthreshold depression (SubD), this illness affects many more people than MDD, and is particularly prevalent in older adults (Meeks, Vahia, Lavretsky, Kulkarni, & Jeste, 2011). Research has shown SubD’s prevalence rate is 31.1% in adults over the age of 65, relative to 6.3% for MDD (Judd & Kunovac, 1998). Prevalence rates also vary depending on the setting, with rates increasing from community (10%) to primary care (25%) to long-term care settings (45-50%) (Meeks et al., 2011). If an individual has SubD, the risk of developing MDD is also increased, with the one-year and two-year conversions to MDD being 10% and 25%, respectively (Broadhead, Blazer, George, & Tse, 1990; Wells, Burnam, Rogers, Hays, & Camp, 1992). In terms of the longitudinal course of late-life SubD, prospective studies of individuals with SubD of at least one year in duration have shown remission rates of approximately 27% (Vuorilehto, Melartin, & Isometsä, 2009). One particular study of patients in primary care found a 55% remission rate for SubD at 18-month follow up compared to a 38% remission rate for MDD (Vuorilehto et al., 2009). The overall findings from the literature show that SubD is common in older adults—especially in less independent settings. These statistics also show the importance of targeting depressive symptoms before they manifest into full MDD as the prognosis is always better for SubD patients.

Research has also uncovered several adverse public health outcomes and individual outcomes for those affected by late-life SubD. In terms of public health outcomes, longitudinal
studies have shown increased healthcare utilization for those with SubD (Beekman, Deeg, Braam, Smit, & Van Tilburg, 1997). Moreover, the individual negative health consequences of late-life SubD are significant and include: cognitive deficits (Elderkin-Thompson et al., 2003), decreased physical health (Beekman et al., 1997), and increased suicidal ideation (Chopra et al., 2005). Clearly, SubD is an important mental health problem that must be addressed.

1.1.2 Frontal-subcortical Structural Changes in Depression

Both subthreshold and major depression have been associated with structural brain changes, which involve a network of frontal-subcortical regions. Although the depression network is expansive, the prefrontal cortex (PFC), hippocampus, and amygdala are among the most studied regions in this network (Palazidou, 2012). Within the PFC, several areas are functionally relevant to the depression network. The ventromedial PFC is necessary for generating social emotions and regulating autonomic responses, pain, aggression, sexual behavior, and eating behaviors (Palazidou, 2012). The orbital PFC corrects behavioral and emotional responses (which are commonly generated in subcortical areas like the amygdala), and the dorsolateral PFC is involved in cognitive control and executive functioning (Palazidou, 2012). Imaging studies have shown volumetric reductions in all three of these PFC regions for people with MDD and late-life depression (Koolschijn, Haren, Lensvelt-Mulders, Pol, & Kahn, 2009; Naismith, Norrie, Mowszowski, & Hickie, 2012; Rajkowska et al., 1999).

The amygdala is a subcortical region that is commonly implicated in depression. This structure is involved in emotional learning/memory and regulating cortical arousal to surprising and ambiguous stimuli. The amygdala also plays a role in rumination, which is the keen attention to one’s own distress and the thoughts and concerns surrounding it (MacDonald, Cohen, Stenger, & Carter, 2000). Research examining amygdala volumes in people with MDD has yielded
inconsistent results, but functional imaging studies consistently show functional abnormalities in this population (Hamilton, Siemer, & Gotlib, 2008; Young, Siegle, Bodurka, & Drevets, 2015).

The hippocampus is another well studied region within the depression literature. This region is relevant to MDD because it plays a central role in learning and memory, is one of the few brain regions where neurogenesis continues to occur in the adult brain (i.e., this region is relatively plastic), and is rich in corticosteroid receptors and functionally linked to the hypothalamic-pituitary-adrenal (HPA) axis (Palazidou, 2012). Many studies have demonstrated volumetric reductions in the hippocampus in depressed populations. Evidence has demonstrated that people with more severe depression have smaller volumes, but clinical improvement can reverse these volumetric changes, possibly due to neurogenesis in this region (Frodl et al., 2004; Videbech & Ravnikilde, 2004).

Other structures that are also implicated in the depression network include the medial thalamus, ventral striatum, hypothalamus, and more (see Figure 1.1). Although this network is very complex, a state of depression appears to be maintained when a deactivated PFC fails to effectively regulate overactive limbic structures (Palazidou, 2012). This dysregulation likely leads to a clinical manifestation of depressive symptomology.
1.1.3 Structural Brain Changes in Subthreshold Depression

Although the current imaging literature on subthreshold depression is relatively limited, the few studies in this area provide support that SubD encompasses structural and functional brain changes similar to those found in patients with MDD, albeit to a lesser extent. Szymkowicz et al. (2018) directly related severity of subthreshold depressive symptoms to frontal-subcortical brain volumes in a sample of middle-aged to older adults. In this study, researchers found that greater depressive symptomology, especially for somatic symptoms, was associated with smaller volumes in limbic brain regions. This finding has been supported by other studies showing reduced gray matter in hippocampal areas for older adults with SubD symptoms (Zhou et al., 2016). Other research provides support for reduced gray matter in orbitofrontal cortex, anterior

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**Figure 1.1**: Connections between frontal and limbic structures in limbic-cortico-striato-pallido-thalamic circuit (Palazidou, 2012)
cingulate (ACC), and thalamus for individuals with SubD (Webb, Weber, Mundy, & Killgore, 2014). It should be noted, however, that not all findings are consistent. Some studies have shown increased volumes, but this could be the result of a few different factors. For instance, low levels of depressive symptoms may be insufficient to detect differences in brain regions. Alternatively, an early inflammatory response may increase cortical thickness and thereby increase volumes in SubD, but prolonged neurotoxic effects may ultimately reduce cortical thickness and brain volume over time (Szymkowicz et al., 2016). Regardless of the explanation, the research supports that individuals with SubD have altered brain volumes in frontal-subcortical regions.

1.1.4 Changes in Neural Circuitry

In MDD, the three neural circuits that appear to be most implicated involve dorsolateral prefrontal cortex (DLPFC), ACC, and orbitofrontal cortex (Naismith et al., 2012). The orbitofrontal cortex is a part of the paralimbic cortical circuit and is involved in higher-order cognitive functions which include integrating of emotion, behavior, and other sensory processes (Naismith et al., 2012). The ACC has been identified as a critical region in the pathophysiology of depression. The dorsal subdivision, which includes the DLPFC and hippocampus, is purported to be involved in executive functioning and helps to regulate the cognitive aspect of emotional responses (Phillips, Drevets, Rauch, & Lane, 2003). The ventral subdivision evaluates the salience of emotional stimuli and aids in the generation and regulation of emotional responses (Phillips et al., 2003). Limbic structures, such as the amygdala and hippocampus, have dense connections with these circuits and play a key role in mental processes such as memory and assigning emotional significance to stimuli (Naismith et al., 2012).

It must be stressed that depression is not the result of acute dysfunction in any single one of these regions or circuits. This demonstrates a crucial point—emphasized by Mayberg in one
of her seminal papers on the limbic-cortical dysregulation model—that depression “can be conceptualized as a multidimensional, systems-level disorder affecting discrete, but functionally integrated, pathways” (Mayberg, 2003). It is not the dysfunction of one or more regions, but the failure of the whole system to maintain homeostatic control under stress.

1.2 Resting-State Networks and Depression

With advances in neuroimaging methodologies, recent studies have examined functional connectivity between discrete brain regions. Much of this network approach research has been done using resting-state networks. The resting-state is an ill-defined condition where an individual is awake and alert but not engaged in any goal-directed cognitive task (Dutta, McKie, & Deakin, 2014). Resting-state functional imaging studies have sought to identify functional patterns of brain activity among people during rest. The discovery of long-range coherent signal fluctuations across widely spaced brain regions indicates the potential existence of a resting-state network (De Luca, Beckmann, De Stefano, Matthews, & Smith, 2006). Using a sample of healthy controls and patients with remitted depression, Veer et al. (2010) identified 13 resting-state networks relevant to depression. Among these networks were salience network, affective network, cognitive control network, and default mode network (DMN)—which tend to be the most commonly disrupted networks in patients with MDD (Dutta et al., 2014; Mulders, van Eijndhoven, Schene, Beckmann, & Tendolkar, 2015). Of all of these, however, the DMN is by far the most studied and uniformly disrupted network throughout the depression literature (Dutta et al., 2014). For this reason, the current study has a central focus on DMN.

1.2.1 Default Mode Network

The DMN was originally identified as a group of brain regions that are active at rest and deactivated during tasks (hence the alternative name of “task-negative network”) (Raichle et al.,
In other words, these brains regions activate when individuals are left to think to themselves without being disturbed by external stimuli, termed self-generated thought (Andrews-Hanna, Smallwood, & Spreng, 2014). Beyond spontaneous thought, the default mode network has also been shown to be involved in remembering the past, envisioning the future, and taking the perspectives of other people (Buckner & Carroll, 2007).

The DMN is often divided into two main sub-networks: the anterior and posterior DMN. The anterior DMN centers on the medial prefrontal cortex (mPFC) while the posterior DMN centers on the posterior cingulate cortex and the precuneus (Andrews-Hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010; Buckner, Andrews-Hanna, & Schacter, 2008). Although both anterior and posterior DMN are involved in self-generated thought, the anterior DMN has a stronger role in emotion regulation and self-referential cognition. This makes sense because the anterior DMN has strong connections to the limbic system. The posterior DMN is more involved in consciousness and memory processing as it has connections to the hippocampal formation (Andrews-Hanna et al., 2014; Mulders et al., 2015). Of note, the most recent literature—which has used high-resolution analyses of individual humans as well as neuronal recordings in animal models—suggests that the DMN is not one network, but a series of interwoven, parallel networks each with their own specialization (Buckner & DiNicola, 2019).

### 1.2.2 Default Mode Network and Depression

As previously mentioned, the default mode network is among the most consistently studied networks that show alterations in patients with MDD. The relationship between the DMN and MDD is almost intuitive; the DMN is involved in self-referential thought, while self-focused ruminative thoughts are characteristic of MDD. Studies have shown support for this relationship using functional neuroimaging (Hamilton, Farmer, Fogelman, & Gotlib, 2015). Most of these
studies involve a comparison between DMN connectivity in depressed and healthy individuals using seed-based functional connectivity or independent component analysis. Although all of these studies find alterations in the subsystems of the DMN in MDD patients, each study suggests slightly different patterns, which is likely the result of the countless number of ways these data can be analyzed (Sambataro, Wolf, Pennuto, Vasic, & Wolf, 2014; Zhu et al., 2012). A recent meta-analysis, which compiled data from seven of these studies, showed that one of the key features of MDD was increased functional connectivity between the DMN and subgenual anterior cingulate cortex (sgACC; also known as subgenual prefrontal cortex) (Hamilton et al., 2015). The sgACC has mainly been studied in the context of depression and low mood, and underlies behavioral withdrawal, resource conservation, and safety behaviors (Hamilton et al., 2015; Yang et al., 2009). The increased functional connectivity between the DMN and sgACC is hypothesized to reflect a functional integration of the properties of both the DMN and sgACC. That is, the sgACC processes related to behavioral withdrawal, in combination with the DMN’s role in self-referential thought and emotion regulation, is proposed to create the ruminative, self-focused, and withdrawn state of mind that is commonly associated with MDD (Hamilton et al., 2015). Findings from this meta-analysis strongly suggest that it is not just the DMN, but the abnormal connections between the DMN and sgACC that account for the depressive rumination and maladaptive thought pattern seen in MDD (Hamilton et al., 2015). Whereas a healthy DMN would be involved in prospection, reminiscing, and daydreaming, the integrated sgACC and DMN network is involved in rumination, brooding, and reflection (Hamilton et al., 2015).
1.3 The Impact of Exercise on Depressive Symptomology

There is a growing interest in treatments that target the fronto-limbic brain changes that were just described. One such intervention is exercise. Decades of exercise research have shown the effectiveness of this intervention for depressive symptom reduction.

In a recent meta-analysis of this literature, Schuch, Vancampfort, Richards, et al. (2016) analyzed data from 25 randomized control trials, which included a total of 1,487 adults with depression. This meta-analysis collapsed data from previous studies into participants who were randomly assigned to an exercise condition (aerobic/resistance) and those randomly assigned to a control condition. After adjusting for publication bias, results demonstrated a large significant improvement favoring the exercise condition. This effect was larger for outpatients, individuals without other psychiatric comorbidities, and when participants were supervised by exercise professionals. This study concluded that there was robust evidence supporting exercise as an evidence-based treatment for depression. Most notably, a fail-safe assessment indicated that over 1,000 studies showing negative results would be needed to invalidate these findings, exhibiting the strength of exercise as an antidepressant. The results of this meta-analysis are supported by numerous other reviews on exercise and depression (Daley, 2008; Gordon et al., 2018; Schuch, Vancampfort, Rosenbaum, et al., 2016; Ströhle, 2009).

Also demonstrating the effectiveness of exercise as an antidepressant, Dimeo, Bauer, Varahram, Proest, and Halter (2001) showed that even a short exercise program could produce a clinically relevant decrease in depression severity scores. In this study, 12 MDD patients were enrolled in a 10-day exercise intervention that consisted of 30 minutes of aerobic exercise each day. Results from this study showed statistically significant and clinically significant reductions in both objective and subjective ratings of depression. These findings are noteworthy because (a)
all participants in this study suffered from treatment-resistant depression, and (b) 10 days is a short period of time to observe clinically significant results. Exercise, even in short bouts, can reduce depressive symptomology.

Furthermore, because the current study centers on older individuals, it is important to note that several meta-analyses specifically focusing on exercise for late-life depression have mirrored the findings from the studies above. Structured exercise has clear antidepressant effects for older adults struggling with depression (Bridle, Spanjers, Patel, Atherton, & Lamb, 2012; Schuch, Vancampfort, Rosenbaum, et al., 2016). The benefits of exercise for depression are likely due in part to the effects of exercise on the brain.

1.4 Exercise and the Brain

Numerous factors contribute to age-related cognitive decline as well as late-life depression, including inflammation, neurovascular decline, and changes in central nervous system structure and function (Laitman & John, 2015). Fortunately for aging adults, research has shown that exercise combats these factors and can prevent and even reverse some age-related declines.

1.4.1 Exercise and Brain Structure

Structural decline in the brain begins to occur in healthy individuals as young as 30 years old, and disproportionately affects the frontal, temporal, and parietal lobes (Jernigan et al., 2001). Moreover, these structural brain changes are associated with the decline of a broad array of cognitive processes (Raz, 2000). Recent evidence suggests volumetric reductions in the brain due to the effects of normal aging can be prevented and even reversed. Colcombe et al. (2006) conducted a 6-month intervention in which 59 older adults were randomly assigned to either an aerobic exercise group or a nonaerobic exercise control group. The effects of this intervention
were powerful; participation in the aerobic exercise regime increased gray and white matter volumes in prefrontal and temporal regions. This evidence strongly suggests that exercise combats age-related neural decline. Other studies have shown that engaging in even low intensity physical activities (e.g., walking) is associated with greater gray matter volumes in older adults. Erickson et al. (2010) studied 299 older adults and showed that individuals who walked 72 blocks or more per week had significantly greater gray matter volumes compared to physically inactive individuals 9 years later. Increased volumes were found in the frontal and occipital cortices, as well as entorhinal and hippocampal regions, which are crucial for memory formation and consolidation.

Multiple mechanisms account for how aerobic exercise effectively impedes and reverses brain deterioration. At the most basic level, exercise has been shown to have a strong impact on the molecular and cellular structure of the brain. Much of this research has been conducted on rodents because (a) their exercise regiments can be tightly controlled and (b) examining cellular and molecular events is intrusive and would be impossible to do in human subjects (Erickson, Gildengers, & Butters, 2013). In particular, rodent exercise studies have shown consistent effects of physical activity on morphology of the hippocampus (Vivar, Potter, & Praag, 2013). Exercise has been shown to increase cell proliferation in the hippocampus, which leads to increased vascularization due to increased demand for nutrients—and these findings extend to several other brain regions including the frontal cortex and cerebellum (Swain et al., 2003). The neurogenesis and angiogenesis that occur because of exercise almost directly combat the neurovascular decline and CNS degradation associated with aging, demonstrating the power of physical activity.

This effect is beautifully demonstrated by Colcombe et al. (2003). In this impactful cross-sectional imaging study, the relationship between physical fitness and gray and white matter
volumes was analyzed. The results distinctly showed that the brain regions (both the gray and white matter) that are most susceptible to the deleterious effects of aging are the same regions that benefit the most from aerobic fitness. These areas include prefrontal, temporal, and parietal cortices. The manner in which exercise almost selectively targets the brain areas most susceptible to age-related decline is remarkable, and this is replicated in numerous other studies (Colcombe et al., 2006; Erickson et al., 2013; Laitman & John, 2015).

1.4.2 Exercise and Resting-State Networks

The effect of exercise on resting-state networks has been understudied. Only a few studies have examined the effect of exercise on resting-state networks, and none have focused on a depressed population. For instance, one study involved 12 overweight/obese adults taking part in a 6-month exercise intervention (McFadden, Cornier, Melanson, Bechtell, & Tregellas, 2013). Here, resting-state functional magnetic resonance imaging (fMRI) showed a reduction in DMN activity in the precuneus, which was associated with both greater fat loss and reduced perceived hunger in these individuals. Interestingly, a similar study found the opposite effect for overweight older adults—*increased* functional connectivity between precuneus and DLPFC after an aerobic intervention (Prehn et al., 2019). In a different study, patients with Parkinson’s disease took part in an acute bout of exercise (Kelly et al., 2017). Resting-state fMRI analyses showed increases in resting-state activity within the substantia nigra, right vmPFC, and left vlPFC, which correlated with self-report of improved quality of life. Another study demonstrated that even a single session of aerobic exercise alters resting-state activity in young healthy adults (Rajab et al., 2014). Interestingly, a final study suggested exercise interventions of different intensities may differentially impact resting-state network functional connectivity (Schmitt et al., 2019). These studies show promising effects of exercise on functional networks, and as a result,
this line of research should be expanded to other populations including individuals with late-life depression. Given the depression-related abnormalities that have been identified within the DMN, if exercise can improve the connectivity of the DMN, perhaps functional connectivity changes are a key mechanism in its antidepressant effect.

1.5 The Role of Default Mode Network in Depressive Symptom Change: A Gap in the Literature

No studies have taken a longitudinal approach in measuring DMN connectivity across more than one time point in a late-life SubD population. This study is the first of its kind to measure DMN connectivity before and after an aerobic exercise intervention, and its relationship with depressive symptom severity (Figure 1.2). This will significantly improve our understanding of how functional changes in the DMN can impact depressive symptomology. If findings from this study support provide support for interrelationships between exercise, DMN functional connectivity, and depressive symptoms, the results will have implications for treatments and preventative interventions for depression by identifying an important treatment target. It is possible that other treatments besides exercise can target the DMN, and for some populations (e.g., frail older adults), physical exercise may be less feasible. This study has important implications as it addresses a critical gap in how resting-state networks may affect depressive symptoms.

Figure 1.2: Hypothesized model of aerobic exercise, default mode network, and SubD symptoms
1.6 Aims of Proposed Study

The current study involved secondary analysis of data from a project that focused on brain changes after exercise in older adults (McGregor et al., 2018). The objective of the current study is to use neuroimaging in the context of an exercise intervention to address the gap in the literature on functional connectivity and depression. Previous literature has shown that individuals with depression show increased functional connectivity in DMN relative to healthy controls (Zeng et al., 2012). Other research has shown that exercise can reduce functional connectivity in DMN, which has been associated with improvements in behavioral outcome measures (McFadden et al., 2013). Therefore, the overarching hypothesis is that aerobic exercise will be associated with reductions in DMN activity in a randomized control trial of community-dwelling older adults, and these resting-state reductions will be associated with decreased depressive symptomology. This hypothesis will be tested through the following specific aims:

Specific Aim 1: Determine the cross-sectional association between depressive symptoms and DMN functional connectivity.

Hypothesis 1: Baseline DMN functional connectivity will be higher in individuals with greater depressive symptoms. Specifically, it is expected that there will be stronger functional connectivity between the DMN and sgACC in individuals with greater depressive symptoms.

Specific Aim 2: Confirm the impact of aerobic exercise on subthreshold depressive symptoms in older adults.

Hypothesis 2: Older adults assigned to the aerobic exercise condition will show greater decreases in subthreshold depressive symptoms after the intervention relative to older adults assigned to the nonaerobic exercise control group.
Specific Aim 3: Determine the interrelationships between aerobic exercise, functional connectivity in the DMN, and depressive symptoms.

Hypothesis 3a: Decreases in functional connectivity in the DMN after the intervention will be greater in the aerobic exercise group relative to the nonaerobic control group.

Hypothesis 3b: Decreased functional connectivity in the DMN after the intervention will be associated with reductions in depressive symptomatology.

2 METHODS

2.1 Participants

Thirty-eight older adults between the ages of 60 and 83 were recruited from the community. Other inclusion criteria included (1) being sedentary, as defined by not engaging in structured physical exercise and/or not engaging in more than 30 minutes of moderate physical activity on four or more days of the week; (2) having no prior diagnosis of MDD or neurological disease, including Alzheimer’s disease, Parkinson’s disease, or stroke; (3) being right-handed; (4) being a native English speaker; and (5) having a physician’s approval for participation in an exercise study. Exclusion criteria included (1) any condition that would interfere with an MRI scan; (2) recent hospitalizations within the past 6 months; (3) untreated diabetes or hypertension; (4) an inability to walk more than 400 meters; and (5) significant cognitive impairments, as defined as a score on the Montreal Cognitive Assessment (MoCA) of <24. Due to missing behavioral and imaging data, a subset of the full sample was used when performing analyses for each aim. See Table 2.1 for a summary of participant demographic information.
Table 2.1: Sample Characteristics

<table>
<thead>
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<th></th>
<th>Specific Aim 1</th>
<th>Specific Aim 2</th>
<th>Specific Aim 3a</th>
<th>Specific Aim 3b</th>
<th>Total Sample</th>
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<td>32</td>
<td>20</td>
<td>19</td>
<td>38</td>
</tr>
<tr>
<td>Age (years)</td>
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<td>71.84 (±5.85)</td>
<td>71.45 (±4.74)</td>
<td>71.74 (±4.69)</td>
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<tr>
<td>Sex (% female)</td>
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<td>62.50%</td>
<td>70.00%</td>
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<td>7.94 (±6.80)</td>
<td>6.90 (±6.22)</td>
<td>7.11 (±6.32)</td>
<td>8.11 (±6.54)</td>
</tr>
</tbody>
</table>

2.2 Aerobic Exercise Intervention

The group exercise intervention started with 20 minutes of Spin aerobic exercise three times a week for 12 weeks. Participants utilized stationary exercise bicycles and were led by a qualified fitness instructor. To increase the intensity, Spin sessions were increased by 1-2 minutes/session until a maximum time of 45 minutes/session was reached. All participants were given heart rate (HR) monitors so that HR activity could be tracked, ensuring that all participants exerted the appropriate amount of effort throughout the exercise sessions. Accounting for previously sedentary lifestyles, the exercise intensity began at low levels (as measured by 50% of target intensity) and increased to a maximum of 75% target intensity.

2.3 Control Intervention Protocol

All aspects of the control intervention were designed to mirror the aerobic exercise intervention. Participants in this condition met for the same frequency and duration as the experimental group. Additionally, control participants reported to the same facility and had the same fitness instructor. Instead of engaging in progressive aerobic exercise, individuals in this condition engaged in balance, stretching, and light muscle toning exercises. Heart rate was monitored to assess intensity of each session and keep HR below aerobic levels (50% of maximal heart rate reserve).
2.4 Cardiovascular Fitness Assessment

As an initial validity check for the aerobic exercise intervention, all participants performed a cardiovascular fitness assessment to determine their VO$_2$ max, or maximum oxygen consumption. VO$_2$ max is a measure of the maximal capacity of the respiratory system to acquire oxygen and supply it to necessary muscles, so that these muscles have the energy to contract (Akalan, Robergs, & Kravitz, 2008). Because the participants in this study were 60 years of age and older, a submaximal fitness test was used in place of a maximal exertion test, which may be far too strenuous for some of the older participants. By extrapolating the submaximal data, it was possible to estimate VO$_2$ max, which is considered a valid estimate of aerobic fitness levels (Beekley et al., 2004). An assessment of VO$_2$ max was conducted before and after the exercise intervention to confirm the effectiveness of the aerobic intervention.

2.5 Depressive Symptom Assessment

The severity of current depressive symptoms was assessed via the Beck Depression Inventory, Second Edition (BDI-II; Beck, Steer, Ball, & Ranieri, 1996), a widely used, 21-item self-report measure that has been validated in older adults (Richter, Werner, Heerlein, Kraus, & Sauer, 1998; Segal, Coolidge, Cahill, & O'Riley, 2008). The BDI-II has high internal consistency in the general population of older adults (Cronbach’s $\alpha = 0.86$). This scale assesses the frequency and severity of depressive symptoms over the past two weeks, making it an ideal scale to use because of its sensitivity to symptom change over time. It produces a total score that indicates elevated depressive symptomology if the score is $\geq 14$ (which would indicate mild depression). The BDI-II was administered before and after the exercise intervention. Depressive symptoms were used as a continuous measure in all statistical analyses, with higher scores on the BDI-II indicating higher levels of depressive symptoms.
2.6 fMRI Acquisition and Pre-Processing

The MRI scans were acquired on either a Siemens 3T Tim Trio MRI scanner or a Siemens 3T Prisma-FiT MRI (Erlangen, Germany). The pre- and post- scans for each subject were completed on the same MRI platform (either the Trio or Prisma) to reduce the influence of scanner differences. Anatomical scans were high-resolution (1mm$^3$) T1-weighted structural images in the sagittal plane. The images were obtained using a 3D magnetization prepared rapid acquisition gradient echo (MP-RAGE) sequence with the following parameters: TE = 3.02 ms, TR = 2600 ms; FOV = 240 mm; FA= 8°; matrix size = 256 × 256, 176 × 1.0 mm sagittal slices. During the resting state scan, the participants were instructed to look at a white fixation cross on a black background. The resting state fMRI (rsfMRI) time course was acquired with a single shot gradient recalled echo planar imaging (EPI) sequence using the following parameters: FoV = 220 mm × 220 mm, matrix = 74 × 74, 48 slices, slice thickness = 3 mm, TR = 3000 ms, TE = 24 ms, FA = 90°, 192 measurements, acquisition time = 9:36 min.

The MR images were processed using AFNI, FSL, and ITKSnap software packages, as well as in-house Matlab scripts. The rsfMRI time course was corrected for slice-timing and global head motion. Independents Component Analysis (ICA) was used to remove systematic hardware, physiological, and motion related artifacts via FSL’s Melodic and FIX. Images were spatially normalized to the Montreal Neurological Institute’s (MNI) template using non-linear transforms (Evans et al., 1993). Frame-to-frame displacement was calculated to censor the rsfMRI time series at a 0.5 mm threshold (Power et al., 2014). The influence of cerebrospinal fluid pulsatility was minimized by masking the ventricles in the rsfMRI time series. Finally, a low-pass filter was applied to the rsfMRI time series using a Chebyshev II filter with cut-off
frequency of 0.1 Hz (Krishnamurthy, Gopinath, Brown, & Hampstead, 2015), and it was smoothed with a 5 mm full-width-half-maximum Gaussian filter.

2.7 Seed-Based rsfMRI Analysis

Based on a prior hypotheses, we seeded from the bilateral anterior DMN (MNI coordinates; x = 2, y = -47, z = -4; Figure 2.1), as previous research has indicated increased functional connectivity of anterior DMN (aDMN) in depressed individuals (Mulders et al., 2015). We also seeded from bilateral sgACC (x = 1, y = -24, z = -10; Figure 2.2), as there is

![Figure 2.1: aDMN seed](image1)

![Figure 2.2: sgACC seed](image2)
strong evidence supporting greater resting-state functional connectivity between this region and the DMN for individuals with greater depressive symptoms (Hamilton et al., 2015). A 5mm radius sphere was used to extract an average seed time course that was cross-correlated with the time courses of all other voxels in the brain. Next, a Fisher z-transform was applied to all the cross-correlation values to normalize the distribution. This is referred to as Z(CC).

2.8 Analyses for Specific Aim 1

The hypothesis for Aim 1 was that baseline DMN functional connectivity will be higher in individuals with greater depressive symptoms. It was specifically hypothesized that there would be stronger functional connectivity between the DMN and sgACC in individuals with greater depressive symptoms based on findings from a previous study showing that people with depression have increased functional connectivity between the DMN and sgACC (Hamilton et al., 2015). To answer this question, a mass univariate analysis was conducted. Here, all participants were concatenated into a single file. Across every participant and every voxel, depressive symptoms at baseline (BDI-II\textsubscript{PRE}) were regressed onto DMN functional connectivity at baseline \([Z(\text{CC})\textsubscript{PRE}]\) using a sliding window analysis. This provided correlation values that indicated a magnitude of prediction (i.e., if functional connectivity was predicted by BDI values). The resulting brain-behavior regression maps were thresholded at \(r^2 = 0.13\) and clusterized at 20 voxels.

2.9 Analyses for Specific Aim 2

The hypothesis for Aim 2 is that older adults assigned to the aerobic exercise condition will show greater decreases in subthreshold depressive symptoms after the intervention as compared to older adults assigned to the nonaerobic exercise control group. To evaluate pre-post
differences between groups, change scores for depressive symptoms as measured by the BDI-II were computed using the equation below:

$$\text{BDI-II}_{\text{DIFF}} = \text{BDI-II}_{\text{POST}} - \text{BDI-II}_{\text{PRE}}$$

Intervention effects were examined using ANCOVA with intervention group as the predictor and BDI change scores as the outcome to determine between-group differences for depressive symptoms. Age and sex were included as covariates. The goal of this analysis was to demonstrate if aerobic exercise reduces depressive symptoms in older adults, as hypothesized, and if that effect is specific to aerobic, not nonaerobic, exercise.

### 2.10 Analyses for Specific Aim 3

In comparing the effects of the aerobic exercise intervention to the balance control group, the difference in Z(CC) between pre- and post- scans was determined on a voxel-wise basis for each individual participant as shown below:

$$\text{Z(CC)}_{\text{DIFF}} = \text{Z(CC)}_{\text{POST}} - \text{Z(CC)}_{\text{PRE}}$$

The first hypothesis of Aim 3 is that decreases in functional connectivity in the DMN after the intervention will be greater in the aerobic exercise group relative to the nonaerobic control group. To address this, the $\text{Z(CC)}_{\text{DIFF}}$ was compared between the exercise and control groups using independent samples t-test ($p = 0.05$, cluster = 20, FWE corrected) for both seeds.

The second hypothesis of Aim 3 is that decreased functional connectivity in the DMN after the intervention will be associated with reductions in depressive symptomatology. To determine if exercise induced changes in functional connectivity predicted changes in depressive symptomology, linear regression was used. Brain-behavior relationships were calculated on a voxel-wise basis. The resulting brain-behavior regression maps were thresholded at $p = 0.05$ and clusterized at 20 voxels.
3 RESULTS

3.1 Results for Specific Aim 1

Participants with greater depressive symptoms (as measured by the BDI-II) at baseline showed greater resting state functional connectivity between (1) bilateral sgACC and right middle frontal gyrus (dorsolateral prefrontal cortex; Figure 3.1), right anterior cingulate, right superior temporal gyrus, left middle occipital gyrus, and right lentiform nucleus; (2) bilateral aDMN and bilateral anterior cingulate (Figure 3.2), right precentral gyrus, right thalamus, right lentiform nucleus, and right culmen of the cerebellum. The aDMN tended to show increased functional connectivity to right as opposed to the left frontal regions of the brain. Results indicated greater baseline depressive symptoms were exclusively related to increased functional connectivity from aDMN to the rest of the brain.

Figure 3.1: Greater depressive symptoms at baseline are associated with increased resting-state functional connectivity from sgACC to DLPFC
3.2 Results for Specific Aim 2

Descriptive statistics for Specific Aim 2 are summarized in Table 3.1. Group level comparisons between the aerobic exercise and balance control condition on BDI-II\textsubscript{DIFF} score revealed nonsignificant post intervention change in depressive symptoms after controlling for age and sex \(F(1, 28) = 0.67, p = 0.422\). Moreover, changes in VO\textsubscript{2} max did not significantly predict BDI-II\textsubscript{DIFF} score when controlling for age and sex \(p = 0.474\).

A follow-up paired samples \(t\)-test comparing BDI-II\textsubscript{PRE} and BDI-II\textsubscript{POST} collapsed across groups revealed a significant reduction in depressive symptoms as a result of participating in the study \(t(31) = 2.33, p = 0.026\).

Figure 3.2: Greater depressive symptoms at baseline are associated with increased resting-state functional connectivity from aDMN to ACC
Table 3.1: Specific Aim 2 Characteristics

<table>
<thead>
<tr>
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<th>Aerobic Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>Age (years)</td>
<td>71.47 (±6.61)</td>
<td>72.24 (±5.20)</td>
</tr>
<tr>
<td>Sex (% female)</td>
<td>66.67%</td>
<td>64.70%</td>
</tr>
<tr>
<td>BDI-II PRE</td>
<td>6.80 (±5.09)</td>
<td>8.79 (±7.91)</td>
</tr>
<tr>
<td>BDI-II POST</td>
<td>5.20 (±6.92)</td>
<td>6.00 (±7.20)</td>
</tr>
<tr>
<td>BDI-II DIFF</td>
<td>-1.60 (±4.61)</td>
<td>-2.76 (±6.07)</td>
</tr>
<tr>
<td>VO2 Max PRE</td>
<td>21.42 (±9.69)</td>
<td>21.60 (±7.38)</td>
</tr>
<tr>
<td>VO2 Max POST</td>
<td>25.15 (±10.46)</td>
<td>24.21 (±7.79)</td>
</tr>
<tr>
<td>†VO2 Max DIFF</td>
<td>4.40 (±3.66)</td>
<td>1.63 (±5.22)</td>
</tr>
</tbody>
</table>

No significant differences. The parenthetical numbers represent standard deviation.
†Indicates only 22 total participants had pre/post VO2 Max scores.

3.3 Results for Specific Aim 3a

Descriptive statistics for Specific Aim 3 are summarized in Table 3.2. After participating in the intervention, participants in the aerobic exercise group exhibited greater functional connectivity than the balance control group between aDMN and right parahippocampal gyrus (Figure 3.3), left precentral gyrus (primary motor cortex), and left superior temporal gyrus. Participants in the balance control condition exhibited greater functional connectivity than the aerobic group between aDMN and left inferior parietal lobule (Figure 3.4), right inferior frontal gyrus (BA 45; Broca’s area), and bilateral medial frontal gyrus (supplementary motor area).
Table 3.2: Specific Aim 3 Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Aerobic Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>Age (years)</td>
<td>69.83 (±5.12)</td>
<td>72.62 (±4.41)</td>
</tr>
<tr>
<td>Sex (% female)</td>
<td>83.33%</td>
<td>61.54%</td>
</tr>
<tr>
<td>BDI-II&lt;sub&gt;PRE&lt;/sub&gt;</td>
<td>5.83 (±3.06)</td>
<td>7.69 (±7.41)</td>
</tr>
<tr>
<td>BDI-II&lt;sub&gt;POST&lt;/sub&gt;</td>
<td>3.33 (±2.66)</td>
<td>5.54 (±6.69)</td>
</tr>
<tr>
<td>BDI-II&lt;sub&gt;DIFF&lt;/sub&gt;</td>
<td>-2.50 (±3.27)</td>
<td>-2.15 (±4.04)</td>
</tr>
</tbody>
</table>

No significant differences. The parenthetical numbers represent standard deviation.

Figure 3.3: Participants in the aerobic group demonstrated greater increases in functional connectivity from aDMN to right parahippocampal gyrus (PHG) than the balance control group.
Results for Specific Aim 3b

Results indicated that reductions in functional connectivity between (1) bilateral sgACC and left temporal pole (Figure 3.5), left precentral gyrus (premotor and primary motor cortex), and left caudate; (2) bilateral aDMN and bilateral inferior parietal lobule (Figure 3.6), posterior cingulate cortex, the left medial temporal pole, and right inferior frontal gyrus (pars opercularis) were associated with reductions in depressive symptoms.

Conversely, results indicated that increases in functional connectivity between (1) bilateral sgACC and right inferior temporal gyrus, left lingual gyrus, right cerebellar tonsil, right middle frontal gyrus, and left supplementary motor area; (2) bilateral aDMN and left inferior occipital gyrus as well as right cingulate gyrus were associated with reductions in depressive symptoms.
Figure 3.5: Decreases in functional connectivity between sgACC and left temporal pole are associated with reductions in depressive symptoms.

Figure 3.6: Decreases in functional connectivity between aDMN and left inferior parietal lobule (IPL) are associated with reductions in depressive symptoms.
4 DISCUSSION

The goal of the current study was to measure DMN connectivity before and after an aerobic exercise intervention, and its relationship with depressive symptom severity, to see how functional changes in DMN can impact depressive symptomology in older adults. Although the benefits of exercise for depression are well studied, the mechanisms underlying this relationship are not well understood. This study demonstrated that participating in an aerobic exercise intervention led to greater decreases in DMN functional connectivity than participating in a nonaerobic control intervention. Moreover, reductions in DMN functional connectivity after the aerobic exercise intervention were associated with reductions in depressive symptoms. This study contributes to a limited literature on the effects of exercise on resting-state functional connectivity and sheds light on the numerous benefits of exercise for late-life SubD.

4.1 Depression and DMN Functional Connectivity

It was hypothesized that baseline DMN functional connectivity would be higher in individuals with greater depressive symptoms. Specifically, it was expected that there would be increased functional connectivity between the DMN and sgACC in individuals with greater depressive symptoms. This hypothesis was supported by the data. At baseline, individuals with greater depressive symptoms exhibited increased functional connectivity between regions of the DMN (specifically the DLPFC) and sgACC as well as within the DMN itself (i.e., aMPFC to anterior cingulate cortex). These results are in line with previous literature on altered DMN functional connectivity in MDD and extend the findings to a late-life SubD sample (Sambataro et al., 2014; Zhu et al., 2012).

Importantly, Hamilton et al. (2015) demonstrated that a key feature of the DMN in individuals with MDD is increased functional connectivity to the sgACC. The combination of
the sgACC’s role in behavioral withdrawal, along with the DMN’s role in self-referential thought, has been posited to explain the stereotypical ruminative and withdrawn state of mind that is so often associated with depression. Even in a sample with subthreshold depressive symptoms, increased connectivity from the sgACC to DMN was found for those with greater symptoms. This indicates that individuals with SubD may possess a biomarker suggestive of more frequent ruminative thought, just as the research shows for individuals with MDD.

4.2 Exercise and Subthreshold Depressive Symptoms

It was hypothesized that older adults assigned to the aerobic exercise condition would show greater decreases in subthreshold depressive symptoms after the intervention relative to older adults assigned to the nonaerobic exercise control group. This hypothesis was unsupported by the data. Group membership (aerobic intervention or balance control) was not associated with any differences in depressive symptom reduction. These findings are in stark contrast to the large body of literature supporting the ameliorating effects of aerobic exercise for depressive symptoms. A follow-up analysis showed, however, that when collapsed across interventions, any participation in the study was associated with a significant decrease in depressive symptoms.

This pattern of findings may have several different explanations. First, this study is likely underpowered due to a small sample size. Next, the baseline level of depressive symptoms in the sample was low (i.e., minimal range), and this may have left little room for improvement. A strong likelihood is that several moderators affected the sample’s treatment response to the aerobic intervention. In one study of nearly 400 community-dwelling older adults, Dotson et al. (2016) found that sex and genotype moderated treatment response so that biological males with the BDNF Met allele benefitted the most from the intervention (Dotson et al., 2016). Additionally, aerobic exercise preferentially improved somatic symptoms of depression in this
study (Dotson et al., 2016). The current study lacks the sample size and variables to test these effects, but future studies should take these variables into consideration. A final explanation for these null findings is that many study participants were so sedentary at baseline that even participating in the balance control condition elevated their heart rate to aerobic fitness levels. This likely made it more difficult to separate group effects and may partially explain why participating in either group was associated with reduced depressive symptoms.

4.3 Exercise’s Effect on DMN Functional Connectivity

It was hypothesized that decreases in functional connectivity in the DMN after the intervention would be greater in the aerobic exercise group relative to the nonaerobic control group. This hypothesis was partially supported by the data. In support of this hypothesis, it was found that functional connectivity from aDMN to the left inferior parietal lobule decreased significantly more for individuals in the aerobic group compared to the control intervention.

The inferior parietal lobule is a major node of the DMN (Buckner & DiNicola, 2019). This region of the brain is strongly associated with self-referential thought, including mind wandering and thinking about the past and future (Buckner, Andrews-Hanna, & Schacter, 2008). This type of undirected thought often stems from the episodic memory system, and the inferior parietal lobule has been shown to activate when retrieving autobiographical and other types of episodic memories (Cabeza, Ciaramelli, & Moscovitch, 2012). Although the role of the inferior parietal lobule in retrieving autobiographical memories is not well understood, activations have most commonly been found to be left-lateralized (Igelström & Graziano, 2017). Of note, results from this study showed left-lateralized decreases in DMN functional connectivity to the inferior parietal lobule. One possible explanation for this finding is that enhanced DMN functional connectivity to the inferior parietal lobule represents an overactive network that results in
excessive internally focused, and possibly depressive or ruminative thought. Aerobic exercise’s ability to reduce connectivity to this region may account for its association with reduced depressive symptoms as discovered in Specific Aim 3.

Contrary to the hypothesis for this aim, there were some increases in functional connectivity in the DMN that were greater for participants in the aerobic group relative to the control group. Most notably, functional connectivity significantly increased from aDMN to the right parahippocampal gyrus for those participating in the aerobic group. The parahippocampal gyrus has been identified as the primary hub of the DMN in the medial temporal lobe during resting-state (Ward et al., 2014). Although findings support resting-state functional connectivity between the DMN and hippocampus, these connections are indirect and mediated by the parahippocampal gyrus. Thus, the parahippocampal gyrus appears to be an important node of the DMN that is involved in associative, topographical, and spatial memory (Aguirre, Detre, Alsop, & D'Esposito, 1996; Ward et al., 2014).

Although this finding contradicts a prior hypotheses, upon further review of the literature, it is line with previous findings. Several studies have found increases in resting-state functional connectivity to the parahippocampal gyrus following aerobic exercise (Tozzi et al., 2016; Voss et al., 2013). These increases in functional integration likely benefit the individual. Notably, lesions in the right parahippocampus have been associated with topographical disorientation in humans (Habib & Sirigu, 1987). The increased functional connectivity between aDMN and right parahipocampus described in this study may represent enhancements in topographical and spatial learning following aerobic exercise. Although the present study did not measure either construct, physical exercise has been repeatedly shown to benefit spatial learning and memory in both human and animal models (Cassilhas, Tufik, & de Mello, 2016).
4.4 Changes in DMN Functional Connectivity and Depressive Symptoms

Lastly, it was hypothesized that decreased functional connectivity in the DMN after the intervention would be associated with reductions in depressive symptomatology. Again, this hypothesis was partially supported by the data. Most notably, decreases in functional connectivity within the DMN (aDMN to both inferior parietal lobule and posterior cingulate cortex) were associated with decreases in depressive symptoms. The positive associations between DMN functional connectivity and depressive symptoms support previous cross-sectional literature on altered patterns of DMN functional connectivity in late-life depression. Alexopoulos et al. (2012) showed that high DMN functional connectivity distinguished older adult with MDD from nondepressed peers. The current study extends these findings and suggests that decreasing depressive symptoms—even in a SubD sample—are associated with decreasing DMN functional connectivity. Additionally, the inferior parietal lobule and posterior cingulate cortex are hallmark nodes of the DMN (Buckner, Andrews-Hanna, et al., 2008; Buckner & DiNicola, 2019). The finding that decreased functional connectivity in the DMN is correlated with reduced depressive symptoms may be an indication of reductions in negative self-referential thought.

Another important finding was that decreases in functional connectivity between sgACC and the DMN (specifically the left temporal pole) were also associated with decreases in depressive symptoms. The lateral temporal pole is one of the lesser studied nodes of the DMN, but it still appears to play an important role in regulation of mood (Buckner, Andrews-Hanna, et al., 2008; Murai & Fujimoto, 2003). Although an explicit hypothesis was not made regarding the sgACC seed for this aim, the assumption is that due to the sgACC’s strong functional connectivity to the DMN in individuals with MDD, this connectivity would decrease as
depressive symptoms decrease (Hamilton et al., 2015). This finding provides additional support for deleterious role of the sgACC node in the DMN.

Contrary to the hypothesis, negative associations between DMN functional connectivity and depressive symptoms were also found when seeding from both regions of interest. With that said, neither the aDMN nor sgACC were negatively correlated to any other regions within the DMN. Other studies have identified a similar pattern of findings. Tozzi et al. (2016) found that following an aerobic exercise intervention, changes in functional connectivity between the right parahippocampal gyrus and the left superior temporal gyrus are negatively correlated with changes in subjective mood. Increases in functional connectivity from the DMN to other regions of the brain following exercise appear to benefit depressive symptoms via different means.

The most plausible explanation of this study’s findings is that, following an aerobic exercise intervention, DMN functional connectivity is altered in a dynamic way, so that connectivity to other regions of the brain is optimized. The DMN decreases connectivity to some areas and increases connectivity to other regions. Findings from this study show that within network decreases in functional connectivity are associated with reduced depressive symptoms. Increases in functional connectivity from the DMN to other regions of the brain, including left inferior occipital gyrus and right cingulate gyrus, are associated with reduced depressive symptoms too. Alterations in DMN function connectivity after aerobic exercise appear to be beneficial for more than just mood symptoms. Findings from this study also show improvements in areas of the brain associated with learning and memory as well.

### 4.5 Limitations

The current study is limited in several important ways. First, because this study is a secondary analysis, several participants are missing data for each aim. Moreover, for Specific
Aim 3, the exercise and balance groups were disproportionate in size due to missing imaging and behavioral data. Promising effects were still found despite this small sample size. Another limitation of this study is the homogenous nature of the sample. The predominantly white female sample makes it difficult to generalize these findings to a broader population. Finally, many participants were so sedentary at baseline that even engaging in the balance control group resulted in aerobic level heart rates at points in the intervention. This may have partially accounted for there being no relationship between group membership and depressive symptom reduction.

Future studies should recruit a larger, more diverse sample. In addition to using the depressive symptom total scores, it is recommended that individual symptom dimensions (e.g., somatic symptoms, depressed mood, well-being) be examined, as previous studies have shown that exercise can selectively target specific depressive symptom dimensions (Dotson et al., 2016). Different exercise intensities and other types of exercise interventions should also be explored, including resistance training, yoga, and tai chi, as previous research has found these factors may differentially impact resting-state functional connectivity in the brain (Liu et al., 2019; Schmitt et al., 2019). Finally, collecting various neurotrophic factors (e.g., brain-derived neurotrophic factor; BDNF) and growth factors would enable researchers to better understand how functional connectivity relates to depressive symptoms at the biological level, as preliminary evidence already suggests these factors play a role (Voss et al., 2013).

4.6 Conclusion

This study demonstrates that (a) increased connectivity within the DMN and to the sgACC is associated with greater depressive symptoms at baseline, (b) decreases in functional connectivity within the DMN after a 12 week aerobic exercise intervention were greater for
participants in the aerobic group relative to the control group, and (c) a positive association between changes in DMN functional connectivity and changes in depressive symptoms was found, but a negative association was found between other regions of the brain. Overall, exercise appears to differentially modulate (i.e., not exclusively increasing or decreasing functional connectivity) DMN functional connectivity in a way that is associated with improvements in overall mood, and is likely associated with improvements in numerous other domains such as memory too. The fact that these results were found in a small sample, with low baseline depressive symptoms, after a relatively short intervention, suggests that exercise affects the aging brain in a powerful way. These findings are important because they suggest changes in resting-state functional connectivity are associated with changes in depressive symptoms in a late-life SubD sample. By studying other interventions that modify resting-state functional connectivity (e.g., psychotropic medication, meditation, or other forms of exercise), better treatments for late-life depression can be developed. Additionally, for older adults who are frail or disabled and cannot engage in aerobic exercise, findings from this study suggest that other treatment modalities that target DMN functional connectivity may be viable as well. The current study will inform preliminary work in this area of research.
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