Multi-Level Characterization of Exercise Effects on Depression: Effects on Depressive Symptoms, Cognitive Function, and Brain Health

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Exercise effects on Depression: Effects on Depressive Symptoms, Cognitive Function, and Brain Health

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Exercise has been established an effective treatment for depression, both as an independent treatment and as an augmentation to standard first-line treatments (e.g., medication, psychotherapy). Further, the benefits of exercise for depression have been demonstrated across age groups (i.e., older and younger adults) and in those with clinical and subclinical levels of depressive symptoms. However, the neural mechanisms underlying the antidepressant effects of exercise have only been examined in two studies with significant limitations. To address this critical gap in the literature, this dissertation leveraged data from two randomized pilot intervention studies to characterize the effects of exercise on depression across clinical, cognitive, and brain-based outcomes. To optimally translate exercise treatments to real-world settings, its efficacy in various depressed subgroups was explored, including younger (20-39 years) and older adults (60-79 years) with Major Depression, and older adults with subclinical depressive symptoms and mild cognitive impairment (MCI).

Briefly, in study 1, exercise as an augmentation to medication treatment for Major Depression resulted in more rapid and stable decline in depressive symptoms, improvement in cognitive performance in younger but not older adults, and increased hippocampal-default mode network connectivity relative to medication treatment alone. Further, in regions showing reductions in cortical thickness with greater depression severity, intervention-related improvement in aerobic fitness was marginally associated with an increase in regional cortical thickness. In study 2, exercise as an augmentation to psychotherapy for older adults with

subclinical depression and MCI was not effective due to suboptimal implementation of the intervention. However, results revealed greater engagement in moderate-to-vigorous physical activity and greater stability of rest-activity patterns prior to the intervention was predictive of greater improvement in cognitive performance and resulted in greater reduction in depressive symptoms over the course of the intervention, respectively. Overarching conclusions from these pilot studies highlight the utility of exercise-based interventions for alleviating clinical and subclinical levels of depression and cognitive decline, possibly via protective effects on neural pathways sensitive to the deleterious effects of depression and cognitive impairment.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

PREFACE

First, I would like to thank my advisor, Kirk Erickson, who has been a great inspiration and had a transformative influence on my career through his consistent, supportive mentorship throughout my graduate education. His support went beyond a typical graduate mentor, as he facilitated the implementation of my dream pilot exercise intervention study in depressed adults and permitted me to lead this clinical trial as an amateur graduate student. In addition to his support and professional mentorship, Kirk's enthusiasm for science is contagious, and this passion pervaded each of our research meetings throughout my graduate training. For instance, if I entered a meeting disheartened about my work, I would leave with a renewed energy and zeal to pursue more projects than I had anticipated. As an exemplar scientist and mentor, he always advised me pursue my own professional aspirations, regardless of whether they were clinical or academic, and ultimately inspired me to pursue an academic career in clinical research.

Second, I would like to acknowledge Meryl Butters, who has had the most influential role in my development as a clinical neuropsychologist. Beyond her research collaborations with me over the last eight years, she was an inspiring clinical supervisor, a consistent professional mentor, a member of my dissertation committee, and will fortunately be my postdoctoral fellowship mentor.

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1.0 SPECIFIC AIMS

Exercise has emerged as a promising non-pharmaceutical intervention for reducing depressive symptoms in clinical and nonclinical populations (Cooney et al., 2013; Rebar et al., 2015). Moreover, exercise improves cognitive functioning in healthy (Patrick J Smith et al., 2010) and cognitively impaired adults (Blondell, Hammersley-Mather, & Veerman, 2014), and may improve cognitive function in depressed adults (Malchow et al., 2013). Exercise has an effect on the volume and function of several brain regions that are involved in cognitive function (Erickson, Leckie, & Weinstein, 2014; Michelle W Voss et al., 2013); these regions, including the prefrontal cortex, anterior cingulate cortex, striatum, and hippocampus, have also been implicated in depression (Singh & Gotlib, 2014). Thus exercise effects on neural architecture and function may be a common neurobiological pathway by which exercise influences both mood and cognitive function.

Despite the benefits of exercise for both depression and cognitive function and the likely overlapping neural mechanisms underlying these effects, these literatures have largely remained historically separate. Few studies have examined the effects of exercise on both depressive symptoms and cognitive function in depressed adults (Hoffman et al., 2008; Kubesch et al., 2003; Vasques, Moraes, Silveira, Deslandes, & Laks, 2011). Further, late life depression is highly comorbid with mild cognitive impairment, and both result in an elevated risk of dementia (Diniz, Butters, Albert, Dew, & Reynolds, 2013); yet, no investigations have examined the

effects of exercise on reducing depression and cognitive impairment in older adults with depression and mild cognitive impairment. The neural benefits of exercise for depressed adults are also unknown; only one small study with poor adherence examined exercise effects on hippocampal volume, resulting in null findings (Krogh et al., 2014). No study to our knowledge has investigated the effects of exercise on brain function in depressed adults. These key gaps in the field point to the need for a comprehensive, multi-level examination of the neurobehavioral effects of exercise on depression.

To this end, I used data from two sources to examine neurobehavioral changes associated with physical activity engagement in adults with depressive symptoms; key outcome measures included change in depressive symptoms, cognitive function, gray matter volume, and resting state functional brain dynamics. The data for this project were derived from the following studies: Study 1) A 12-week pilot randomized controlled trial designed to test neural changes associated with engagement in aerobic exercise as an adjunct treatment to antidepressant medication (venlafaxine). Fifteen participants were randomized to an antidepressant medication group or an antidepressant medication + exercise group. All participants met with a clinician for medication management on a biweekly basis throughout the intervention, and those randomized to the exercise group additionally received supervised exercise 3-times a week for 12 weeks. Participants underwent the following assessments at baseline and post-intervention: structural and resting-state functional neuroimaging assessments in a 7-T MRI scanner, physical fitness testing (VO_2 submax), neuropsychological testing, and depression severity assessments (Montgomery Asberg Depression Rating Scale). Study 2) A 16-month pilot randomized trial designed to reduce depressive symptoms and prevent Major Depression in older adults with mild cognitive impairment (MCI) and subthreshold depressive symptoms. This study tested the effects

of a 16-week (4-month) problem-solving therapy (PST) intervention and as an exploratory aim the effects of exercise were tested as an adjunct to PST to reduce depressive symptoms. Long-term depression outcomes were examined at a 12-month follow-up post-intervention. Participants were randomized to one of three groups: 1) enhanced usual care 2) PST or 3) PST + exercise. Physical activity levels were assessed using accelerometers at baseline, post-intervention (4 month), as well as at the long-term follow-up visit (16 month). Depressive symptoms, assessed using the patient health questionnaire (PHQ-9), and cognitive function were also assessed at those three time points. Using these data, I proposed the following aims:

1) Examine whether greater amounts of physical activity are associated with a reduction in depressive symptoms.

H1.1 (Study 1): The antidepressant medication + exercise group would show a more rapid reduction in depressive symptoms relative to the medication only group. Exploratory hypothesis: Greater increases in physical fitness (VO_2) levels from pre- to post- intervention would be associated with a decrease in depressive symptoms in adults with Major Depression.

H1.2 (Study 2): Increased physical activity (PA) and/or improved regularity in rest activity rhythms (RARs) over a 16-week period would be associated with a decrease in depressive symptoms from pre- to post-intervention, as well as from post-intervention to the 16- month follow-up visit in older adults with MCI and mild depressive symptoms.

2) Examine whether greater amounts of physical activity are associated with changes in cognitive function among adults with depressive symptoms.

H2.1 (Study 1): The antidepressant medication + exercise group would show greater improvements on cognitive measures relative to the medication only group. Exploratory hypotheses: Increased physical fitness (VO_2) levels from pre- to post-intervention would be

associated with a decrease in depressive symptoms in adults with Major Depression. Depressed older adults may show greater cognitive improvements relative to younger adults.
H2.2 (Study 2): Increased physical activity may be associated with an improvement in performance on cognitive measures from pre- to post-intervention, as well as from post-intervention to the 16-month follow-up visit in older adults with MCI and mild depressive symptoms.

3) Examine whether 12-weeks of aerobic exercise leads to changes in gray matter volume and resting-state functional dynamics in adults with Major Depression.

H3 (Study 1): The antidepressant medication + exercise group would show greater increases relative to the medication only group from pre- to post- intervention in volume and functional connectivity in the hippocampus, prefrontal cortex, and anterior cingulate cortex. Functional connectivity within the default mode network and hippocampal connectivity with cortical regions may increase with exercise, given that they have shown to be influenced by exercise in prior studies (Burdette et al., 2010; Voss, Erickson, et al., 2010; Voss, Prakash, et al., 2010). As an exploratory hypothesis, it was also predicted that change in fitness levels would be associated with increased voxelwise gray matter volume and functional connectivity.

2.0 BACKGROUND

2.1 EXERCISE EFFECTS ON DEPRESSION

Depression is a significant global public health concern; it is the leading cause of disability worldwide and is currently estimated to affect 350 million people (WHO, 2012). Given the significant heterogeneity in etiologies, symptomatology, and functional disability associated with depression across individuals, the focus of depression treatment research has shifted from testing generalized treatment efficacy towards identifying subtypes of depression using brain-based factors, in addition to symptomatology, and tailoring treatment regimens based on the unique and interactive effects of individual-level and intervention-specific factors on treatment response. In this new wave of depression treatment research, exercise has emerged as an effective non-pharmacological treatment for depression, both as an augmentation and as an independent treatment, with comparable efficacy to first-line treatments (e.g., psychotherapy and medication) (Committe, 2018).

Numerous meta-analytic investigations have confirmed exercise is an effective treatment for depression across the lifespan at clinical and subclinical levels of depressive symptoms, and have identified important moderators of treatment effectiveness (i.e., intervention duration, duration of bout of exercise, depression severity, risk of bias) (Bailey, Hetrick, Rosenbaum, Purcell, & Parker, 2018; Cooney et al., 2013; Krogh, Hjorthoj, Speyer, Gluud, & Nordentoft, 2017; Kvam, Kleppe, Nordhus, & Hovland, 2016; Rethorst, Wipfli, & Landers, 2009; Schuch,

Vancampfort, Richards, et al., 2016). A Cochrane Review and meta-analysis of 35 randomized controlled trials (RCTs) (N= 1356) found that exercise is moderately effective in reducing depressive symptoms relative to a control condition in adults with clinical depression (Standardized mean difference ((SMD) = -0.62 (95% CI: -0.81 to - 0.42)) (Cooney et al., 2013); control conditions ranged from waitlist or treatment as usual groups, to placebo interventions (i.e., social engagement, health education), to first-line treatments for depression (i.e. CBT, pharmacotherapy). Significant heterogeneity was found between study outcomes (I^2 = 63%), possibly due to high variability in duration (range: 10 days-16 weeks) and type of exercise and control interventions. A sensitivity analysis of the long-term effects of exercise on depressive symptoms (8 studies, N = 377), suggested that exercise has a small long-term effect on depressive symptoms post-treatment (SMD -0.33, 95% CI -0.63 to -0.03). Subgroup analyses also indicated that there is no evidence of a difference in the effectiveness of exercise, psychotherapy (7 trials), and pharmacotherapy (4 trials), in treating depression, although this conclusion was based on a limited number of trials. In sum, this meta- analytic review concluded that exercise is moderately effective in reducing acute depressive symptoms in adults with clinical depression, and may have long-term benefits.

Another meta-analysis of 35 RCTs (N=2498) examining the effects of exercise on depression reported positive effects of exercise relative to control conditions on reduction in depressive symptom severity and depression remission (depressive symptom severity: SMD= -0.66 (95% CI -0.85 to -0.46); remission: Risk Ratio for lack of remission: 0.78 (95% CI 0.68 to 0.90) (Krogh et al., 2017). Exercise effects on reduction of depressive symptom severity corresponded with an effect on the Hamilton 17-item Depression Scale of -4.1 points (95% CI -5.3 to -2.9) (Krogh et al., 2017). Substantial heterogeneity was found in effect sizes reported

across studies (I^2 = 81%). Subgroup analyses exploring this heterogeneity in effect sizes revealed that studies reporting larger effect sizes included those with shorter durations (<10 weeks), fewer participants (<50 participants), high- intensity/high-dose exercise (limited to 4 trials), and higher risk of bias (e.g., lack of blinding of participants and outcome assessors, for-profit studies). Notably, exercise effects on depression did not significantly differ between those with major and minor depression. Long-term benefits of exercise on depressive symptoms were not found in this meta- analysis (N=7 studies; SMD= -0.10 95% CI: -0.28 to 0.09). These meta-analytic findings confirm the beneficial effects of exercise for depression, while also highlighting several intervention-specific factors that may contribute to variability in effect sizes reported across studies.

Importantly, exercise is an effective treatment for depression across the lifespan. Although the majority of the evidence reviewed thus far focuses on young to middle-aged adults, meta-analytic evidence from RCTs specifically focused on adolescents/young adults and older adults suggests exercise may be a particularly viable treatment option for depression in these age groups (Bailey et al., 2018; Schuch, Vancampfort, Richards, et al., 2016). For instance, a meta-analysis of 16 RCTs (N=771) examining the effects of a PA on depressive symptoms in adolescents and young adults with clinical depression (aged 12-25 years) reported a large effect of PA (SMD= -0.82 (95% CI: -1.02 to -0.61); I^2= 38%) relative to a control condition (i.e., both active and no treatment control conditions included) (Bailey et al., 2018). The effect size remained similar when only including studies with an active control condition (N=7). Likewise, a meta-analysis of 8 RCTs (N=267) in older adults reported a large effect of exercise on depressive symptoms relative to a non-active control group (SMD= -0.90 95% CI: -0.29 to -1.51) (Schuch, Vancampfort, Rosenbaum, et al., 2016). In this study, meta-regression also revealed a

marginal moderating effect of baseline depression severity on the antidepressant effects of exercise in older adults, such that exercise was more effective in reducing depressive symptoms in those with greater severity of depressive symptoms at baseline (B=0.156, p=0.06). In addition to being an effective treatment option for depression in adolescents and older adults, exercise may preferable to pharmaceutical treatment in these age groups, given the frequency and severity of side effects of antidepressant medications in these populations.

As mentioned above, exercise has shown to be an effective intervention for reducing depressive symptom severity in clinical and subclinical depression, although effects may be magnified in those with clinical relative to subclinical depression (Cooney et al., 2013; Rebar et al., 2015; Rethorst et al., 2009). Given that those with clinical depression have more vulnerable brains than non-clinical populations (e.g., disruptions in neurocircuitry, regional volumetric reductions) they may be more sensitive to exercise-related brain changes, which may in turn result in a greater reduction in depressive symptoms. Further, those with subclinical depressive symptoms have less 'room for improvement,' which may result in floor effects in studies including only participants with very mild levels of depressive symptoms (Cooney et al., 2013; Rebar et al., 2015; Rethorst et al., 2009).

Despite likely differences in the relative benefit of exercise for depressive symptoms in clinical vs. non-clinical populations, two high-quality meta-analyses provide support for the benefits of exercise in reducing depressive symptoms in adults with subclinical symptoms of depression (defined differently across studies, typically using standard clinical thresholds on self-reported depression symptom measures) (Conn, 2010; Rethorst et al., 2009). Specifically, a meta-analysis of 41 RCTs (N=2408) comparing moderate to vigorous exercise with a no-treatment control condition in adults with subclinical depressive symptoms reported exercise is

moderately effective in reducing subthreshold levels of depressive symptoms (ES=-0.59 (95% CI: -0.50 to -0.67) relative to no treatment (Rethorst et al., 2009). Studies examined in this meta-analysis included 20 to 60 bouts of aerobic or resistance training 2 to 3 times per week, and ranged between 4 and 16 weeks in duration; some studies were double-blinded. The specificity of these effects must be interpreted with caution, given that the comparison groups in these studies received no treatment rather than engaging in an active control condition. Another meta-analysis of 38 supervised (N=1598) and 22 unsupervised (N=1081) physical activity (PA) RCTs reported both supervised and unsupervised PA interventions were moderately effective in reducing subthreshold depressive symptoms (Supervised PA: ES= -0.37 (95% CI: -0.50 to -0.24); Unsupervised PA: ES= -0.52 (95% CI: -0.77 to -0.28)) (Conn, 2010). Although slightly larger effect sizes were reported for unsupervised relative to supervised PA interventions, greater heterogeneity in effect sizes was found for unsupervised (I^2= 64%) relative to supervised interventions (I^2= 30%). In sum, exercise has shown to be a promising behavioral intervention for reducing depressive symptoms regardless of diagnostic thresholds.

Consistent with these meta-analytic findings, the recent scientific report released by the 2018 Physical Activity Guidelines Advisory Committee concluded there is strong evidence demonstrating the effects of physical activity on reducing depressive symptoms in individuals with and without Major Depression across the lifespan (Committe, 2018). Moderate to large effect sizes were consistently reported for physical activity effects on depressive symptoms across 13 systematic reviews and meta-analyses (range of Hedge's g= -0.53 to -1.39), with larger effects observed in those with Major Depression (Hedge's g= - 1.03) relative to those with subclinical depression (Hedge's g= -0.59) (Committe, 2018). No difference was observed between the effectiveness of exercise relative to psychotherapy or pharmaceutical treatments in

reducing depression severity, suggesting exercise may be as effective as more conventional treatment approaches for depression (Committe, 2018).

Despite the high comorbidity between depression and cognitive impairment in late- life, investigations of exercise effects on depression in older adults with cognitive impairment are rare(Barreto Pde, Demougeot, Pillard, Lapeyre-Mestre, & Rolland, 2015; Diniz et al., 2013) (Arkin, 2003; Heyn, Abreu, & Ottenbacher, 2004; Teri et al., 2003; C. L. Williams & Tappen, 2008); however, see (MacRae et al., 1996; Rolland et al., 2007). One single-blind randomized 12-month Tai Chi intervention in older adults with amnestic MCI (N=389) reported a reduction in depressive symptoms in the Tai Chi group relative to the stretching and toning control group among those who completed the intervention, although study attrition was significantly higher in the Tai Chi group (46%) relative to the stretching control group (23%) (Lam et al., 2012). Disproportionally high attrition in the experimental group may result in a biased sample of those who completed the intervention (e.g., those with greater perceived intervention-related benefits and/or with premorbid characteristics facilitating intervention adherence). Exercise effects on depressive symptoms in institutionalized older adults with dementia have been more frequently examined with mixed results (Arkin, 2003; Barreto Pde et al., 2015; Heyn et al., 2004; Teri et al., 2003; C. L. Williams & Tappen, 2008); however, see (MacRae et al., 1996; Rolland et al., 2007)). One meta-analysis (N=7 studies) found a moderate effect of exercise on depression symptoms in older adults diagnosed with dementia (SMD = −0.306; 95% CI: −0.571 to−0.041), with moderate heterogeneity between studies (I^2 = 46.8%). These effects remained significant for individuals living in institutional settings (p=0.03) but were no longer significant when comparing exercise to social control groups (p=0.08) (Barreto Pde et al., 2015). These results suggest that exercise may be effective in reducing depressive symptoms relative to ‘no

treatment' but not relative to an active control condition in adults with dementia. Collectively, these findings must be interpreted with caution due to poor intervention adherence (i.e., only two studies reported >50% adherence and one of the largest effect sizes were reported from a study that did not report adherence rates). Key factors contributing to the variability in this limited literature include insufficient use of active control groups, implementation of exercise intervention (e.g., multicomponent vs. exercise only training) risk of attrition bias, depressive symptom measures used, depression severity, variability in severity of cognitive impairment, and comorbid health conditions (e.g., CAD, stroke). In sum, the evidence is limited and mixed regarding the benefits of exercise for depression in older adults with cognitive impairment.

2.1.1 Types And Durations Of Exercise

Given that exercise is a broad term used to define any type of structured physical activity, it would be useful to understand which types and durations of exercise may be most beneficial for depression. Through an exhaustive literature review of 41 meta-analyses and systematic reviews examining exercise effects on depression, the 2018 PAGAC concluded that exercise treatments for depression have typically lasted approximately 12 weeks and included aerobic or resistance training, or a combination of these exercise modalities. The majority of interventions included across meta-analyses examining exercise effects on depression included aerobic training, providing substantial support for a moderate positive effect of aerobic exercise on depressive symptoms. A meta-analysis of 33 studies (N= 1877) specifically focused on the benefits of resistance training likewise reported a moderate positive effect of resistance training interventions on depressive symptoms (SMD= 0.66 (95% CI, 0.48-0.83) $p < .001$), although significant heterogeneity was found in effect sizes reported across studies (I^2= 76%). A recent

meta-analysis of 10 studies comparing the effects of aerobic and resistance training for clinical depression found no differences between the two types of exercise with regard to effects on depressive symptoms (Silveira et al., 2013). Moderate to large beneficial effects of exercise for depressive symptoms (SMD= -0.61) were observed collapsing across exercise modalities (Silveira et al., 2013). These results suggest that both aerobic and resistance training are likely beneficial in the treatment of depression. Further, a large RCT in depressed older adults (N=121) examined the effects of six months of exercise as an adjunct to pharmacotherapy for depression, and found that both moderate-intensity aerobic exercise and low-intensity stretching and toning-based exercise resulted in significantly higher remission rates (moderate intensity: 81% remission; low intensity: 73% remission) relative to pharmacotherapy alone (45% remission). These findings highlight the challenges in detecting significant benefits of exercise treatments for depression in studies including low- intensity stretching and toning control groups. Effects of non-traditional forms of exercise for depression have also been reported (i.e., yoga, Tai Chi, Qigong, dance), although the interpretability of these conclusions is limited by poor methodological rigor of these intervention studies (Committe, 2018). Regarding exercise duration, limited evidence suggests a dose-response effect of exercise on depression symptoms in adults. Even brief durations of exercise (i.e., 20 minutes per day) have been shown to be sufficient to reduce depression symptoms, with larger effects observed for longer durations (Committe, 2018). The ideal duration for exercise interventions targeting depression remains unclear, but the evidence largely suggests that 12-weeks of exercise is sufficient to observe clinically meaningful reductions in depression severity.

2.1.2 Summary

A large body of methodologically rigorous meta-analytic evidence indicates moderate to large beneficial effects of exercise on depression severity throughout adulthood in individuals with clinical and subclinical depressive symptoms. Evidence regarding exercise effects on depression in older adults with cognitive impairment is limited and mixed, with inconclusive evidence in those with MCI (N=2 studies) and small to moderate effects inconsistently reported in those with dementia. Multiple exercise modalities have demonstrated benefits for depression (e.g., aerobic, resistance, yoga, tai-chi), with limited evidence supporting dose-response effects. The majority of exercise treatments for depression have reported clinically significant reductions in depression severity in as few as 12 weeks (Committe, 2018).

2.2 EXERCISE EFFECTS ON COGNITIVE FUNCTION

2.2.1 Effects in Cognitively Healthy Adults

Epidemiological, cross-sectional, and experimental evidence supports the benefits of exercise for cognitive function in cognitively healthy non-depressed adults (Bherer, Erickson, & Liu-Ambrose, 2013; S. Colcombe & Kramer, 2003; Committe, 2018; Roig, Nordbrandt, Geertsen, & Nielsen, 2013; Patrick J Smith et al., 2010). In young and middle-aged adults, effect sizes are small (Range: 0.12-0.15) for exercise effects on cognition, with effects reported across several domains (i.e., executive functioning, attention, processing speed, and memory) (Roig et al., 2013; P. J. Smith et al., 2010). One meta-analysis (N=16 studies) focused on the effects of

aerobic exercise on memory performance found a small effect for immediate (SMD= 0.15; 95% CI = 0.02, 0.27) but not for delayed memory (SMD = 0.07; 95% CI =−0.13, 0.26; p = 0.51). Another meta-analysis (N=29 studies) similarly reported modest benefits of aerobic exercise for cognitive functioning but across a range of domains, including attention and processing speed (g = .158 [95% CI: .055 to .260], P = .003), executive functioning (g = .123 [95% CI: .021 to 225], P = .018), and memory (g = .128 [95% CI: .015 - .241], P = .026) (Smith et al., 2010). Overall, evidence suggests modest benefits of aerobic exercise for cognitive function in cognitively healthy younger and middle-aged adults.

In cognitively healthy older adults, one meta-analysis (18 RCTs) identified beneficial effects of aerobic exercise relative to non-aerobic control conditions on cognitive performance across several domains (attention, processing speed, visuospatial functioning, executive functioning), with greatest improvements observed in executive function (Hedge's g = 0.68). The disproportionately large effect of aerobic exercise on executive functioning in older adults may in part be attributed to earlier age-related declines observed in executive functioning relative to other domains (Hindin & Zelinski, 2012). Interestingly, another meta-analysis (N=25 studies) did not report benefits of aerobic exercise for cognitive functioning (Kelly et al., 2014), but rather identified positive effects of resistance training (N=3) relative to stretching and toning on executive functioning and a positive effect of Tai Chi (N=2) relative to a non-exercise control condition on attention and processing speed. The discrepancy between these meta-analytic findings may arise from inclusion of different studies, heterogeneity among effect sizes reported across aerobic exercise trials, and variability in measures used to assess cognitive domains. Despite these inconsistencies, meta-analytic evidence in cognitively healthy older adults collectively indicates that multiple exercise modalities may have beneficial cognitive effects.

2.2.2 Effects in Older Adults with MCI

Moderate evidence from randomized trials also supports the positive effects of exercise on cognitive function in cognitively impaired older adults (Groot et al., 2016; Heyn et al., 2004; P. J. Smith et al., 2010; Zheng, Xia, Zhou, Tao, & Chen, 2016). A recent meta-analysis of 11 RCTs in older adults with MCI found positive effects of aerobic exercise on global cognitive functioning and immediate and delayed memory recall (Zheng et al., 2016) 2016). The above-mentioned meta-analysis by Smith et al. (Patrick J Smith et al., 2010) compared aerobic exercise effects on cognitive function between adults who were cognitively healthy and those with MCI, and found no difference in the domain of attention and processing speed, a weaker effect on executive function in those with MCI, and a greater effect on memory in those with MCI. It is possible that those with greater memory impairment, who have more to 'gain', may show greater improvement in response to exercise training. Further, a meta-analysis of exercise trials in older adults with MCI (n= 9) and with dementia (n = 21) found a moderate positive effect of exercise on overall cognitive performance (ES= 0.57 95% CI= 0.43-1.17), primarily including trials with non-aerobic exercise regimens (Heyn et al., 2004). Another meta-analysis (N=18) in older adults with dementia reported a similar effect size (SMD=0.42 95% CI=0.23-0.62), with sensitivity analyses showing this effect was robust to different etiologies for dementia (i.e., AD vs. non-AD) and was greater for combined aerobic and non-aerobic exercise interventions (SMD= -0.59 95% CI=0.32-0.86) (Groot et al., 2016). In sum, the evidence suggests that both aerobic and non-aerobic exercise benefit cognitive function in older adults with MCI, with limited evidence supporting selective effects on learning and memory. In interpreting this literature, it is also important to consider that in older adults with MCI, stability of cognitive functioning relative to

decline over the course of an exercise intervention may be considered a positive outcome (J. C. Smith, Nielson, Woodard, Seidenberg, & Rao, 2013).

2.2.3 Exercise Effects on Cognitive Function in Depressed Adults

Impaired cognitive functioning constitutes a salient feature of depression throughout adulthood, and can exacerbate its functional consequences and blunt treatment response (Greer, Grannemann, Chansard, Karim, & Trivedi, 2015) (Koenig et al., 2015; S. Wagner, Helmreich, Lieb, & Tadic, 2012) (Bora, Harrison, Yucel, & Pantelis, 2013; Lee, Hermens, Porter, & Redoblado-Hodge, 2012; Rock, Roiser, Riedel, & Blackwell, 2014). The evidence is mixed regarding cognitive domains that are most affected in depression; nonetheless acutely depressed adults perform worse than their never-depressed counterparts on tasks assessing most cognitive domains, including attention, processing speed, visuospatial ability, memory, and executive function. A recent meta-analysis of 15 studies (N= 644 MDD, 570 controls) examined cognitive impairment in adults during their first episode of depression, and found that depressed adults performed worse than never depressed controls in the domains of psychomotor speed (ES= 0.48), attention (ES= 0.36), visual learning and memory (ES= 0.53), and several executive functions, including set-shifting ability (ES= 0.22), verbal fluency (ES =0.59), and cognitive flexibility (0.53) (Lee et al., 2012). Another meta-analysis of 15 studies (N=375 MDD, 481 controls) specifically examined impairment in executive function in depressed young adults and found that depressed individuals performed worse than the never-depressed controls with regard to response inhibition (ES=1.18), cognitive flexibility (ES=1.11), semantic fluency (ES= 0.92), and planning and organization (ES= 0.44) (S. Wagner, Doering, Helmreich, Lieb, & Tadic, 2012).

Cognitive impairment associated with depression in late-life likewise encompasses most cognitive domains, and may be more severe relative to depression earlier in adulthood (Bora et al., 2013; Koenig et al., 2015; Rock et al., 2014; Trivedi & Greer, 2014). Cognitive deficits that may be most pronounced in late-life depression include impaired information processing speed and executive functioning. In fact, some evidence suggests that reduced information processing speed and/or working memory capacity may mediate cognitive impairment linked to late-life depression (Butters et al., 2004; Nebes et al., 2000; Sheline et al., 2006). One of the largest cross-sectional studies (N= 120 acute MDD, N=128 never-depressed controls) to examine cognitive impairment in late-life depression found that depressed older adults performed more poorly than never depressed controls on measures assessing a broad range of cognitive domains, including episodic memory, attention and processing speed, verbal ability, visuospatial ability, and aspects of executive functioning. The greatest differences were observed in attention and processing speed, consistent with previous literature (Koenig et al., 2015). Importantly, co-occurring cognitive impairment and depression in late-life significantly elevates the risk of incident dementia (Diniz et al., 2013; Vu & Aizenstein, 2013). A recent community cohort study (N=2160) in older adults found that depressive symptoms increased risk for incident dementia (Hazard Ratio (HR) = 1.7; 95% CI: 1.2-2.3), but those with depression and MCI were at an especially high risk for progression to vascular dementia (HR= 4.3; 95% CI: 1.1-17.0) (Richard et al., 2013).

State vs. Trait Effects

Increasing evidence suggests that to a large extent, cognitive impairment persists after remission from depression (Trivedi & Greer, 2014). A recent meta-analysis of 27 studies (N= 895 remitted MDD, 997 never-depressed controls) reported that remitted adults with a history of depression performed lower than never-depressed controls across all cognitive domains, including verbal fluency, attention, processing speed, memory, and executive function; the most pronounced differences were observed with inhibitory control (Cohen's d = 0.74) (Rock et al., 2014). Further, individuals with late-onset (>60 years) depression exhibited worse cognitive performance across most domains relative to those with earlier onset depression (Cohen's d = 1.20). In concert with these findings, a study by Koenig and colleagues (N=120 acutely depressed, N= 190 euthymic remitted N=128 never depression) found no difference in cognitive functioning across domains between acutely depressed and remitted older adults and found that both groups performed poorer than never-depressed older adults (Koenig et al., 2015). A modest amount of evidence also supports beneficial effects of antidepressant treatment on cognitive performance for select domains, including psychomotor speed, memory, and response inhibition, (Rock et al., 2014; Rosenblat, Kakar, & McIntyre, 2016; S. Wagner, Doering, et al., 2012). However, this evidence is mixed and based on studies with small sample sizes.

Exercise effects on cognitive impairment in depressed adults

Two recent meta-analyses (N=8; N=9) of exercise effects on cognitive impairment in depressed adults failed to find a positive effect of exercise on global cognition or individual cognitive domains (Brondino et al., 2017; Sun, Lanctot, Herrmann, & Gallagher, 2018). However, sensitivity analyses in Sun et al. (Sun et al., 2018) indicated combined exercise and cognitive training interventions and low-intensity exercise interventions with higher adherence

rates had a positive effect on global cognition (Sun et al., 2018) Consistent with the results of these sensitivity analyses, one study found that exercise combined with cognitive training resulted in improvements in processing speed, working memory, and visual learning in depressed adults, relative to relaxation combined with cognitive training (Oertel-Knochel et al., 2014). Another large randomized trial (N=202) found that aerobic exercise, relative to antidepressant medication, had a positive effect on sustained attention and processing speed (Hoffman et al., 2008). Cognitive performance did not differ between the aerobic exercise and placebo control group post-intervention; however, exercisers showing the greatest improvements in fitness levels (i.e., top tertile) performed better than the placebo control group on a measure of verbal fluency and marginally better on a working memory task. These findings suggest that exercise may have positive, albeit limited effects on performance in select cognitive domains in depressed adults, but also highlights the possibility of a threshold or dose-response effect of fitness on cognitive performance.

Overall, the evidence regarding exercise-related improvements in cognitive function in depressed adults is limited and equivocal, highlighting the need for further high-quality trials to investigate these questions. Key barriers to consider in future investigations of the cognitive benefits of exercise in depressed individuals include the enduring nature of some cognitive deficits after depression remission and insufficient knowledge regarding the type and duration of exercise that would be optimal to achieve cognitive improvements in any population.

2.3 EXERCISE EFFECTS ON BRAIN STRUCTURE AND FUNCTION IN DEPRESSION

2.3.1 Neural Circuit Dysfunction in Depression

Depression is associated with widespread disruptions in neurocircuitry throughout the brain (Iwabuchi et al., 2015; Kaiser, Andrews-Hanna, Wager, & Pizzagalli, 2015; L. M. Williams, 2016). Investigators have used resting-state functional connectivity approaches to examine functional abnormalities in depression, in which regional brain activity at rest is correlated with activity in other brain regions, and this regional synchronicity in activation patterns is thought to reflect functional interactions between regions. Depressed adults have shown broad reductions in interhemispheric connectivity (G. Wagner et al., 2013), as well as abnormalities in connectivity within and between intrinsic-connectivity networks. One recent meta-analysis of seed-based resting state functional connectivity (rsFC) studies (N=27) comparing individuals with depression with their non-depressed counterparts found large-scale network-level abnormalities in depressed individuals, including *hypo*connectivity within the frontoparietal network (FPN), which is involved in top-down regulation of attention and emotion, *hyper*connectivity within the default mode network (DMN), which subserves internally oriented and self-referential thought, *hyper*connectivity between the DMN and FPN, and *hypo*connectivity between the salience network, involved in the detection and processing of salient events, and medial prefrontal regions involved in emotion regulation(Kaiser et al., 2015). Another meta-analysis (N=10) examining localized disruptions in connectivity (i.e., within specific regions) found the most consistent and robust abnormality to be elevated localized connectivity within the medial prefrontal cortex (mPFC), with greater connectivity in

medication-free patients with a history of multiple depressive episodes (Iwabuchi et al., 2015). These results suggest that in depressed individuals, elevated connectivity within the mPFC may reflect this region's involvement in internally oriented, self-referential functions consistent with the DMN, rather than reflecting its typical role in emotion regulation. Inefficient circuitry within the mPFC has also been considered a marker of rumination, a signature symptom of depression. In a theoretical review of the literature examining neural circuit dysfunction in depression and anxiety, Williams (2016) argues for a taxonomy of types of neural circuit dysfunction implicated in depression and anxiety, including the DMN, SN, positive affect network (i.e., reward), attentional network, and cognitive control network; Williams suggests that these network-level disruptions may map onto specific clinical symptom clusters and may in turn, have specific treatment implications. This may help explain the variability in findings of case-control and treatment studies related to depression using rsFC, as well as help explain the heterogeneity in clinical manifestations of depression.

2.3.2 Structural Brain Abnormalities in Depression

Regional gray matter abnormalities have been have identified in acutely depressed adults relative to age-matched non-psychiatric controls in numerous meta-analytic studies (See (Gujral, Aizenstein, Reynolds, Butters, & Erickson, 2017)for review); the most reliable regional abnormalities identified through structural MRI studies include the anterior cingulate cortex, other prefrontal regions (i.e., OFC, dlPFC, dmPFC), and the hippocampus.

Reduced volume in the anterior cingulate cortex (ACC) may be the most replicated regional gray matter abnormality found in depression(Bora, Harrison, Davey, Yucel, & Pantelis, 2012; Bora et al., 2013; Du et al., 2012; Koolschijn, van Haren, Lensvelt-Mulders, Hulshoff Pol,

& Kahn, 2009; Lai, 2013; Sacher et al., 2012) The ACC is a medial prefrontal cortical structure, including sub-regions with distinct functions; the dorsal ACC has been implicated in higher-level executive and motor functions, the subgenual ACC is involved in emotional and interoceptive processing, and the pregenual ACC is thought to integrate cognitive and emotional information (Gasquoine, 2013). The subgenual cingulate, located in the anterior ventral portion of the ACC, is a key region implicated in depression (Drevets, Savitz, & Trimble, 2008). Meta-analytic reviews have also documented volumetric reductions in other prefrontal cortical (PFC) regions in depressed individuals relative to healthy controls, namely in the orbitofrontal cortex (OFC) (Bora, Harrison, et al., 2012; Du et al., 2012; Kempton et al., 2011; Koolschijn et al., 2009), dorsolateral PFC (dlPFC) (Bora, Fornito, Pantelis, & Yucel, 2012; Zhao et al., 2014), and dorsomedial PFC (dmPFC) (Bora, Fornito, et al., 2012; Sacher et al., 2012).

The hippocampus is also one of the most studied brain regions in the context of depression. The hippocampus has an important role in stress regulation, as it exerts inhibitory control over HPA-axis activity, and is also more broadly involved in cognitive and affective processing via its widespread connections with other limbic and prefrontal regions (Duman & Monteggia, 2006). Reductions in hippocampal volume appear to be a robust structural abnormality observed in depressed adults relative to nondepressed controls. These volumetric reductions may be related to duration, number of episodes, or age of onset of depression, but inconsistencies between meta-analytic findings preclude a clear understanding of moderators (Bora, Fornito, et al., 2012; Cole, Costafreda, McGuffin, & Fu, 2011; Du et al., 2012; Kempton et al., 2011; Koolschijn et al., 2009; McKinnon, Yucel, Nazarov, & MacQueen, 2009; Schmaal et al., 2015; Zhao et al., 2014).

2.3.3 Neural Mechanisms underlying Antidepressant Effects of Exercise

Converging evidence suggests that exercise and antidepressant medication may alleviate depression through similar neuromolecular mechanisms, including increased expression of neurotrophic factors, increased availability of serotonin and norepinephrine, increased regulation of HPA-axis activity, and reduced chronic systemic inflammation (Garza, Ha, Garcia, Chen, & Russo-Neustadt, 2004; Russo-Neustadt, Beard, Huang, & Cotman, 2000). Exercise-induced changes in molecular systems influence the development of new neurons, increase synaptic connections between neurons, and increase cerebral vasculature (See Stillman et al. (2016) for review). These micro-structural changes further influence widespread changes in structural and functional networks in the brain (Erickson et al., 2014; Voss, Vivar, Kramer, & van Praag, 2013). Considering that exercise and antidepressant medication may exert effects on depression through overlapping molecular pathways, it is possible that they also influence overlapping neural systems. Antidepressant pharmaceutical treatment increases the volume of the hippocampus, anterior cingulate, and orbitofrontal cortex, increases white matter integrity, and induces changes in functional dynamics of frontal-limbic neural networks (e.g., DMN) in depressed adults (Fu, Steiner, & Costafreda, 2013; Singh & Gotlib, 2014). However, we still have a poor understanding of exercise effects on neural systems in depressed adults.

Only two studies have examined brain mechanisms associated with exercise effects on depression. Krogh and colleagues (2014) tested the effects of aerobic exercise on hippocampal volume in depressed adults using a 12-week randomized controlled trial, and found no volumetric differences between the exercise group (N=41) and the active control group (N=38) from baseline to post-intervention. However, these findings must be interpreted with caution due to intervention adherence (mean= 30%). One pilot study (N=16) examined the effects of an 8-

week aerobic exercise intervention on task-related functional changes in the hippocampus during an associative memory task in low-fit depressed and non-depressed adults (Gourgouvelis, Yielder, & Murphy, 2017). The results revealed a decrease in task-evoked hippocampal activity (i.e., enhanced neural efficiency) from baseline to post-intervention in both depressed and non-depressed adults. In light of the dearth of mechanistic investigations of exercise effects on depression, well-documented exercise-induced changes in brain structure and function in non-depressed samples may shed light on neural changes that may occur with exercise training in depressed adults (Erickson et al., 2014; Voelcker-Rehage & Niemann, 2013b; M. W. Voss et al., 2013).

2.3.4 Exercise Effects on Resting-State Functional Connectivity

Widespread changes in connectivity patterns have been observed with exercise training (Voelcker-Rehage & Niemann, 2013a). A recent systematic review of 14 studies examining exercise effects on functional connectivity within the DMN in non-depressed adults reported aerobic exercise may increase functional connectivity within the hippocampus, cingulate cortex, and the parahippocampal gyrus (Li et al., 2017). One cross-sectional study in older adults related higher levels of cardiorespiratory fitness to increased connectivity in the default-mode network (DMN) (Voss, Erickson, et al., 2010) and found that fitness was associated with increased connectivity between the posterior cingulate cortex and the frontal medial cortex, medial temporal gyrus, medial frontal gyrus, and parahippocampal gyrus. A large cross-sectional study in young adults (N=242) reported more widespread fitness associations with whole-brain connectivity patterns, such that activity in a broad range of fitness-related regions (i.e., frontal, temporal, parietal, and cerebellar) was related to intrinsic network connectivity in the FPN,

DMN, and dorsal and ventral attention network (Talukdar et al., 2017). Intervention studies (range: 4-12 months) in non-depressed older adults have additionally demonstrated a range of aerobic exercise-related changes in intrinsic network connectivity, including increased hippocampal connectivity with the anterior cingulate (Burdette et al., 2010), decreased hippocampal connectivity with the primary motor cortex (Flodin, Jonasson, Riklund, Nyberg, & Boraxbekk, 2017), increased connectivity between the DMN and ECN (Flodin et al., 2017; Prehn et al., 2017), and increased connectivity within the DMN (Voss, Prakash, et al., 2010). Taken together, cross-sectional evidence suggests cardiorespiratory fitness may be associated with connectivity across a range of networks in young adults and may be selectively associated with DMN connectivity in older adults (Talukdar et al., 2017; Voss, Erickson, et al., 2010). Further, experimental evidence in older adults suggests prolonged aerobic exercise training may result in changes in hippocampal connectivity with frontal regions and in network-level connectivity within and between the DMN and ECN (Burdette et al., 2010; Flodin et al., 2017; Prehn et al., 2017; Voss, Prakash, et al., 2010). Given that abnormalities in default mode network connectivity may be a core neural feature of depression (Tahmasian et al., 2013), exercise treatments for depression may have the potential to alter these disruptions in neural circuitry.

2.3.5 Exercise effects on Gray Matter Volume

Two meta-analytic investigations of exercise-induced changes in hippocampal morphology have found that prolonged aerobic exercise training results in increases in hippocampal volume(Firth et al., 2018; Li et al., 2017), with one of these studies (N=14 studies; N=767) reporting exercise-related prevention of volumetric decrease over time in the *left*

hippocampus, while the other study (N=14 studies; N=631) reports significant exercise-induced bilateral volumetric increases in the total and anterior hippocampus (Li et al., 2017). A seminal study investigating the effects of aerobic exercise on hippocampal volume in sedentary older adults (N=120) found 12-months of moderate intensity aerobic exercise (brisk walking) 3 times/week (N= 60) resulted in a ~2% increase in hippocampal volume (Erickson et al., 2011). Regional specificity was also observed, such that the aerobic exercise resulted in volumetric increases in the anterior hippocampus. This sub-region includes both the hippocampal head, which has been linked to emotional and motivational functioning (Kheirbek & Hen, 2011) and the dentate gyrus, where neurogenesis occurs (Kempermann, Kuhn, & Gage, 1998). In addition, exercise-induced improvements in CRF (~7.8%) were related to increases in hippocampal volume. Taken together, the overlap between hippocampal volume reductions in depression and exercise-induced increases in hippocampal volume suggests that this region may be a likely neural target of exercise treatments for depression.

Moderate experimental evidence also suggests exercise-related volumetric increases in prefrontal regions, including the anterior cingulate cortex. One 6-month randomized intervention study (N=59) (S. J. Colcombe et al., 2006) found that a brisk walking intervention was effective in improving CRF, and resulted in increased volume of bilateral PFC and ACC and left lateral temporal lobe. The stretching and toning group showed no increases in gray matter volume throughout the intervention. Another 6-month randomized trial in sedentary older adults (N= 62) using a similar protocol interestingly found that change in self-reported PA from pre- to post-intervention was positively associated with increased PFC and ACC volume, irrespective of intervention group. Self-reported PA was measured by weekly energy expenditure, which accounted for both leisure and sport-related PA, weighted by the intensity of the activity. These

findings suggest that PA engagement outside of structured sessions during an intervention can have significant effects on brain structure. Despite inconsistencies in these findings, outcomes from both interventions suggest that prefrontal cortical regions, including the ACC, may be another likely neural target of exercise treatments for depression.

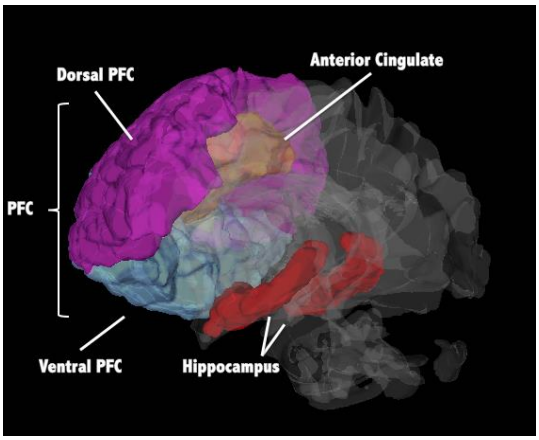

Figure 1. Gray Matter Regions that show abnormalities in depression but also show volumetric improvements with prolonged exercise engagement or improved fitness

2.3.6 Summary

Meta-analyses of structural and functional abnormalities in depressed adults relative to adults with no psychiatric illness have identified volumetric reductions in the hippocampus, ACC, and other prefrontal regions, as well as aberrant connectivity patterns within and between a broad range of networks (i.e., DMN, SN, ECN, positive affect network, attentional network). Fortunately, randomized exercise trials in non-depressed adults have demonstrated exercise training-induced volumetric increases in the hippocampus, anterior cingulate, and other prefrontal regions, as well as alterations in hippocampal-frontal connectivity and in network-level connectivity within and between the DMN and ECN. These data point to the overlap between regional and network-level brain abnormalities associated with depression and exercise-

induced structural and functional changes in the brain. These regions and networks of overlap may serve as neural targets of exercise treatments for depression.

Present Study

Numerous trials have established that exercise is an effective non-pharmaceutical approach for reducing depressive symptoms in younger and older adults with clinical and subclinical depression. However, few investigations have explored cognitive-correlates of exercise treatments for depression, and structural and functional neural changes that may underlie the antidepressant effects of exercise. Given that depression and cognitive impairment are highly comorbid in late-life, exercise may have dual-benefits for cognitively impaired older adults with depressive symptoms. Yet, we still have a poor understanding of the combined effects of exercise on depression and cognitive function, because these literatures have historically remained separate.

To bridge these literatures, and to better characterize the clinical, cognitive, and neural changes associated with exercise treatments for depression, the current study will examine neurobehavioral changes associated with exercise in 1) older adults with MCI and subclinical depressive symptoms , and 2) clinically depressed younger and older adults. Data for this study will be drawn from two sources: 1) A 16-month pilot intervention testing the long-term effects of problem-solving therapy and exercise as an adjunct to PST in reducing depressive symptoms in older adults with MCI, and 2) A 12-week pilot treatment trial testing the neural mechanisms of aerobic exercise as an adjunct to antidepressant medication. Using data from both of these samples, I will first examine whether greater amounts of physical activity is associated with a reduction in depressive symptoms. This will clarify whether physical activity associations with depressive symptoms observed in these samples mirror effect sizes observed in the literature.

Next, in both of these samples, I will examine whether greater amounts of physical activity is associated with improvements in performance on cognitive tasks. This will contribute to the currently limited data examining the cognitive benefits of exercise treatments for depression. This will also be the first study to examine the benefits of physical activity for cognitive function in those with co-occurring depressive symptoms and MCI. Third, I will use high-resolution structural and resting-state functional neuroimaging data from the exercise-augmented medication trial for depression to explore aerobic exercise effects on brain structure and function above and beyond the effects of antidepressant medication. My predictions will focus on regional and network-level brain abnormalities associated with depression in adults. Addressing these aims will ultimately provide a preliminary multi-level characterization of exercise effects on depression across age groups (younger and older adults), symptom levels (clinical and subclinical depression), and levels of cognitive impairment (MCI and non-MCI).

3.0 EXPERIMENT 1: EXERCISE EFFECTS ON DEPRESSIVE SYMPTOMS, COGNITIVE FUNCTION, AND BRAIN HEALTH IN ADULTS WITH MAJOR DEPRESSION

Experiment 1 involved a 12-week pilot randomized controlled trial examining neural mechanisms underlying the effects of moderate intensity aerobic exercise as an adjunct to antidepressant pharmaceutical treatment (i.e., venlafaxine XR) for Major Depression in younger (aged 20-39) and older (aged 60-79) adults. The intervention included two groups of 10 participants each: pharmacotherapy + aerobic exercise and pharmacotherapy alone (with treatment as usual, TAU). The aerobic exercise group attended a one hour session of structured physical activity three days per week for 12 weeks. Primary outcome measures included intervention-related changes in 1) hippocampal seed-based functional connectivity patterns, 2) markers of structural integrity (e.g., volume, thickness) in regions linked to depression (e.g., hippocampus, ACC), 3) depression symptoms, and 4) cognitive functioning in domains commonly affected by depression (e.g., attention, executive function, learning and memory). Further, associations of cardiorespiratory fitness (VO_2 submax) and objective physical activity measures with outcome measures were also tested.

Given that this was a pilot study, the **primary** aim of this study was to establish the infrastructure, protocol, and procedures for recruiting, screening, enrolling, and maintaining a sample of 20 adults with major depression in a 12-week exercise intervention. We did not expect

intervention effects on outcome measures to achieve statistical significance, but rather were interested in exploring trends in brain-related changes and neurocognitive changes that may co-vary with treatment-related reductions in depressive symptoms. Identifying *possible* mechanisms of exercise effects on depression can help inform future treatment trials that are fully powered to test these mechanisms.

3.1 METHODS

3.1.1 Participants

Table 1. Experiment 1 Inclusion Criteria

Age 20-39 or 60-79 years old
PRIME-MD diagnosis: Major Depressive Disorder (MDD) or Depression NOS
Montgomery Asperg Depression Rating Scale $\geq$ 15
In-town and available to commute to Oakland during the course of the study
Study nurse practitioner approval to participate in ann12wk exerrcise intervention
Eligible to undergo MRI at 7T strength

Table 2. Experiment 1 Exclusion Criteria

Inability to provide informed consent
3MS < 84 or dementia
Lifetime diagnosis of bipolar I or II disorder, schizophrenia, schizoaffective disorder, schizophreniform disorder, delusional disorder, or current psychotic symptoms
Abuse of or dependence on alcohol or other substances within the past 3 months
High risk for suicide AND unable to be managed safely in the clinical trial
Contraindication to venlafaxine XR as determined by study physician

including history of intolerance of venlafaxine XR in the study target dosage range (venlafaxine XR at up to 300 mg/day)
Failure to respond to at least six weeks of venlafaxine (>300 mg/d)
Inability to communicate in English
Non-correctable clinically significant sensory impairment
Unstable medical illness, including delirium, uncontrolled diabetes mellitus, hypertension, hyperlipidemia, or cerebrovascular or cardiovascular risk factors that are not under medical management
Subjects taking psychotropic medications that cannot be safely tapered or discontinued prior to study initiation
History of antipsychotic induced leukopenia, neutropenia, or agranulocytosis
Exclusion criteria for MR scans include: cardiac pacemaker, aneurysm clip, cochlear implant, pregnancy, IUD, shrapnel, history of metal fragments in the eye, neurostimulators, weight >250 lbs., tinnitus, or claustrophobia
Report current medical condition or treatment for a medical condition that could affect balance, gait, or contraindicate participation in moderate intensity physical activity
Observed gait condition or use of walking assisted device
Current congestive heart failure, angina, uncontrolled arrhythmyia, or other symptoms indicative of an increased acute risk for a cardiovascular event; within the previous 12 months having a myocardial infarction, coronary artery bypass grafting, or angioplasty; conditions requiring chronic anticoagulation
Eating disorders
Report exercise > 3 days/week for > 20 minutes/day over the past 3 months
Report plans to relocate to a location not accessible to the study site or having employment, personal, or travel commitments that prohibit attendance to at least 80% of the scheduled intervention sessions and all of the scheduled assessments.

3.1.2 Recruitment Methods

Recruitment strategies involved referrals by word of mouth and referrals by clinicians in primary care and specialty mental health sectors, IRB approved advertisements in the community, in the print, and on air media (e.g., KDKA radio), postings on the internet and message boards (e.g., Craigslist, UPMC Extra, message boards in UPMC hospitals), use of (IRB # 0602151) “The Advanced Center for Intervention and Services Research for Late-Life Mood

Disorders (ACISR/LLMD) Research Registry", (IRB# PRO08010419) CTSI's Research Participant Registry, and presentations to lay groups of elderly and their families.

Intervention

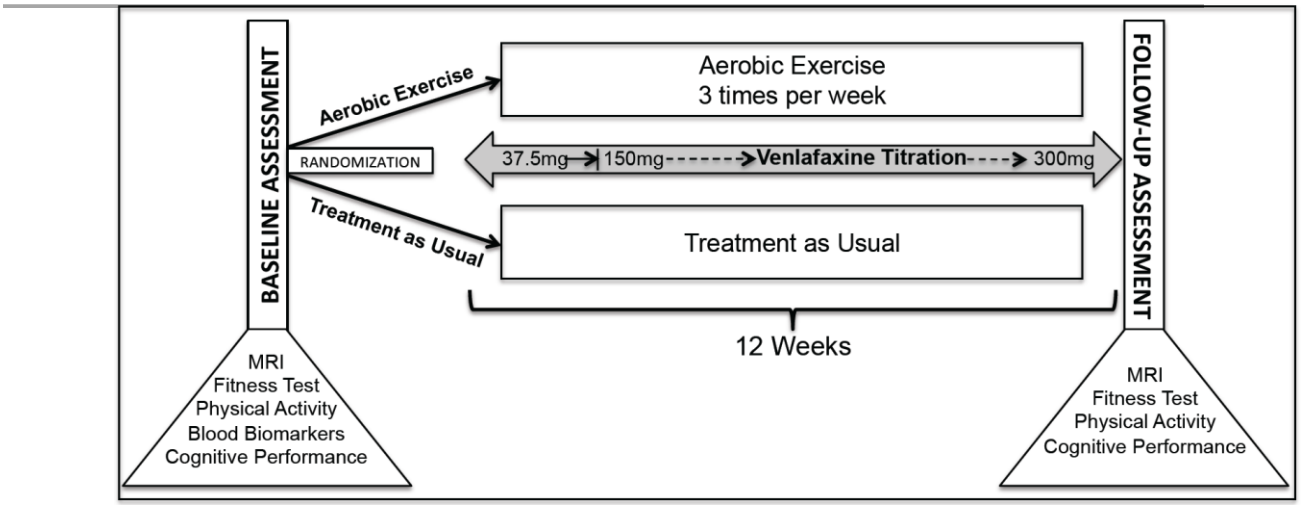

Figure 2. Study Timeline and Assessment Schedule for Experiment 1

3.1.3 Measures

Preliminary Screening (Phone Screens)

Potential participants with symptoms of depression who learned about the study called the Geriatric Psychiatry Neuroimaging Lab (PI: Howard Aizenstein, M.D., Ph.D) for eligibility screening. During this screening, potential participants were administered an MRI screening questionnaire to determine their eligibility to undergo an MRI. Once it was determined that the potential participant was eligible for neuroimaging and willing to continue with the research study, s/he was administered the Patient Health Questionnaire (PHQ-9) and Physical Activity Readiness Questionnaire (PAR-Q) (Thomas, Reading, & Shephard, 1992) by a research clinician to determine eligibility to participate in the aerobic exercise intervention. If the PHQ-9 was

scored 10 or higher and the potential participant met eligibility criteria to undergo neuroimaging and participate in physical activity, then the participant was invited to come in for further evaluation, at which time s/he signed the formal study consent form and then completed additional study assessments to determine eligibility to participate in the study.

Psychiatric Screening Evaluation

All participants were either younger adults (20-39 years old) or older adults (60-79 years old) suffering from depression (Major Depressive Disorder (MDD) as per the Primary Care Evaluation of Mental Disorders (PRIMEMD) criteria (Spitzer et al., 1994). A physician investigator in the study initially explained the risks and benefits of participating in the study prior to potential participants signing an informed consent form approved by the University of Pittsburgh Institutional Review Board (IRB). Participants then completed the baseline research psychiatric assessments administered by a research clinician at the Late-life Mood Disorders Clinic. Participants were screened with the PRIMEMD and MINI Neuropsychiatric Interview (Sheehan et al., 1998). The PRIMEMD and MINI composite assesses current and lifetime depression and other psychiatric disorders. It is used to clarify psychiatric inclusion and exclusion criteria. To determine eligibility, we used the DSM-IV criteria for dementia and Modified Mini Mental State Exam (3MS). The Montgomery Asberg Rating Scale for Depression (MADRS) was also administered, and subjects scoring 15 or greater were eligible for the study (Montgomery & Asberg, 1979). At the time of enrollment, and prior to receiving any study medication, all participants completed a medical history and physical examination to determine whether they can safely take the study medication and to determine whether there might be a medical illness that is causing the symptoms of depression. All ineffective psychotropic medications were tapered and discontinued before starting the study medication, venlafaxine XR.

Participants were required to be antidepressant-free for a minimum of seven days prior to completing a baseline brain MRI.

Screening Measures

Primary Care Evaluation of Mental Disorders (PRIME-MD): This was used as a diagnostic screening tool to confirm diagnosis of Major Depression, and to screen out individuals with exclusionary psychiatric diagnoses (i.e., bipolar disorder)(Spitzer et al., 1994).

Physical Activity Readiness Questionnaire (PAR-Q): This was used to assess any contraindications for physical activity while screening potential participants over the phone (Thomas et al., 1992). The PAR-Q is a 9-item questionnaire with dichotomous responses. Participants scoring >2 on this questionnaire required PCP approval for participation in the study.

Baseline and Follow-Up Assessments

Before randomization into one of the two intervention groups (venlafaxine XR only vs. venlafaxine XR + exercise), and prior to receiving any study medication, participants underwent a series of baseline assessments to evaluate depression severity, physical activity levels, fitness levels, cognitive performance, and brain imaging. These assessments could be done in up to four visits or could be combined into fewer depending on the participant's preference. Each of these assessments is described below:

Physical Activity Level Assessment:

Physical activity levels were assessed using a Sensewear physical activity-monitoring device over a period of 1-week at baseline and post-intervention. This device is worn on the upper left arm by the triceps and records body temperature, movement, energy expenditure, and sleep efficiency. Participants were asked to wear the device for a period of 1 week except while showering or swimming. Physical activity measures collected using this device were processed using BodyMedia SenseWear software.

Depression Severity:

The Montgomery-Asperg Depression Rating Scale (MADRS) was used to assess severity of depressive symptoms (Montgomery & Asberg, 1979). This is a 10-item questionnaire, in which each item yields a score of 0-6, with a total possible score of 60. Scores ranging between 0-6 indicate minimal depressive symptoms, and a symptom rating of <7 is frequently used to assess remission from a depressive episode. Scores ranging from 7-19 are indicative of mild depression, scores ranging from 20-34 are indicative of moderate depression, and scores >34 are indicative of severe depression. The MADRS has shown to have good reliability and validity (Maier et al., 1988).

Cardiorespiratory Fitness Level Assessment:

Participants were provided with 5-10 minutes of warm-up stretching exercises. The participant then walked on a motor-driven treadmill at a self-selected speed between 2.0-4.0mph. Participants walked at his/her self-selected speed, and there were 2% grade increments every two minutes to a maximal heart rate of 85% of the age-based maximum (220-age) or a rating of perceived exertion equal to or greater than 15 for those individuals whose heart rate response

was blunted due to medication. The submaximal VO_2 assessment usually lasted approximately 15 minutes, at which time the participant was helped off of the treadmill and allowed a cooldown session. Blood pressure was also monitored both before and after the fitness test to ensure that changes in blood pressure resulting from exercise were all normal.

Cognitive Performance Assessment:

A comprehensive neuropsychological battery was administered by trained clinicians. The neuropsychological battery focused on cognitive domains most affected by normal aging, including attention/processing speed, episodic memory, and executive functions. It also included a brief measure of premorbid IQ. All of the tests have demonstrated reliability and validity. The cognitive assessments in this battery and domains assessed are described below and summarized in Table 1

Attention and Processing Speed

Basic attention was assessed by the RBANS Digit Span subtest (forward span), an auditory digit repetition task. Attention and psychomotor speed (processing speed) was assessed using the RBANS Coding task, a speeded task in which participants were asked to match digits to symbols. Participants' performance on these two tests was combined to create an Attention Index score, which was used in data analyses, in addition to individual cognitive tasks. The Wechsler Assessment of Intelligence Scale-4th edition (WAIS-IV) Digit Span subtest, a 3-part digit repetition task, was also used to assess basic attention and working memory (Benson, Hulac, & Kranzler, 2010).

Executive Functioning

1) Perceptual inhibition was assessed using the Computerized Motor and Perceptual Inhibition Test (MAPIT) (Jennings, Mendelson, Redfern, & Nebes, 2011). The MAPIT task is a computerized assessment of perceptual and motor inhibition, and has previously been shown to detect age-differences in inhibition processes (Jennings et al., 2011). In this task assessing perceptual inhibition, the participant is shown an arrow pointing left or right and positioned on the screen on the side congruent or incongruent with the direction of the arrow. Participants are asked to respond to the key consistent with the direction of the arrow regardless of the spatial position of the arrow on the screen. (Jennings et al., 2011).

2) Verbal response inhibition was assessed using condition 3 of the DKEFS Color Word Interference Task, in which participants were asked to inhibit the automatic dominant response of reading while naming colors aloud.

3) The D-KEFS Trail Making Task is a speeded visual scanning and motor sequencing task, in which set-shifting is assessed by comparing the participant's response time in completing a motor sequencing task while switching between numbers and letters in order, relative to the response time for completing a simple motor sequencing task.

4) The D-KEFS Color Word Interference Task condition 4 assesses the ability to flexibly switch between rules for inhibiting specific verbal responses (reading vs. color naming) during a speeded verbal recitation task.

Memory

Delayed verbal memory was assessed using the RBANS word-list recall and recognition tasks and RBANS story-recall task. In these tasks, participants are asked to freely recall words

from a 10-word list learned 20-minutes earlier, recognize words from that 10-word list out of 20 of words, and freely recall a 2-sentence story that they learned 20-minutes earlier, respectively. Delayed nonverbal memory was assessed by asking participants to reconstruct a geometric figure from memory that they copied 20-minutes earlier. Participants' performance on these 4 measures were combined using RBANS age-based norms to create a Delayed Memory Index score, which was used in data analyses, in addition to the individual cognitive tasks. Delayed verbal memory was also assessed using the CVLT-II delayed recall and recognition tasks; in these tasks, participants were asked to freely recall words from a 20-word list learned 20-minutes earlier and recognize words from that 20-word list.

Visuospatial Function

Visuospatial function was assessed using two tasks that were described earlier in Experiment 1: the RBANS figure copy and line orientation subtests. Participants' performance on these two tasks were combined using RBANS age-based norms to create a Visuospatial Function Index, which was used in data analyses, in addition to individual subtest scores.

Verbal Fluency

Semantic fluency was assessed using an RBANS semantic fluency task described in Experiment 1. Phonemic fluency was assessed using a the Controlled Oral Word Association Test (COWAR), in which participants were asked to generate as many words as possible beginning with a particular letter within one minute (Benton, Hamsher, & AB, 1982). Participants were asked to complete three trials in response to three letters (FAS), and trial scores were summed.

Table 3. Summary of Cognitive Measures used in Experiment 1

Experiment 1	
Cognitive Domains	**Cognitive Measures**
Attention & Processing Speed	WAIS-IV Digit Span Task RBANS Coding Subtest
Executive Function	DKEFS Color-Word Interference Conditions 3 & 4 Computerized Perceptual Inhibition Test DKEFS Trail Making Test Condition 4 vs. 5 Contrast Scaled CVLT-II Proactive and Retroactive Interference Scaled Score
Learning and Memory	RBANS List Learning Raw Score CVLT-II List Learning T-score CVLT-II Delayed Recall RBANS Modified Delayed Memory Index
Visuospatial Skills	RBANS Modified Visuospatial Constructional Index
Language Skills	RBANS Language Index

Neuroimaging

Participants underwent structural and resting-state functional MRI scanning on a 7 Tesla (7T) Siemens scanner. This 7T system is a Siemens retrofit of a GE magnet. As part of this retrofit, the scanner was upgraded to 32 independent receive channels, each other them with multi-nuclear capabilities. To achieve high slew rate, the scanner is fitted with a head only, removable gradient set capable of 80 mT/m gradients and 800mT/m/s slew rate. The 7T supports parallel transmission capabilities with the addition of a parallel transmission unit from Siemens Medical Systems. This unit provides 8 independent transmission channels as well as support for additional gradient controllers that could be used for dynamic shimming applications. All of these development activities are supported by an onsite systems engineer from Siemens Medical Systems and MR faculty with expertise in MRI hardware.

High resolution T1 weighted brain images were collected using a 3D Magnetization Prepared Rapid Gradient Echo Imaging (MPRAGE) protocol, collecting 256 contiguous slices. Scanning parameters include an echo time (TE) of 2.5 ms, repetition time (TR) of 3,000ms, and field of view (FOV) of 176 x 223 mm. Participants also underwent a functional scan, during which they were asked to focus on a fixation cross while not thinking about anything in particular and not falling asleep. T2*-weighted blood oxygen-level dependent (BOLD) acquisition using gradient-echo echoplanar imaging (EPI) was collected using the following parameters: repetition time = 2500 ms, echo time = 20 ms, field of view= 176 x 223, slices = 155). After completion of the baseline scan, participants were administered Venlafaxine XR or Venlafaxine XR + aerobic exercise in a double-blind randomized design. Participants underwent another structural and functional MRI scan on the 7T scanner after completing the intervention. Three participants completed baseline and post-intervention MRI scans on a 3 Tesla Scanner due to a temporary shutdown of the 7T scanner for 6 weeks. The same imaging protocols were completed (i.e., MPRAGE and EPI) and similar scanning parameters were used.

3.1.4 Data Analysis

3.1.4.1 Behavioral Data Analysis (Aims 1.1 and 2.1)

Repeated Measures ANOVA was used to examine whether treatment with aerobic exercise + antidepressant medication led to a greater reduction in depressive symptoms (Aim 1.1) relative to antidepressant medication alone over 12-weeks. Specifically, group differences in change in depressive symptoms were examined over seven time-points (week 1, 2, 4,6,8,10,12) using a group x time interaction, adjusting for titration of antidepressant medication. Exercise-related changes in cognitive functioning was also tested using repeated measures ANCOVAs,

adjusting for age and years of education. For all models, group differences at baseline and post-intervention and change over time were tested to understand whether adding exercise to medication treatment for depression magnifies antidepressant effects and/or improvements in cognitive functioning. Given the high likelihood that this dataset is underpowered to detect significant interaction effects, t-tests were additionally used to test the presence of post-intervention group differences in depressive symptoms/cognitive function that were not present at baseline. If so, group differences at baseline were examined. Sensitivity analyses using regression models were conducted to examine the association of change in fitness and levels with change in depressive symptoms and change in cognitive performance.

3.1.4.2 Aim 3 Neuroimaging Data Analysis

Longitudinal Structural Neuroimaging Data Analysis

Preprocessing:

Structural MR data from baseline and post-intervention scans were preprocessed using tools in the FMRIB Software Library (Image Analysis Group, FMRIB, Oxford, UK; http://www.fmrib.ox.ac.uk/fsl/; (S. M. Smith et al., 2004)). All high-resolution MPRAGE images were pre-processed using the following steps: (1) non-brain matter was removed using the brain extraction technique in FSL (S. M. Smith & Nichols, 2009). (2) All brain-extracted images were visually inspected for any residual non-brain matter, and any residual matter was then manually removed from the image. (3) Next, these brain-extracted images were segmented into gray matter, white matter, and cerebrospinal fluid using FSL's automated segmentation technique (Zhang, Brady, & Smith, 2001). Values were thresholded at >.2 to eliminate voxels that are of questionable tissue type. (4) Next, all images (across time points) were averaged to create a

study-specific template that was adjusted for sample and time specific variation. The partial volume estimate maps of gray matter were then registered to the study specific template (Jenkinson & Smith, 2001). (5) Each voxel of each registered gray matter image was modulated by applying the Jacobian determinant from the transformation matrix (Good et al., 2001b). (6) These modulated images were concatenated into a 4D image, which was smoothed using a 3 mm Gaussian kernel. Statistical analyses were conducted on these segmented, registered, modulated, and smoothed gray matter images.

Longitudinal Whole-Brain Volumetric Analyses

Intervention-related volumetric changes across the whole-brain were examined using voxel-based morphometry (VBM), a classic semi-automated approach for identifying voxelwise partial volume estimates. VBM analysis computes the probability that each voxel in a structural MR image is cerebrospinal fluid, gray matter, or white matter and yields statistical maps for each voxel type (see (Ashburner & Friston, 2000) for a detailed description of VBM methods). Voxels are then classified into the structural category with the highest probability and can be statistically analyzed between subjects. Separate statistical maps are created for gray matter voxels and white matter voxels, which can then be used for volumetric analysis. For the current study, I limited my investigation to gray matter statistical maps, as the advent of Diffusion Tensor Imaging has resulted in infrequent use of VBM to assess white matter volume. VBM has shown to be a reliable method for analyzing gray matter data from healthy older adults (S. J. Colcombe et al., 2006; Good et al., 2001a; Good et al., 2001b); and provides estimates that are similar to manual tracing in this population (Kennedy & Raz, 2009).

Longitudinal VBM analyses have been done in prior depression treatment trials to examine differences treatment effects on brain structure (R. Smith, Chen, Baxter, Fort, & Lane,

2013). Longitudinal regression models were conducted using FSL to examine the main effects of group and time, and a group x time interaction in predicting change in regional partial volume estimates, while adjusting for age and scanner type (i.e., 3T vs. 7T). Given that this dataset was underpowered to detect interactions, independent t-tests were additionally used to examine the presence of post-intervention group differences in voxelwise gray matter volume that were not present at baseline. This analysis was used to identify possible trends in exercise-related regional volumetric changes that can be tested in larger clinical trials.

Vertex-based morphological Brain Changes

Additionally, vertex-based estimates of regional gray matter thicknesss were generated using Freesurfer, version 6.0. Additionally, vertex-based estimates of regional gray matter thicknesss were generated using Freesurfer, version 6.0. The methods used to in the surface-based processing pipeline in Freesurfer are described in detail in Fischl et al., 1999. Briefly, 1) the image is registered with the MNI305 atlas, 2) the B1 bias field is estimated by measuring variation in white matter intensity, and images are bias-corrected on a voxelwise basis, 3) non-brain better is removed, 4) voxels are classified as white matter or non-white matter, 5) the white surface (between white and gray matter) and pial surface (between gray matter and CSF) are generated for each hemisphere and further refined, 6) the white and pial surfaces are overlaid on the original T1-weighted image, and 7) the distance between the white and pial surface is used to estimate gray matter thickness at each location in the cortex.

In this study, the exploration of exercise-related changes in cortical thickness was limited to prefrontal, anterior cingulate, and medial temporal cortical regions, given that these have previously been associated with depression and appear to be sensitive to and exercise-related structural brain changes. Regional cortical thickness was calculated using the following steps: 1)

registration of the MPRAGE to the MNI atlas, 2) removal of non-brain matter, 3) segmentation of white matter segmentation, 4) generation of the 'white surface' in each hemisphere (i.e., surface between white matter and gray matter), 5) generation of the pial surface (i.e., surface between gray matter and CSF) , and 6) measurement of the distance between the white and pial surfaces at each location on the cortex .

Volumetric changes in Hippocampal Subfields

Numerous automated methods have been developed to segment the hippocampus in high-resolution structural MR images (Dill, Franco, & Pinho, 2015). An automated segmentation tool in Freesurfer, version 6.0 was used to segment hippocampal subfields using the T1 image only. This automated segmentation method uses a statistical model of image formation around the hippocampus to segment hippocampal subfields in each hemisphere, using Bayesian inference, and has been validated against manual tracing of hippocampal subfields (Leemput et al., 2009). Change in volume (in mm^3) of these hippocampal subfields was examined using paired-samples t-tests.

Functional Connectivity Analysis

Preprocessing

Functional MR data from baseline and post-intervention scans were pre-processed using tools in the FMRIB Software Library (Image Analysis Group, FMRIB, Oxford, UK; http://www.fmrib.ox.ac.uk/fsl/; (S. M. Smith et al., 2004)). Preprocessing of the functional data included four key steps: 1) removing non-brain matter from the images using the brain extraction technique (BET) tool in FSL (S. M. Smith & Nichols, 2009), 2) rigid body motion correction, 3) temporal filtering with a low pass and high pass filter, and 5) spatial smoothing using a 6 mm

3D Gaussian kernel. Functional MR data from baseline and post-intervention scans were pre-processed using tools in the FMRIB Software Library (Image Analysis Group, FMRIB, Oxford, UK; http://www.fmrib.ox.ac.uk/fsl/; (S. M. Smith et al., 2004)). Preprocessing of the functional data included four key steps: 1) removing non-brain matter from the images using the brain extraction technique (BET) tool in FSL (S. M. Smith & Nichols, 2009), 2) rigid body motion correction, 3) temporal filtering with a low pass and high pass filter, and 5) spatial smoothing using a 6 mm 3D Gaussian kernel. First, non-brain matter was removed from both the functional image and structural anatomical image. All brain-extracted images were visually inspected for any residual non-brain matter, and any residual matter was manually removed from the image by creating a brain mask and multiplying the manually revised brain mask by the original image. The data was then corrected for motion in 6 directions using the MCFLIRT tool in FSL. If excessive motion (peaks >1.7 mm) was found, the total motion for each participant in each direction was included as a covariate in the regression analyses to correct for motion. Next, the low pass filter was applied at 0.1 Hz (25) and the high-pass filter was separately applied at 0.01 Hz in the process of completing the first-level analysis for each participant. Finally, the data was spatially smoothed by adjusting voxel values based on nearby voxel values using a 3D 6 mm Gaussian kernel.

Registration

After completing preprocessing steps, the preprocessed functional images were registered to each participant's respective structural anatomical MPRAGE image for baseline and post-intervention scans. FSL's Linear Registration Technique (FLIRT) was used to transform each participant's functional image into standard space. Registration for each participant was visually checked before proceeding to statistical analyses.

Seed region extraction: Given the important role of the hippocampus in depression and its sensitivity to exercise-based interventions, a seed-based resting state analysis was conducted, using the left and right hippocampus as the primary seeds. In this type of analysis, the mean time series signal (across volumes) from regions-of-interest (i.e., seeds) is extracted from each participant and is correlated with every other voxel in the brain. All seed regions were determined separately for pre- and post-intervention MR images.

The left and right hippocampal seeds were segmented from the MPRAGE image using FreeSurfer image analysis suite (version 6.0; http://surfer.nmr.mgh.harvard.edu). The tool performs subcortical structural segmentation using the method presented in Fischl et al. (2002). First, each image is linearly aligned with an average template. A frequency histogram of possible structures (defined by the spatial template prior) is used to compute the probability of a given anatomical label (e.g., hippocampus) occurring at a given location. The prior of a given spatial arrangement of different labels (i.e., subcortical structures) is also incorporated into the segmentation. Using this process, the hippocampal seeds were determined from the MPRAGE image for each participant at each time point. The hippocampal seeds were then registered to the 4D functional image, and the mean time series (during the 6.5 minute passive viewing paradigm) was extracted for the left and right hippocampus.

Analysis

First, Pearson and Chi-square statistics were used to summarize demographic, physical, cognitive, and brain characteristics as appropriate. Mean differences between groups for all outcome measures were examined using independent samples t-tests. All analyses were two-tailed. Next, within-subject analyses were conducted on the preprocessed resting state data. Separate general linear models were conducted for both hippocampal seeds (left and right) on

each individual participant at each time point, controlling for the six rigid body directional motion parameters. Including the volume-by-volume motion parameters allowed for additional control against motion-related noise by accounting for the variability of movement throughout the time series for each participant. This within-subject analysis yielded two statistical parametric maps representing brain regions that were either positively or negatively functionally correlated with the seed regions (left and right hippocampus) for each participant at each time point (baseline, post-intervention). Fisher's r-to-z transformations were conducted on these maps and resulting z-score statistics were analyzed in the group-level analysis. The first goal in examining functional connectivity patterns in this dataset was to examine whether adding aerobic exercise to antidepressant medication treatment for depression yields greater changes in hippocampal connectivity patterns relative to treatment with antidepressant medication alone in adults with Major Depression. As such, the first step was to determine brain regions where connectivity changed across time as a function of group. Given the very small sample size of this study and the high likelihood of being insufficiently powered to detect Time x Group interaction effects, a more simplistic analytic approach (i.e., independent samples t-test examining group differences at each time point) was used to explore group differences in intervention-related change in hippocampal functional connectivity patterns. First, group differences in hippocampal functional connectivity patterns were examined post-intervention. Next, group differences in hippocampal functional connectivity patterns were tested at baseline. Group differences in hippocampal connectivity patterns post-intervention that were not present at baseline were hypothesized to be due to intervention-related effects. To examine the direction of change in functional correlations observed post-intervention (i.e., increase in positive correlation vs. attenuation of negative correlation) and to conduct additional analyses with behavioral variables,

the beta-values and z-scores in clusters that were functionally correlated with the hippocampal seeds post-intervention were extracted at both time points for each participant. These regions were then compared against participant fitness to examine whether change in fitness related to change in connectivity. Pearson correlations were run between percent change values (i.e., post-intervention – baseline, normalized by baseline value) for functional connectivity and percent change values for estimated VO_2 max and functional connectivity post-intervention was examined. We hypothesized that group differences in functional connectivity post-intervention would likely be attributable to intervention-related changes in fitness levels. If similar regions were correlated with the hippocampal seeds in both sets of analyses (i.e., group differences and change in fitness), it may suggest that change in fitness mediates group differences in functional connectivity observed post-intervention (although a formal mediation analysis was not conducted). To examine general medication-treatment related changes in hippocampal connectivity patterns, the association between percent change in depression severity (i.e., MADRS score) and functional connectivity post-intervention was examined. Finally, the association between depression severity at baseline and functional connectivity at baseline was examined in order to help interpret post-intervention group differences in functional connectivity post-intervention.

3.1.5 Predictions

Effects of Aerobic Exercise on Depression

I predicted that both treatment groups would demonstrate a clinically significant decline in depressive symptoms, with most participants experiencing full remission from depression after completion of the trial. In addition, the ADM + EX group would demonstrate a greater decline in depression severity, an earlier trajectory of decline, and greater stability of decline in depressive symptoms during the 12-week intervention relative to the ADM only group. Finally, increases in fitness levels and daily physical activity levels would be associated with a decline in depression severity.

Effects of Aerobic Exercise on Cognitive Function in Depressed Adults

I predicted that both treatment groups would demonstrate improvements in cognitive efficiency. The ADM + EX group would demonstrate a greater increase in cognitive performance within domains commonly affected by depression (i.e., attention, processing speed, executive functioning, learning and memory) relative to the ADM only group. Finally, greater improvements in cognitive performance would be observed in older adults relative to younger adults across treatment groups.

Effects of Aerobic Exercise on Hippocampal Connectivity Patterns

I predicted that both treatment groups would demonstrate a *reduction* in hippocampal connectivity with DMN regions, with the ADM + EX group showing broader reductions in hippocampal connectivity with DMN regions relative to the ADM only group, suggestive of greater improvements in neural efficiency.

Effects of Aerobic Exercise on Brain Morphology

a. Although 12-weeks is a relatively brief time course for detecting gross structural changes in the brain, changes *may* be observed in both treatment groups for brain markers of structural integrity (i.e., gray matter thickness, surface area, volume) in regions commonly showing volumetric abnormalities in depression (i.e., ACC, mPFC, HC, ventral striatum, amygdala). Possible volumetric changes may be magnified in the ADM + EX group relative to the ADM only group (e.g., greater number and/or broader areas).

b. Exploratory analyses of intervention-related volumetric changes in hippocampal subfields may distinguish hippocampal subfields sensitive to the effects of aerobic exercise relative to the effects of SNRI medication in depressed adults (e.g., dentate gyrus). Older adults may be more likely to demonstrate structural brain changes across treatment groups relative to younger adults, given that LLD is associated with broader reductions in structural brain integrity relative to depression in younger adults. Specifically, older adults may demonstrate structural changes in regions associated with depression and age-related atrophy (e.g., PFC).

3.2 RESULTS EXPERIMENT 1

3.2.1 Feasibility

The primary aim of this pilot study was to establish the feasibility of conducting an exercise intervention study in depressed older and younger adults. Detailed results regarding

recruitment can be found in Appendix A. Briefly, 192 adults were screened over the phone. Primary reasons for exclusion after screening included 1) not meeting DSM-5 criteria for a Major Depressive Episode 2) lack of interest in participation after learning about the study 3) current or past diagnosis of bipolar disorder or a psychotic spectrum disorder, 4) exercising more than three days per week, more than 20 minutes per day over the last three months, 5) ineligibility due to age-criteria (i.e., too young for older adult group) 6) contraindications for MRI, and 7) unwillingness to taper off of current antidepressant medication or safety concerns related to tapering off of current medication regimen. Thirty-one participants (16%) enrolled in the study, of which 15 participants (48%) started treatment. Key reasons for exclusion after enrolling in the study included history of exclusionary medical or comorbid psychiatric diagnoses identified after enrollment, administrative reasons (i.e., difficulty with transportation, moved), and participant withdrawal of consent. Of the 15 participants who were randomized to treatment groups (i.e., MED=8 EX=7), 11 participants (73%) completed the study (i.e., MED=5 EX=6). Two participants were lost to follow-up, one participant was non-adherent to study procedures (e.g., refusing ratings), and one participant withdrew consent. All participants completing the study completed MRI, biomarker, cognitive, clinical, fitness, and physical activity assessments without difficulty or endorsing burden related to the quantity of assessments or length of time required to complete study assessments.

Barriers to Feasibility and Possible Solutions

The principal barrier to feasibility of this study was identifying optimal recruitment strategies to enroll depressed older adults. Recruitment difficulties of this sub-set of the participant sample largely accounted for the prolonged study timeline (i.e., 24 months to

completion vs. target of 12 months) and resulted in disproportionately higher enrollment of younger adults relative to older adults (i.e., 10 younger adults vs. 5 older adults). Primary recruitment strategies used included advertisement in University of Pittsburgh Clinical and Translational Science Institute (CTSI) Research Registry via internet and paper-based advertising, advertisements via radio, bus, and newspaper, Online advertisement via Craig's List and ClinicalTrials.gov, flyers and brochures distributed locally around the University of Pittsburgh campus and senior living centers, collaborations with medical providers at two primary care clinics, and recruitment presentations at senior centers. Successful recruitment strategies included the research registry (n=5), paper-based or radio advertisements (n=4), flyers (n=2), online advertisements (n=2), referral from medical provider (n=1), and self-referral through word of mouth (n=1).

The most successful recruitment strategy for older adult participants was the CTSI research registry. Unfortunately, this strategy was utilized heavily only late in the course of the study after other approaches had failed. (i.e., less than 6 months before the end of study recruitment). The pattern of recruitment over the course of the study revealed that recruitment was most successful in the spring and summer seasons; older adults may be especially sensitive to weather-related variability in recruitment due to transportation barriers and greater anxiety regarding driving in inclement weather conditions. Significant time and resources were invested towards setting up a collaboration with the Pennsylvania Pharmaceutical Assistance Contract for the Elderly (PACE) program to assist with recruitment of older adults; however, this recruitment strategy ultimately could not be implemented due to the PACE program's ethical concerns regarding promotion of a specific medication to their members for the purposes of this study. Educational/recruitment presentations at local senior centers did not yield new participants but

were helpful in understanding sociocultural barriers to recruitment of depressed older adults. Feedback during these presentations revealed the broader older adult community's bias against participation in a pharmaceutical treatment study in general, and more specifically against the use of pharmaceuticals to address a mental health condition; audience members frequently expressed they may be interested if this was a strictly non-pharmacological intervention (i.e., exercise only). Further, audience members at these senior centers expressed reluctance to promote this study to their family and friends, even if they were concerned about their mental health, due to stigma associated with both having mental health symptoms and mental health treatment utilization. Ultimately, older adult recruitment challenges in this study may primarily be attributed to insufficient allocation of resources towards advertising platforms that target older adults (e.g., radio, newspaper, and research registry), wasted resource allocation to an unimplemented recruitment strategy (i.e., PACE), inadequate efforts to establish collaborations with local primary care providers, and limited availability of resources to maintain a continuous presence in primary care clinics with which collaboration was established. Despite these recruitment challenges , we learned how to improve recruitment towards the end of the funding period for the intervention and learned a number of strategies to ensure feasibility for similar future studies.

Future studies can avoid the above-mentioned recruitment challenges by allotting a greater amount of resources to 'active' relative to 'passive' recruitment efforts, with an emphasis on recruitment strategies targeting older adults. Active recruitment approaches that may have a high yield include initiating meaningful collaborations with primary care offices through in-person visits and periodic presentations to staff members; maintaining a presence in the clinic may ultimately lead to a consistent referral source. A second recruitment approach that was not

implemented in this pilot study is presenting to groups of mental health providers in different contexts to raise awareness of the study. Future studies should also ensure the allocation of adequate resources to multiple recruitment platforms in parallel rather than using serial recruitment approach (i.e., relying heavily on one recruitment strategy at a time). In order to better target older adults, future studies may also consider allocation of funds for transportation arrangements as necessary, given that this can be a key barrier to study participation among older adults. Further, research registries should be tapped into at frequent intervals using online and paper-based advertising, especially during the spring and summer, since this yielded the greatest success in the present study.

3.2.2 Participant Characteristics

Fifteen participants (10 younger adults (YA) and 5 older adults (OA)) with Major Depression were randomized to receive Venlafaxine XR (YA=5, OA=3) or Venlafaxine XR and supervised aerobic exercise (YA=5, OA=2) for 12-weeks. Among the younger adult participants, attrition was significantly higher for the medication only group (60%) relative to the medication + exercise group (20%). Among younger adults in the medication only group, one participant was lost to follow-up immediately after completing baseline study assessments, one participant was unable to be contacted from weeks 5-11 but returned to complete post-intervention assessments, and a third participant was lost to follow-up after completing eight weeks of the study. Among younger adults randomized to the medication + exercise group, only one participant was lost to follow-up immediately after completing baseline study assessments. Among the older adult participants, there was 0% attrition among both treatment groups. Of those who completed the study, all participants were reportedly adherent to the medication

regimen, and participants randomized to the exercise intervention attended 91% of the sessions on average out of 36 sessions. Exercise adherence did not significantly differ between younger and older adults (YA=93% OA=90%).

Treatment groups differed on sex distribution, with the OA MED group including only women. Other treatment groups did not differ from each other on sex. Across older and younger adults, the MED group included 80% women whereas the EX group included 50% women. Education did not significantly differ across groups. The OA EX and YA EX groups included significantly more non-Caucasian participants relative to the MED groups. Duration of current Major Depressive Episode was significantly longer for participants in the OA MED and YA MED groups relative to the EX groups. None of the participants in the EX groups were using antidepressant medication at the time of enrollment in the study, whereas 40% of the participants in the MED groups (combined OA and YA) had to be tapered off of an antidepressant medication at baseline prior to starting the study medication. Body Mass Index (BMI), cardiorespiratory fitness (i.e., EstimatedVO_2 Max), and physical activity levels did not differ between treatment groups at baseline (See Table 2).

Table 4. Participant Characteristics at Baseline

	Medication Only		Medication +Exercise	
Variable	Older (N=3)	Younger (N=5)	Older (N=2)	Younger (N=5)
Age	62.33	33.60	67.50	28.60
Sex (% Female)	100	60	50	60
Education	15.33	14.40	16.00	16.40
Race (%White)	100	80	50	60
MADRS Baseline	22.33 (3.51)	24.50 (5.20)	24.50 (0.71)	24.50 (6.46)
	23.57 (4.35)		24.50 (5.01)	
Duration MDE (weeks) Baseline	208.44 (269.91)	55.8 (47.0)	27.50 (34.64)	28.2(29.3)
	113.00 (168.25)		28.00 (27.78)	
Age at 1st MDE	53.00 (8.89)	24.00 (4.63)	41.5 (16.26)	17.20(8.3 4)
	34.88 (16.13)		24.14 (15.20)	
% Antidepressant Use Baseline	33	20	0	0
	40		0	
BMI Baseline	30.35 (1.70)	32.04 (3.61)	26.62 (4.19)	28.34 (7.40)
	31.41 (3.00)		27.85 (6.33)	
Est. VO_2 Max Baseline	27.73 (8.13)	26.73 (3.47)	26.12 (6.78)	30.40(6.6 2)
	27.11 (5.10)		29.18 (6.42)	
Hours of Daily PA Baseline	0.64 (0.42)	1.94 (0.85)	2.74 (1.3)	1.42 (1.13)
	1.39 (0.95)		1.86 (1.26)	

3.2.3 Intervention Fidelity

The EX group showed an increase in fitness (mean Δ= 3.74% SD=10.74) whereas the MED group showed a decline in fitness (mean Δ= -8.30% SD=16.52) from baseline to post-intervention. Group differences in change in fitness were non-significant due to high within-group variability (t=-1.66 p=0.132). Among younger adults, the EX group showed an increase in fitness from baseline to post-intervention (mean Δ=8.76% SD=6.68), whereas the MED group showed a decline in fitness from baseline to post-intervention (mean Δ= -2.23% SD=12.54). Similar to the overall sample, group differences between the young adult MED and EX groups

were non-significant due to high variability within the MED group (t= -1.085 p=0.454). Among older adult participants, both the EX and MED groups showed a decline in fitness (EX: mean=-6.29% SD=11.86; MED: mean=-14.36 SD=20.35). The MED group showed a greater decline relative to the EX group on average, but group differences were non-significant due to high within-group variability (t=-0.492 p=0.657).

Treatment group differences in change in physical activity (PA) were examined using the following indicators: 1) daily hours of PA 2) hours of sedentary time 3) active energy expenditure 4) metabolic equivalents 5) time in moderate activity 6) time in vigorous activity 7) number of 10-minute bouts across time device is worn, and 8) minutes in 10-minute bouts of PA across time device is worn. A paired-samples t-test was conducted separately for each treatment group to examine change in indicators of PA from baseline to post-intervention. The EX group did not show an increase in any indicator of PA. The MED group also did not show an increase in any indicator of PA. Both the MED and EX groups showed a non-significant decline in total hours of sedentary time (MED: t=1.938 p=0.125; EX: t= 1.907 p=0.115). As reported earlier, treatment groups did not significantly differ on indicators of PA at baseline. However, the EX group engaged in a greater amount of activity in 10-minute bouts relative of MED group post-intervention (t= -2.602 p =0.029) (See Table 3).

Table 5. Intervention Fidelity Outcomes

	MEDICATION ONLY		MEDICATION + EXERCISE	
Variable	**Older (N=3)**	**Younger (N=2)**	**Older (N=2)**	**Younger (N=4)**
% Adherence (Completed Study)	100%	40%	100%	80%
	63%		86%	
% Change Estimated VO_2 Max	-14.36% (20.35)	-2.23% (12.54)	-6.29% (11.86)	8.76% (6.68)
	-8.30% (16.52)		3.74% (10.74)	
% Requiring Venlafaxine Titration > 150 mg	33%	50%	100%	25%
	40%		50%	
% Exercise Adherence (Sessions Attended)	--	--	93%	90%
			91%	
% Remission from Depression (MADRS Score < 10)	67%	100%	0%	100%
	83.3%		67%	
MADRS Final	8.33	10.50	11.50	4.25
	9.57		6.67	
Raw Change MADRS	-11.33 (6.66)	-14.50 (9.88)	-14.00 (7.07)	-18.25 (6.29)
	-13.14 (8.15)		-16.83 (6.21)	
% Change MADRS	-65.48%	-62.64%	-57.31%	-82.86%
	-63.85% (32.56)		-74.34% (16.37)	

Table 6. Physical Activity and Fitness Outcomes

	MEDICATION ONLY		MEDICATION + EXERCISE	
Variable	**Older**	**Younger**	**Older**	**Younger**
Est. VO2 Max Baseline	27.73	26.73	26.12	30.40
Est. VO2 Max Final	23.52	24.55	24.23	33.89
Change Est. VO2 Max	-4.22	-0.65	-1.89	3.19
% Change Est. VO2 Max	-14.36	-2.23	-6.29	8.76
Avg. Steps Per Day Baseline	5032.11	10716.93	18037.21	6548.52
Avg. Steps Per Day Final	4148.76	14586.55	5805.79	9895.05
Avg. Daily Measured Active EE Baseline	201.64	692.52	911.04	422.70
Avg. Daily Measured Active EE Final	212.47	968.89	324.03	694.21
Minutes of PA Per Day Baseline	38.78	116.92	164.78	85.34
Minutes of PA Per Day Final	38.28	171.36	74.82	124.63
# of BOUTS Baseline	1.67	6.25	9.00	15.75
# of BOUTS Final	0.67	3.67	6.50	15.25
Minutes In BOUTS Baseline	21.33	86.25	161.50	293.00
Minutes In BOUTS Final	7.33	51.67	110.0	264.00
Hours of Armband Data Baseline	183.62	142.72	82.38	203.10
Hours of Armband Data Final	127.26	76.08	75.93	155.23
Sleep Efficiency Baseline	73.05	76.68	83.06	82.46
Sleep Efficiency Final	71.95	58.06	79.67	79.23

3.2.4 Depression Outcomes

Participants in both treatment groups showed a significant reduction in depressive symptoms (MED: mean =-63.85% SD=35.56; EX: mean= -74.34% SD=16.37), with 83% achieving remission (i.e., MADRS score < 10) in the MED group and 67% achieving remission in the EX group. Groups did not significantly differ with regard to number of participants

requiring medication titration > 150 mg (i.e., standard dose). All younger adult participants in both groups achieved remission, whereas two out of three older adults in the MED group and zero out of two older adults in the EX group achieved remission. Notably both OA EX group members achieved near remission (i.e., MADRS final score =11 & 12, respectively). There was no group difference in trajectory of decline in depressive symptoms during the course of the intervention (Repeated Measures ANOVA: F= 0.227 p= 0.966); however, the EX group demonstrated a more stable decline in depressive symptoms after the first 4 weeks relative to the MED group (See Figures 2a and 2b). Given that 5 out of 6 participants in the EX group and 2 out of 5 participants in the MED group showed improvements in fitness, the trajectory of change in depressive symptoms was examined as a function of a binary variable reflecting improvement in fitness. Trajectory of change in depressive symptoms did not significantly differ between those showing improvement in fitness relative to those not showing improvement in fitness; however, the stability of decline in depressive symptoms appeared even more prominent in the group showing improvement in fitness (i.e., more so than examining intervention group differences). Further, change in depression severity was examined as a function of age group, which revealed significant group differences (Repeated Measures ANOVA Age Group x MADRS: F= 2.412 p=0.039) such that younger adults showed more rapid and stable decline in depressive symptoms relative to older adults.

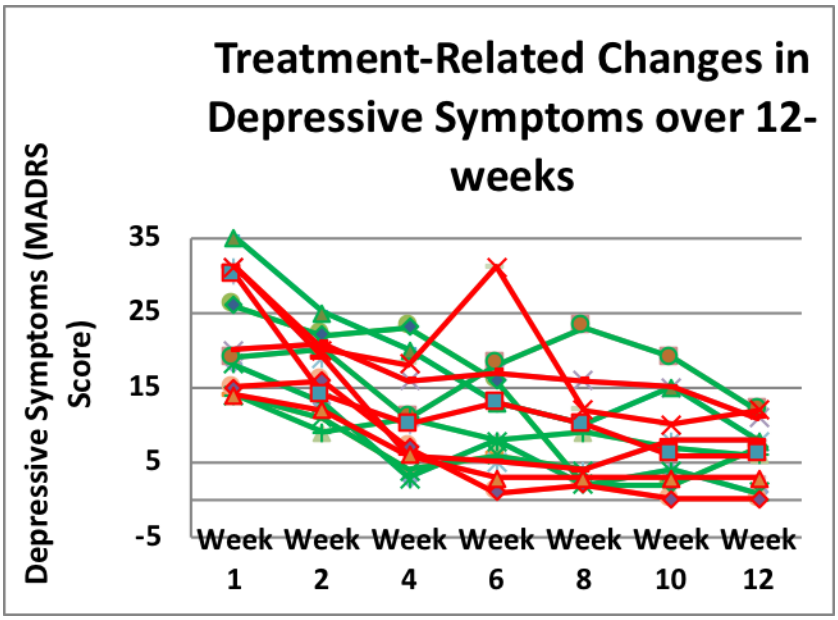

Figure 3 Spaghetti Plot showing individual trajectories of change in depression symptoms over the course of the intervention. RED=EXERCISE GROUP GREEN=MEDICATION ONLY GOUP

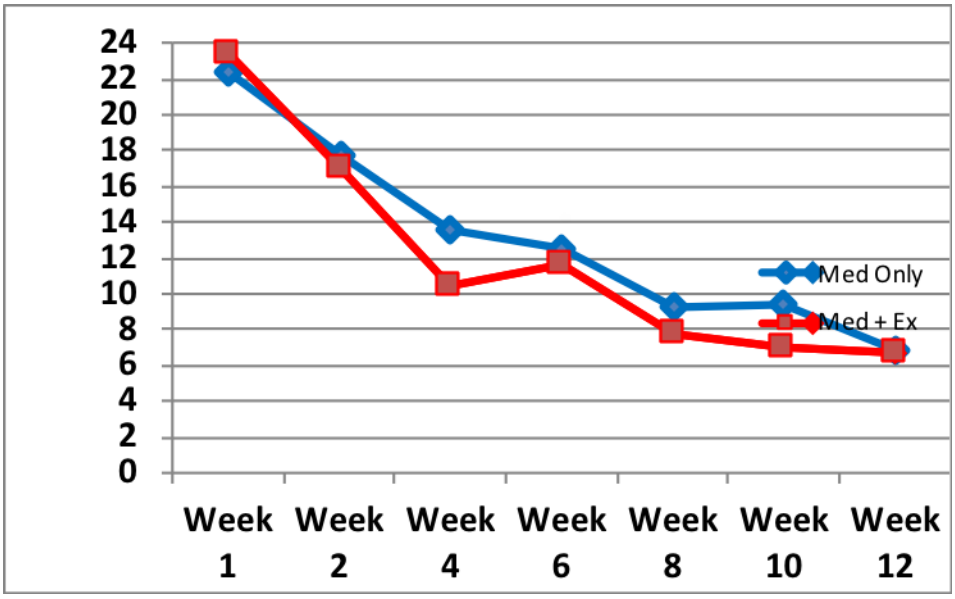

Figure 4. Group differences in Change in Depression Symptoms over the course of the Intervention.

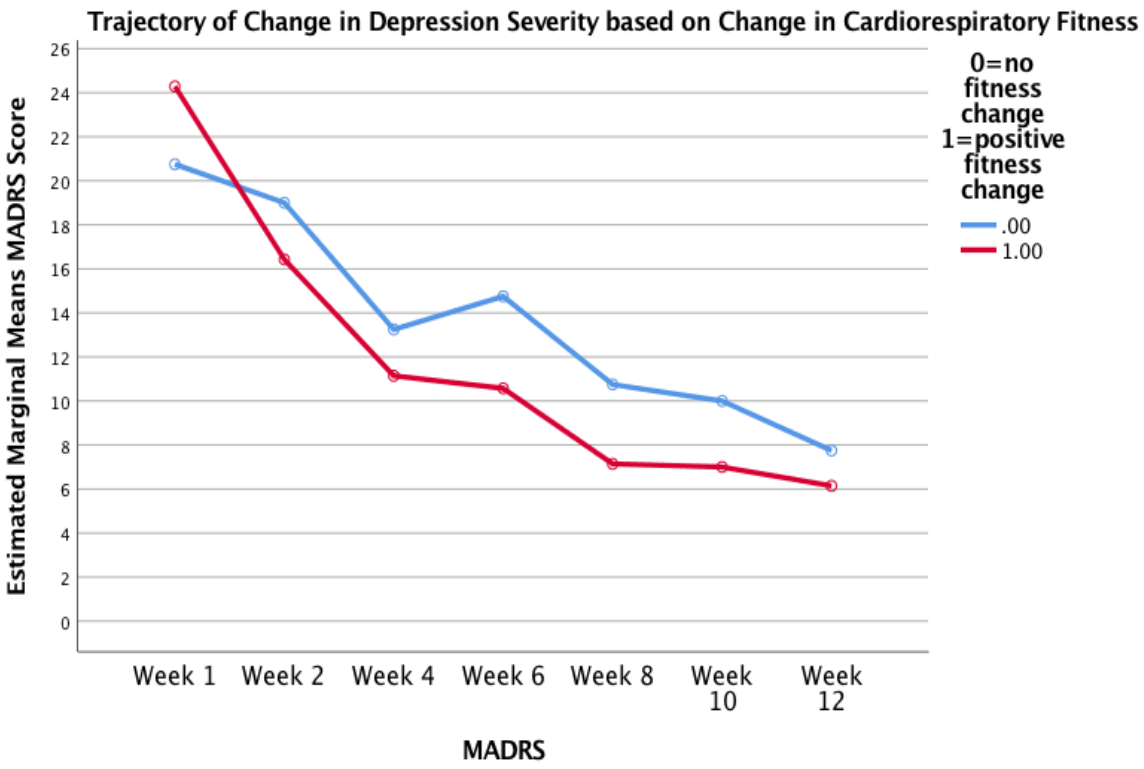

Figure 5. Trajectory of change in Depressive Symptoms over the course of the Intervention, split by participants showing increases versus no improvement or decreases in fitness levels.

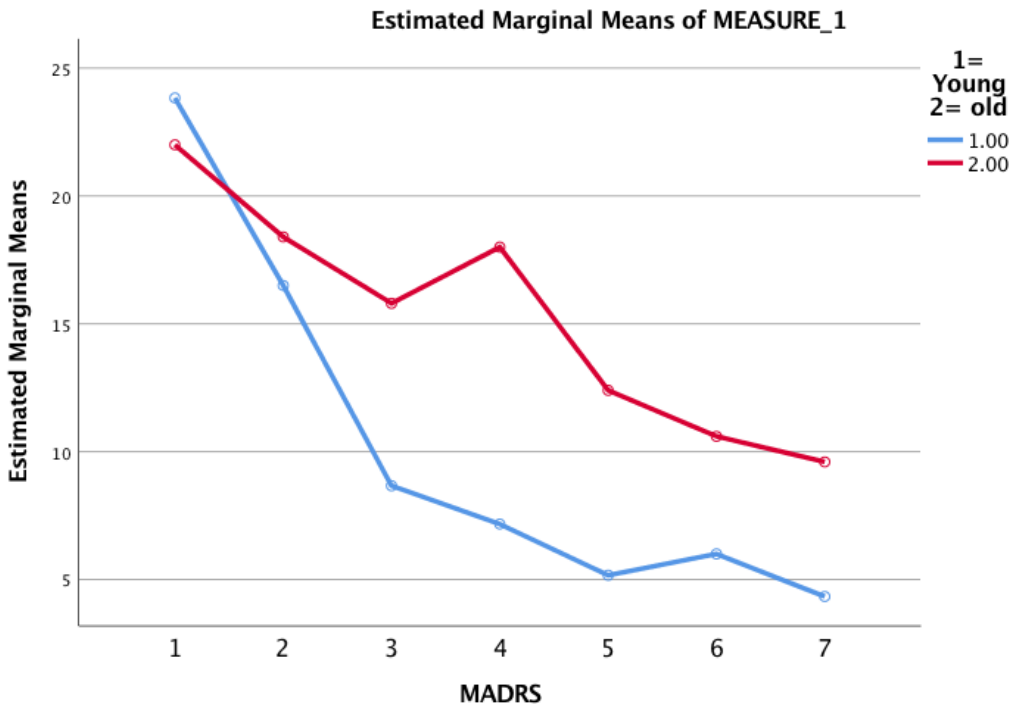

Figure 6 Separate Trajectories of Change in Depressive Symptoms for Older and Younger Adults across intervention groups.

3.2.5 Cognitive Outcomes

Participants across treatment groups did not differ on performance across most cognitive measures at baseline, with the exception of the EX group performing marginally better on measures of attention (t= -2.310, p=0.05) relative to the MED group. Generalized medication treatment effects (i.e., across both treatment groups) included improvement in attention (RBANS Attention Index (t= -2.495 p=0.037) and marginal improvement in verbal learning (CVLT List Learning: t=-2.115 p=0.064). The MED group showed improvement in global cognition (RBANS Total Index Score: t= -7.071 p0.006), response inhibition (D-KEFS Color Word

Interference Condition 4: t=-3.207 p=0.03), and verbal learning (RBANS Immediate Memory Index: t=-6.403 p=0.003). The EX group did not show significant changes in performance on any cognitive measures due to high within-group variability.

Given that late-life depression (LLD) is highly comorbid with cognitive impairment and cognitive deficits observed in LLD are more resistant to improvement with treatment, cognitive performance was also examined separately in older and younger adults. Consistent with age-related cognitive decline, older adults performed worse than younger adults on a measure of processing speed (RBANS Coding subtest Raw Score: t= 3.645 p=0.003) and showed a trend toward greater vulnerability to retroactive interference (CVLT retroactive interference Z-score t= -2.043 p=0.067) across both treatment groups at baseline. After completion of the intervention, older adults continued to perform worse the younger adults for processing speed (RBANS Coding subtest Raw Score: t= 2.975 p=0.016) and also performed worse than younger adults for basic attention (WAIS-IV Digit Span Forward Span: t= 3.159 p=0.010).

Among younger adults, the YA EX group performed better than the YA MED group on measures of visuospatial skills (RBANS Visuospatial/Constructional Index: t= -5.253 p=0.006) and psychomotor set-shifting (D-KEFS Trails Condition 4 vs. 5: t=-3.746 p=0.02), and marginally better than the MED group for global cognitive functioning (RBANS Total Index: t= -2.466 p=0.07) and working memory (WAIS-IV Digit Span Backwards Span: t=-2.242 p=0.088) at baseline. After completion of the intervention, the YA EX group continued to perform better than the YA MED group on a measure of psychomotor set-shifting (t= -2.416 p=0.07), but the difference became marginal. Although group differences in performance on the following measures were non-significant at baseline, after completing of the intervention, the YA EX group performed marginally better than the YA MED group on measures of basic attention

(WAIS-IV Digit Span Forward Span: t=-2.309 p=0.082), as well as verbal learning, memory recall, and recognition (CVLT List Learning: t= -2.705 p=0.071; CVLT Long-Delay Free Recall Z-score: t= -2.121 p=0.10; CVLT discriminability index Z-score: t=-2.359 p=0.078). Among older adults, the OA EX group performed marginally worse than the YA MED group on measures of visuospatial skills (RBANS Visuospatial/Constructional Index: t= 2.934 p=0.06) at baseline. After completion of the intervention, the OA EX group performed worse than the OA MED group on measures of language skills and verbal memory recall (RBANS Language Index: t=8.33 p=0.014; CVLT Long Delay Free Recall Z-score: t=3.919 p=0.03) and marginally worse than the OA MED group on a measure of verbal memory recognition (CVLT discriminability index Z-score: t=2.643 p=0.077) (See Table 5).

In a sensitivity analysis, improvement in fitness was strongly associated with better performance for perceptual inhibition (r=-0.645, p=0.044).

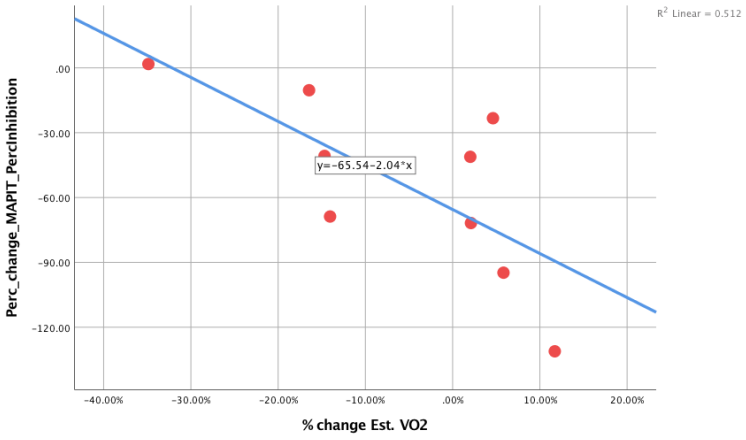

Figure 7. Correlation between %Change Fitness and %Change Perceptual Inhibition

Table 7. Experiment 1 Cognitive Outcomes

		Medication Only		Medication + Exercise	
	Variable	**Older N=3**	**Younger N=2**	**Older N=2**	**Younger N=4**
	Global Cognition				
RE	RBANS Total Index Score (SS)	95.00 (14.11)	80.00 (7.07)	77.00 (0.00)	101.00 (13.78)
OST	RBNS Total Index Score (SS)	100.5 (17.68)	85.50 (7.77)	81.50 (3.54)	102.75 (19.74)
	Attention/Processing Speed				
RE	RBANS Attention Index	78.67 (6.51)	78.50 (9.19)	76.50 (28.99)	97.50 (19.62)
OST	RBANS Attention Index	91.00 (8.49)	79.00 (21.21)	78.50 (26.16)	108.00 (16.73)
RE	RBANS Coding Subtest Raw Score	35.33 (5.03)	47.00 (4.24)	30.50 (0.71)	56.75 (11.47)
OST	RBANS Coding Subtest Raw Score	42.00 (2.83)	44.50 (12.02)	27.50 (6.36)	59.00 (9.83)
RE	Digit Span Forward Span	5.67 (1.15)	6.50 (2.12)	4.50 (0.71)	7.0 (1.41)
OST	Digit Span Forward Span	5.67 (1.15)	6.0 (1.41)	4.50 (0.71)	8.0 (0.82)
RE	Digit Span Backward Span	4.67 (1.15)	3.50 (0.71)	4.00 (1.40)	5.25 (0.96)
OST	Digit Span Backward Span	5.00 (1.00)	3.50 (0.71)	4.00 (1.40)	4.75 (0.97)
	Learning and Memory				
RE	RBANS Delayed Memory Index	107.33 (13.05)	89.50 (6.36)	84.00 (18.39)	99.50 (18.12)
OST	RBANS Delayed Memory Index	110.50 (14.85)	91.00 (4.24)	83.00 (16.97)	87.25 (24.66)
RE	CVLT-II List Trials 1-5 T-score	57.67 (16.44)	39.50 (3.54)	43.00 (22.63)	56.75 (14.43)
OST	CVLT-II List Trials 1-5 T-score	59.00 (18.74)	44.00 (1.41)	36.00 (7.07)	64.50 (15.02)
RE	CVLT-II Short Delay Recall Z-score	0.50 (1.80)	-2.00 (1.41)	-1.00 (2.12)	0.13 (1.38)
OST	CVLT-II Short Delay Recall Z-score	0.33 (2.08)	-1.75 (1.77)	-2.5 (0.71)	0.25 (0.96)
RE	CVLT-II Long-Delay Free Recall (Z)	0.17 (1.31)	-1.50 (0.00)	-1.25 (1.77)	0.00 (1.47)
OST	CVLT-II Long-Delay Free Recall (Z)	0.67 (0.76)	-2.00 (1.41)	-2.00 (0.71)	0.38 (1.25)
RE	CVLT-II Discriminability	0.50 (1.32)	-0.25 (0.35)	-0.75 (0.35)	-0.13 (1.11)
OST	CVLT-II Discriminability	0.83 (0.76)	-0.75 (1.06)	-0.75 (0.35)	0.63 (0.48)
	Visuospatial Skills				
RE	RBANS Visuospatial Const. Index	100.33 (14.01)	75 (4.24)	69.00 (4.24)	113.25 (9.39)
OST	RBANS Visuospatial Const. Index	94.33 (15.57)	97.00 (7.07)	85.50 (2.12)	106.25 (9.88)

	Executive Functioning				
RE	CWI3 Baseline	9.67 (0.57)	8.50 (2.12)	9.00 (2.83)	11.25 (3.40)
OST	CWI3 Final	9.67 (0.57)	9.50 (4.95)	8.50 (2.12)	10.25 (4.57)
RE	CWI4 Baseline	10.67 (2.08)	8.50 (3.54)	9.50 (2.12)	11.00 (3.74)
OST	CWI4 Final	11.33 (1.53)	10.50 (3.54)	8.50 (2.12)	12.00 (2.71)
RE	Trail Making 4vs.5 Baseline	8.67 (4.16)	4.50 (2.12)	10.00 (0)	9.50 (1.29)
OST	Trail Making 4vs.5 Final	10.00 (1.00)	5.50 (3.54)	5.50 (3.53)	10.00 (1.41)

3.2.6 Structural Brain Outcomes

Intervention-related change in brain structure was examined using two methods: 1) voxel-based morphometry, a semi-automated probabilistic method used to obtain voxelwise volume estimates of gray matter across the whole-brain and 1) a vertex-based automated segmentation method used to calculate regional gray matter thickness and surface area, in addition to volume in mm^3. For the purposes of this study, only gray matter thickness and volume were used in analyses.

3.2.6.1 Voxel-based morphometry

After obtaining partial volume estimates of gray matter using voxel based morphometry, intervention effects were examined using 1) a repeated measures ANOVA, 2) visual comparison of group differences at baseline and post-intervention using independent-samples t-tests at each time point, and 3) two sets of correlation analyses examining the association of change in fitness and change in depression severity with change in voxelwise volume estimates across the whole-

brain. Significant change in voxelwise estimates of volume over the course of the 12-week intervention was not observed across all participants (i.e., main effect of time), nor was a significant group x time interaction observed in predicting volumetric changes, after correcting for multiple comparisons using FSL's threshold free cluster enhancement method (TFCE). Significant group differences in gray matter volume estimates were not observed at baseline or post-intervention after correction using TFCE. The association between change in fitness and change in depression severity with whole-brain voxelwise gray matter volume was also non-significant after correction using TFCE. However, see Figures X and Y below for raw t-statistic maps showing cross-sectional and longitudinal group differences that did not survive correction for multiple comparisons. Per these maps, the EX Group showed a trend toward a greater increase in regional gray matter volume in the medial orbitofrontal cortex and motor cortex relative to the MED group, whereas the MED group showed a trend toward a greater increase in right insular, caudate, and medial occipital cortex volume relative to the EX group, although not statistically significant. An examination of group differences in gray matter volume estimates post-intervention revealed that the EX group trended toward greater regional volume relative to the MED group post-intervention in the prefrontal cortex, posterior cingulate cortex, and parieto-occipital junction while group differences in these regions were not observed at baseline; however, this association did not survive correction for multiple comparisons. The MED group trended toward greater volume in the subgenual cingulate cortex at baseline (non-significant after correction) but did not show notable trends towards greater regional volume relative to the EX group post-intervention.

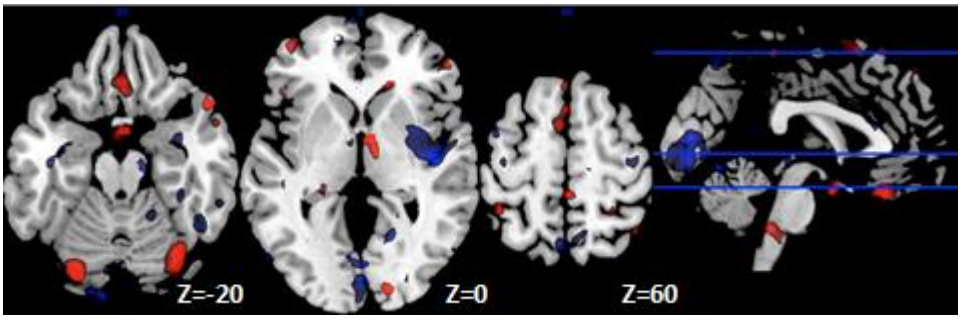

Figure 8. Uncorrected T-statistic maps thresholded at p<0.05 illustrating regions in which intervention groups differed in volumetric change from baseline to post-intervention (based on group x time interaction in repeated measures ANOVA).

Red=EX group showed greater volumetric increase over time relative to MED group

Blue= MED group showed greater volumetric increase over time relative to EX group

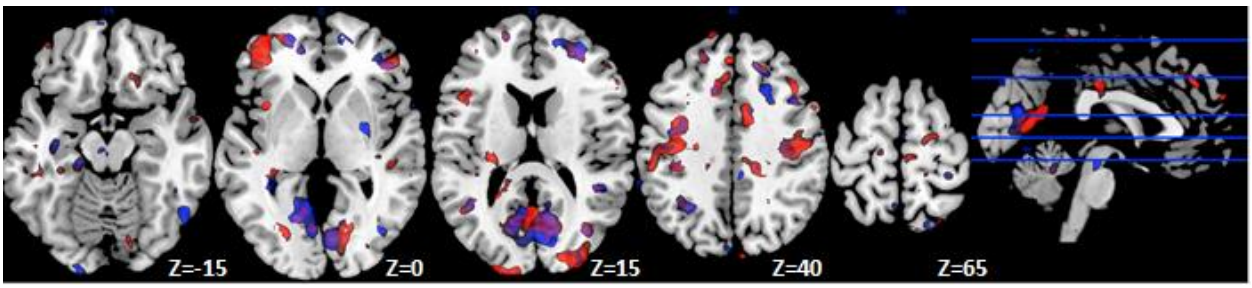

Figure 9. Uncorrected T-statistic maps thresholded at p<0.05 illustrating regions in which EX group > MED group in voxelwise gray matter volume estimates across the whole-brain

Blue= EX group > MED group at baseline

Red=EX group > MED group post-intervention

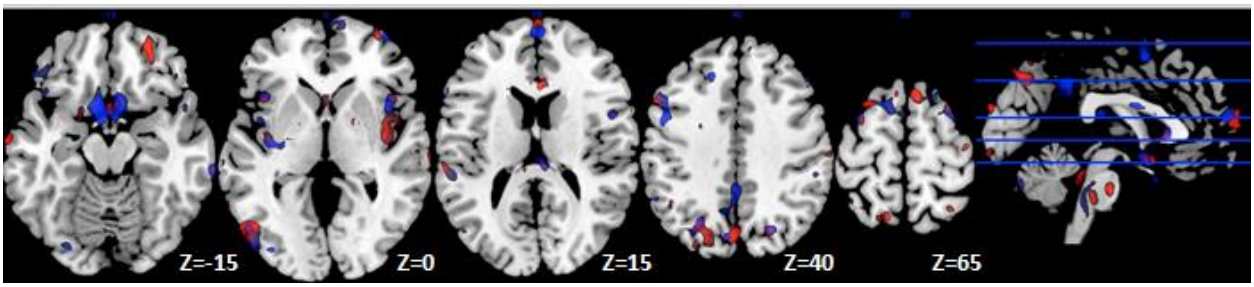

Figure 10. Uncorrected T-statistic maps thresholded at p<0.05 illustrating regions in which MED group > EX group in voxelwise gray matter volume estimates across the whole-brain

Blue= MED group > EX group at baseline

Red= MED group > EX group post-intervention

3.2.6.2 Vertex-based Structural Brain Outcomes

Based on apriori hypotheses regarding regions associated with depression, regions in the medial prefrontal cortex, anterior cingulate cortex, hippocampal/parahippocampal regions, amygdala, and dorsal and ventral striatum were examined in the vertex-based structural data analyses. First, the association between depression severity at baseline at regional gray matter thickness and volume in mm^3 in regions within the broad areas listed above was examined. Depression severity was negatively associated with gray matter thickness in the following regions at baseline after adjusting for age, sex, education, and intracranial volume: 1) right medial orbitofrontal cortex (OFC) (Beta = -0.98, p=0.016, r^2=0.72) right rostral anterior cingulate cortex (ACC) (Beta = -0.71, p=0.023, r^2=0.38), and 3) right parahippocampal gyrus (PHCG) (Beta = -0.88, p=0.003, r^2=0.59) (See Figures 11-17). These associations remained significant after adjusting for duration of current depressive episode and age of onset of first depressive episode in sensitivity analyses. Further analyses related to intervention-related morphological brain changes were limited to these regions. Generalized treatment-related

changes in gray matter thickness of these regions were examined using paired-samples t-tests across all participants, and emerged non-significant for all three regions (R medial OFC: t=-0.924 p=0.379; R PHCG: t= 0.882 p= 0.401; R rostral ACC: t=-0.501 p=0.628). Treatment group differences in change in gray matter thickness of the R medial OFC, R PHCG, and R rostral ACC were also non-significant, likely due to significant within-group variability. Although not statistically significant, the EX group showed an *increase* in mean gray matter thickness of the R medial OFC and R rostral ACC, whereas the MED group showed a *decrease* in mean thickness of these regions; further, the EX group showed *no change* in gray matter thickness of the R PHCG whereas the MED group showed a *decrease* in thickness. Change in depressive symptoms was not associated with change in gray matter thickness of the R medial OFC, R PHCG, or the R rostral ACC ($p > 0.05$). However, greater increases in fitness were marginally associated with greater increases in R medial OFC thickness (r=0.57, p=0.08). Although not statistically significant, greater increases in fitness showed a similar trend towards an association with increased thickness of the R rostral ACC thickness (r=0.53, p=0.11), and R PHCG (r=0.49 p=0.15). Additionally, 60% of the EX group relative to 20% of the MED group showed an increase in R PHCG thickness, and 80% of the EX group relative to the 40% of the MED group showed an increase in R rostral ACC thickness (See Figures 12 and 14).

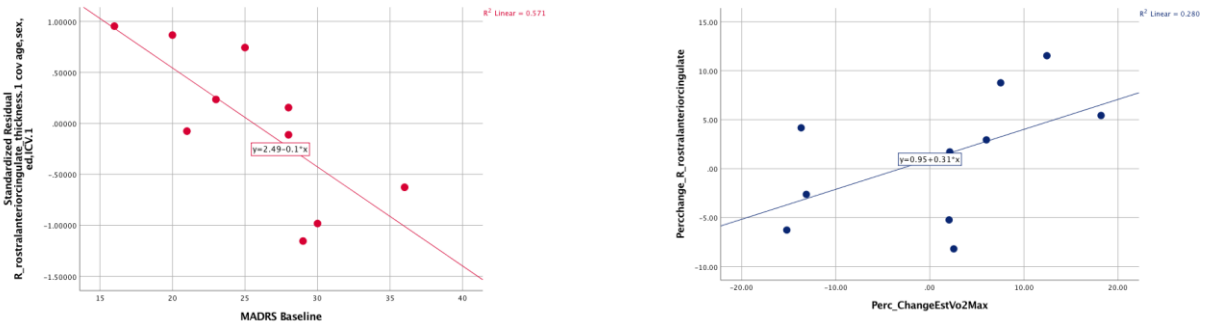

Figure 11 Association between Baseline Depression Severity and R rostral ACC cortical thickness

Figure 12 Association between % Change in Fitness and % Change in R rostral ACC cortical thickness

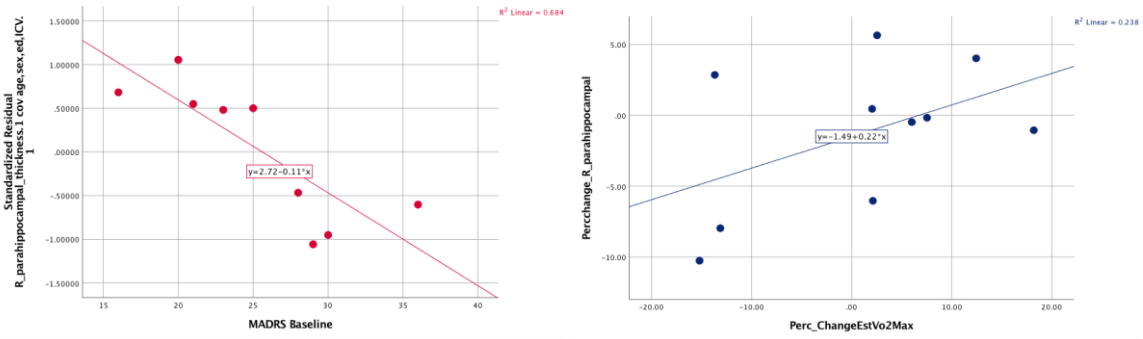

Figure 13 Association between Baseline Depression Severity and R parahippocampal gyrus cortical thickness

Figure 14 Association between % Change in Fitness and % Change in R parahippocampal gyrus cortical thickness

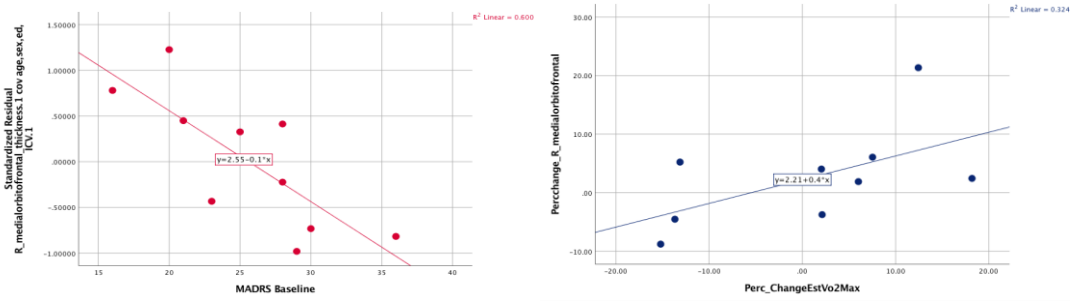

Figure 15 Association between Baseline Depression Severity and R medial OFC cortical thickness

Figure 16 Association between % Change in Fitness and % Change in R medial OFC cortical thickness

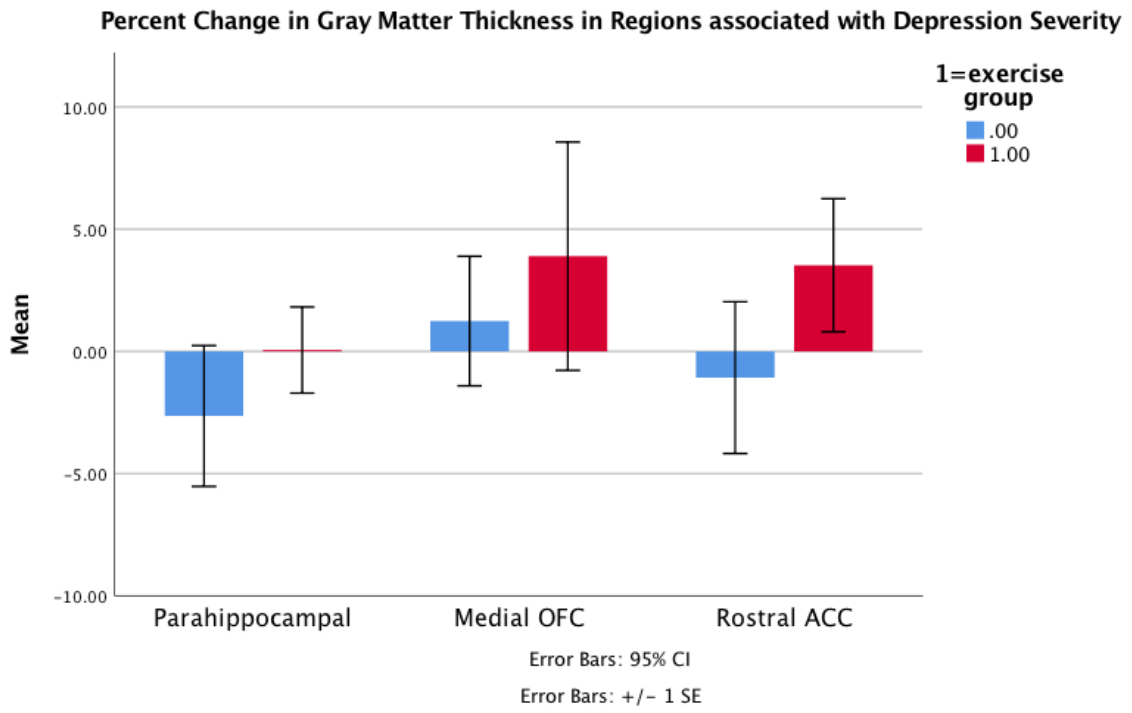

Figure 17. Group Differences in Mean Change in Cortical Thickness from Baseline to Post-Intervention in Regions in with Cortical Thickness was Negatively Associated with Depression Severity at Baseline

3.2.6.3 Brain-Behavior Relationships

Exploratory analyses were conducted examining whether increase in gray matter thickness in the R medial OFC, R PHCG, and R rostral ACC was associated with improvement on measures of cognitive function. Increase in thickness of the R medial OFC was associated with improved performance on measures of verbal learning and memory (CVLT List Learning: r= 0.713 p=0.03; CVLT Long-Delay Free Recall: r=0.739 p=0.02), and was marginally associated with improved performance on a measure of set-shifting (D-KEFS Color Word Interference Test Condition 4: r=0.61 p=0.08). Increase in thickness of the R rostral ACC was

also associated with improvement in verbal learning (CVLT List Learning: r=0.67 p=0.048) (See Figures 18-21).

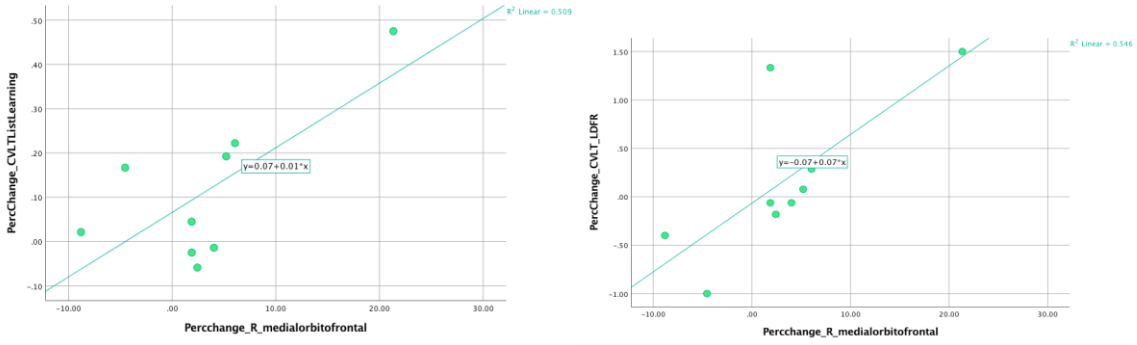

Figure 18 Association between %Change in cortical thickness in R medial OFC and %Change in Verbal Learning

Figure 19 Association between %Change in cortical thickness in R medial OFC and %Change in Verbal Memory

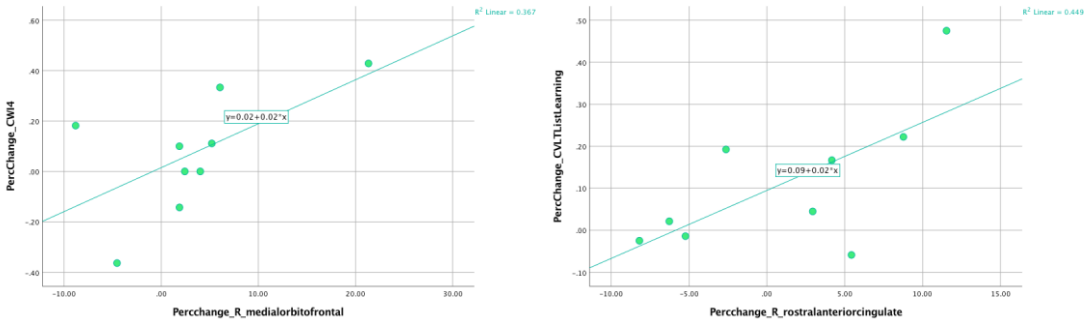

Figure 20 Association between %Change in cortical thickness in R medial OFC and %Change in Executive Functioning (LEFT)

Figure 21 Association between %Change in cortical thickness in R rostral ACC and %Change in Verbal Learning (RIGHT)

3.2.6.4 Hippocampal Subfield Outcomes

Using paired t-tests to examine group differences in change in volume of hippocampal subfields, no significant volumetric changes were observed for subfields in the left hippocampus. An examination of group differences in volumetric changes in the right hippocampus across older and younger adults revealed a volumetric decline in the right whole hippocampus (t= 6.324, p=0.003), parasubiculum (t= 3.178, p=0.034), and the hippocampus-amygdala transition area (t= 3.071, p=0.037) in the MED group but not in the EX group (all ps > 0.10). The EX group exhibited a volumetric decline in the right CA1 subfield of the hippocampus (t= 4.135, p=0.014). In subgroup analyses of OA and YA separately, the YA MED group showed an increase in subiculum volume (t= -37.71, p=0.001) whereas the OA EX group showed a decline in subiculum volume (t=27.159, p= 0.023). The YA EX group showed a volumetric decline in the granule cell layer of the dentate gyrus (t= 4.747, p=0.042) and the CA4 (t=4.610, p=0.044) (See Tables 6 and 7).

Table 8. Left Hippocampal Subfield Volumes in mm^3

	MEDICATION ONLY		MEDICATION+EXERCISE	
LEFT HIPPOCAMPAL SUBFIELDS	**Older (N=2)**	**Younger (N=3)**	**Older (N=2)**	**Younger (N=3)**
WHOLE HIPPOCAMPUS				
BASELINE	3259(173)	2491(876)	3253(606)	3084(61)
FOLLOW-UP	3262(302)	3001(535)	2600(1461)	3139(497)
SUBICULUM				
BASELINE	448(31)	314(108)	410(92)	355(73)
FOLLOW-UP	457(75)	388(69)	323(207)	386(57)
PRESUBICULUM				
BASELINE	312(39)	242(97)	281(62)	279(48)
FOLLOW-UP	315(55)	293(65)	216(117)	313(37)
PARASUBICULUM				
BASELINE	58(1)	51(26)	57(5)	59(16)
FOLLOW-UP	63(.03)	63(23)	43(22)	64(9)
GRANULE CELL LAYER OF DENTATE GYRUS				
BASELINE	263(3)	218(23)	277(55)	255(51)
FOLLOW-UP	264(8)	258(55)	235(130)	257(39)
CA1				
BASELINE	614(84)	443(153)	622(88)	548(144)
FOLLOW-UP	614(84)	538(87)	475(253)	553(105)
CA3				
BASELINE	167(6)	145(39)	206(38)	178(42)
FOLLOW-UP	168(14)	170(30)	175(100)	176(32)
CA4				
BASELINE	229(4)	183(52)	237(47)	217(45)
FOLLOW-UP	228(8)	216(46)	204(114)	216(39)
HIPPOCAMPAL TAIL				
BASELINE	502(36)	368(166)	478(74)	543(112)
FOLLOW-UP	478(1)	431(84)	392(194)	508(137)
HIPPOCAMPUS-AMYGDALA TRANSITION AREA				
BASELINE	48(1)	45(19)	49(26)	60(23)
FOLLOW-UP	53(2)	59(12)	41(35)	57(10)
HIPPOCAMPAL FISSURE				

BASELINE	186(57)	138(54)	169(5)	144(4)
FOLLOW-UP	198(31)	149(23)	132(60)	145(50)
FIMBRIA				
BASELINE	79(1)	72(27)	81(17)	92(20)
FOLLOW-UP	86(4)	84(20)	56(38)	93(16)
MOLECULAR LAYER				
BASELINE	540(37)	409(136)	555(103)	498(109)
FOLLOW-UP	539(65)	499(89)	439(252)	515(78)

Table 9. Right Hippocampal Subfield Volumes in mm^3

	MEDICATION ONLY		**MEDICATION+EXERCISE**	
RIGHT HIPPOCAMPAL SUBFIELDS	**Older (N=2)**	**Younger (N=3)**	**Older (N=2)**	**Younger (N=3)**
WHOLE HIPPOCAMPUS				
BASELINE	3320(80)	3161(375)	3450(233)	3108(384)
FOLLOW-UP	3248(61)	3090(388)	3435(390)	2901(420)
SUBICULUM				
BASELINE	448(16)	388(46)	408(62)	364(52)
FOLLOW-UP	448(19)	400(46)	400(63)	357(54)
PRESUBICULUM				
BASELINE	285(22)	254(33)	280(39)	281(15)
FOLLOW-UP	267(27)	256(31)	285(55)	249(15)
PARASUBICULUM				
BASELINE	55(12)	65(16)	54(8)	66(15)
FOLLOW-UP	52(11)	62(18)	51(2)	60(7)
GRANULE CELL LAYER OF DENTATE GYRUS				
BASELINE	265(8)	265(33)	297(24)	264(37)
FOLLOW-UP	270(17)	249(42)	299(50)	250(35)
CA1				
BASELINE	633(33)	610(54)	704(9)	567(106)
FOLLOW-UP	606(19)	605(60)	690(1)	541(94)
CA3				
BASELINE	183(15)	184(17)	197(22)	184(34)
FOLLOW-UP	188(19)	170(21)	194(51)	172(31)
CA4				
BASELINE	226(3)	225(26)	252(15)	225(31)
FOLLOW-UP	231(10)	211(34)	255(43)	211(29)

HIPPOCAMPAL TAIL				
BASELINE	538(16)	497(74)	555(27)	495(54)
FOLLOW-UP	524(7)	475(46)	571(42)	427(120)
HIPPOCAMPUS -AMYGDALA TRANSITION AREA				
BASELINE	61(3)	66(7)	64(3)	63(11)
FOLLOW-UP	54(5)	63(9)	61(4)	57(5)
HIPPOCAMPAL FISSURE				
BASELINE	195(51)	133(21)	168(25)	142(11)
FOLLOW-UP	193(63)	143(10)	171(8)	126(37)
FIMBRIA				
BASELINE	87(18)	85(32)	66(9)	92(22)
FOLLOW-UP	77(8)	87(32)	60(2)	97(19)
MOLECULAR LAYER				
BASELINE	539(2)	523(57)	571(55)	507(70)
FOLLOW-UP	530(5)	513(65)	569(82)	481(67)

3.2.7 Hippocampal Functional Connectivity Outcomes

Given that a repeated measures ANOVA was unable to be conducted on this sample, independent samples t-tests were conducted to examine group differences in hippocampal functional connectivity. At baseline, the EX group showed greater right hippocampal connectivity with the left inferior frontal gyrus, precentral gyrus, and posterior cingulate cortex relative to the MED group (See Table 8). Post-intervention, the EX group exhibited greater right hippocampal functional connectivity relative to the MED group with four broad regions for which group differences were not observed at baseline: 1) R medial temporal lobe, central operculum, and insula 2) R inferior temporal lobe 3) R precuneus, and 4) R supramarginal gyrus and superior temporal gyrus and (See Figure 22). Paired t-tests revealed that functional connectivity of the right hippocampus with the R medial temporal lobe and the R supramarginal gyrus significantly increased in the EX group over time (MTL: t=-6.325, p=0.003; SMG: t= -

4.276, p=0.013). There was a trend towards an increase in right hippocampal connectivity with the R precuneus over time, although this did not reach statistical significance (t=-2.02, p=0.11). The MED group also showed a significant increase over time in R hippocampal functional connectivity with the supramarginal gyrus (t=-3.031, p=0.039), although to a lesser extent than the EX group. An exploratory analysis of associations between depression severity and hippocampal connectivity at baseline revealed *lower* hippocampal functional connectivity with a broad range of prefrontal and temporal regions at *higher* levels of depression severity. Interestingly, there was significant overlap between regions showing *lower* hippocampal functional connectivity at higher levels of depression severity at baseline and regions with which the exercise group showed an *increase* in hippocampal functional connectivity from baseline to post-intervention.

Table 10. Hippocampal Functional Connectivity Results

	Number of Voxels	COG X	COG Y	COG Z
Post-Intervention EX > MED R Hippocampal Connectivity				
R Middle Temporal Gyrus/Central Operculum/Insula	425	48	-18	20
R Inferior temporal gyrus	345	48	-58	-12
R Precuneus	240	2	-56	66
R Supramarginal Gyrus/Superior Temporal Cortex	949	58	-30	12
R Cerebellum	310	28	-54	-28
Baseline EX > MED R Hippocampal Connectivity				
L Inferior Frontal Gyrus/Precentral Gyrus/Posterior Cingulate	473	4	-14	44
Baseline Depression Severity Negative Association with L Hippocampal Connectivity				

R Middle Temporal Gyrus	755	54	-14	-12
R Frontal Pole	881	40	38	16
R Middle Frontal Gyrus	541	32	16	46
L Heschl's Gyrus	337	-48	-20	8
R Superior Frontal Gyrus	267	10	22	52
R Lateral Orbitofrontal Cortex	249	48	36	-12

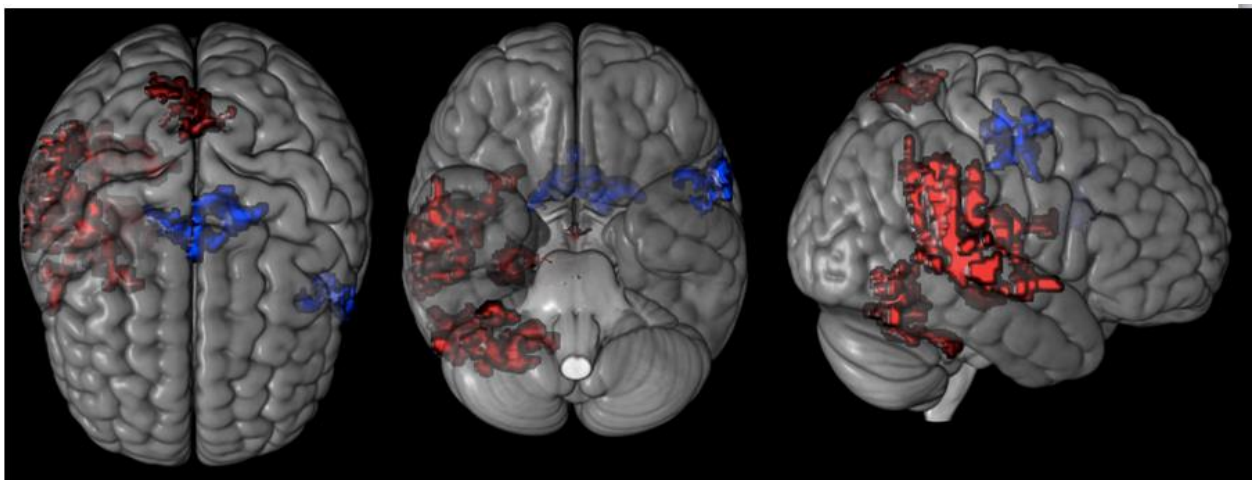

Figure 22 Post-Intervention Group Differences in Right Hippocampal Functional Connectivity

RED: EX>MED HC Connectivity Post-Intervention; BLUE: EX>MED HC Connectivity at Baseline

3.3 EXPERIMENT 1: CONCLUSIONS

Results from this 12-week double-blind randomized controlled pilot intervention study examining the benefits of adding aerobic exercise to pharmaceutical treatment for Major Depression in older and younger adults revealed several exercise-related benefits for depression, cognitive function, and brain health outcomes. There was disproportionate attrition in the MED group relative to the EX group, but intervention adherence was high across groups in those who

completed the intervention (N=11). Notably, exercise intervention adherence was 91%, which was higher than typical supervised exercise adherence rates reported in the literature (Gujral et al., 2017b). With regard to intervention fidelity, participants in the EX group achieved a mean increase of ~4% in fitness, whereas the MED group showed a mean decline of ~8% in fitness. Group differences in fitness were non-significant post-intervention due to within group variability. Specifically, intervention-related change in fitness varied by age group, such that the EX OA group showed a mean decline of ~6% in fitness, while the EX YA group showed a mean increase of ~8% in fitness. The extent of fitness-related improvement observed in the EX YA group in this intervention is comparable, if not higher than rates of improvement in fitness levels reported in other aerobic exercise interventions of similar durations (Firth et al., 2018).

3.3.1 Depression Outcomes

Generalized medication treatment outcomes included 73% remission from depression across all participants. We hypothesized that those randomized to the exercise condition would demonstrate a more rapid and greater extent of decline in depressive symptoms relative to participants receiving medication treatment alone. These predictions are based on the animal literature demonstrating overlapping neuromolecular pathways between the antidepressant effects of medication and exercise (e.g., reduction in systemic inflammatory signaling, increased expression of neurotrophic factors, altering kinetics of neurotransmitter systems) (Phillips, 2017). Our hypotheses were partially confirmed, such that both treatment groups showed a similar trajectory of decline in depressive symptoms, but the EX group exhibited a trend towards more rapid and stable decline in depressive symptoms relative to the MED group (although not statistically significant). We were unable to test whether augmentation with exercise would result

in “magnified” antidepressant effects. The use of medication titration for managing persistence of depressive symptoms to promote remission for all participants in treatment precluded a clear examination of group differences in the “extent” of decline in depressive symptoms. The ability to detect group differences in trajectories of change in depressive symptoms was further limited by an outlier in the EX group, whose depressive symptoms fluctuated dramatically during the course of the study and whose trajectory of symptom changes could have significantly biased group differences observed in this small sample. Further, intervention group differences in depressive symptom trajectories was likely influenced by age-group differences, such that OA exhibited a slower decline in depression relative to YA (across treatment groups).

3.3.2 Cognitive Outcomes

With regard to exercise-related cognitive benefits, different patterns of cognitive performance were observed for OA and YA. The OA EX group performed worse than the OA MED group for memory and language functioning post-intervention. Further, OA across treatment groups performed worse than YA on measures of attention and processing speed, consistent with general age-related cognitive decline. It is unclear whether the pattern of cognitive changes observed in the OA EX group is generalizable beyond this sample; nonetheless, the divergent findings between age groups highlights the persistence of cognitive impairment even after remission from depression in older adults but not in younger adults (Koenig et al., 2015).

Among YA, both treatment groups showed an improvement in attention and learning, which is consistent with cognitive changes commonly observed after remission from depression (Greer et al., 2015) After completion of the intervention, the YA EX group performed better than

the YA MED group on measures of attention, learning, and memory, while these differences in cognitive performance were not present at baseline. These results suggest that the YA EX showed *greater* improvement on measures of attention and learning relative to the YA MED group. Other evidence pointing to the potential cognitive benefits of exercise engagement (or fitness-related improvement) includes an association between improvement in fitness and improvement in performance on a task assessing perceptual inhibition (i.e., an aspect of executive functioning), observed across age groups. This association between change in fitness and change in cognitive performance did not clearly translate to intervention group differences, given that the OA EX group *did not* show improvement in fitness and 40% of the participants in the MED group *did* show improvement in fitness.

3.3.3 Structural Brain Outcomes

In addition to examining depression and cognitive outcomes, a key innovation in this pilot study was the ability to explore neural mechanisms underlying the antidepressant effects of exercise as an augmentation to medication treatment. The availability of high-resolution structural MRI data acquired from the 7T MR scanner allowed for a rich exploration of exercise-related changes in brain morphology using multiple methods to leverage several morphological indices, including 1) probabilistic voxelwise volume estimates across the whole-brain, 2) regional volume estimates (in mm^3) in subcortical regions in which reduced volume has been commonly found in depression (i.e., whole hippocampus and hippocampal subfields, amygdala, dorsal and ventral striatum), and 3) vertex-based estimates of gray matter thickness in cortical regions showing structural abnormalities in depression (i.e., PFC, ACC, parahippocampal gyrus). An examination of group differences in change in voxelwise estimates of gray matter volume

across the whole brain revealed a trend towards a greater increase in regional gray matter volume in the medial OFC and motor cortex in the EX group relative to the MED group, although this was not statistically significant after correction for multiple comparisons.

We predicted that favorable morphological changes (e.g., volumetric increases) related to exercise may be observed in regions showing depression-related structural abnormalities (e.g., volumetric reductions). The rationale for this prediction was based on the assumption that 1) regions that are sensitive to the effects of depression are likely to demonstrate plasticity in the context of exercise training, due to the opposing neuromolecular cascades associated with depression and exercise (), and 2) regions showing volumetric *reductions* due to any cause have greater 'room' for *growth* or improvement. Our prediction of favorable exercise-related regional morphological changes was in part tempered by considering that the duration of our study (i.e., 12-weeks) was at least 50% shorter than the duration of most mechanistic exercise interventions demonstrating volumetric brain changes in non-depressed adults (Firth et al., 2018). However, by testing exercise-related changes in multiple markers of brain morphology, we observed several interesting patterns of morphological changes that may be related to exercise.

A preliminary exploration of group differences in change in hippocampal volume estimates (in mm3) revealed a volumetric decline in the right whole hippocampus and anterior hippocampal subfields (i.e., parasubiculum and hippocampus amygdala transition area) in the MED group but not in the EX group, while the EX group showed a volumetric decline in the CA1 subfield of the right hippocampus. There was no evidence of additional subcortical volumetric changes in regions associated with depression in either treatment group. The meaning of group differences observed in volumetric changes in hippocampal subfields remains ambiguous, given that treatment-related volume loss in either group would not be expected. It is

possible that exercise may be protective against hippocampal volume loss when compared to treatment with medication alone for depression, although these findings must be interpreted with caution due to the limited sample size and the novel methodological approach used to segment the hippocampus in this study that has not been well validated.

An examination of exercise-related changes in cortical thickness revealed that in regions showing reductions in cortical thickness with greater depression severity at baseline (i.e., R medial OFC, rostral ACC, parahippocampal gyrus) revealed a trend such that improvement in fitness was associated with an increase in cortical thickness over the course of the intervention. These findings are particularly notable, because the regions in which reduction in cortical thickness was linked to greater depression severity have consistently shown structural abnormalities in depression in the meta-analytic literature (Gujral et al., 2017). Further, the selective association between increase in cortical thickness in these regions and improvement in fitness, but not decline in depression severity, suggests that change in fitness may mediate these structural brain changes, although this was not formally tested. These results also highlight the utility of exploring several markers of brain morphology, given that regional estimates of cortical thickness (but not volume estimates in the same regions) explained a remarkable amount of variance in depressive symptom severity at baseline (medial OFC: 72%, PHC: 59%, and rostral ACC: 38%) and change in cortical thickness in these regions shared substantial variance with change in fitness (>20%) in this study.

3.3.4 Brain-Behavior Relationships

The utility of understanding intervention-related changes in brain outcomes stems from the assumption that brain-related changes underlie behavioral changes. Even in this small

sample, changes in brain morphology were associated with cognitive changes such that an increase in cortical thickness in the right medial OFC was associated with improved performance for learning and memory and executive functioning (marginal). Additionally, an increase in cortical thickness in the right rostral ACC was associated with improved performance for verbal learning. Interpreted in the context of previously reported findings that these regions show reductions in cortical thickness with greater depression severity and are sensitive to improvements in fitness, these results suggest that in regions affected by depression, fitness-related increases in cortical thickness *may* translate to improvements in cognitive functioning, although this was not formally tested in this study.

3.3.5 Hippocampal Functional Connectivity Outcomes

Concerning exercise-related changes in functional brain outcomes, a hippocampal seed-based approach was used in these preliminary analyses, given the sensitivity of the hippocampus to exercise-related changes (e.g., exercise-induced volumetric increases in the hippocampus). Briefly, the EX group, relative to the MED group, exhibited greater right hippocampal connectivity with right-lateralized default-mode network regions post-intervention, namely with the precuneus, and superior and inferior temporal gyri, and supramarginal gyrus. These group differences were not present at baseline. Exploration of group differences in change in connectivity patterns in these regions revealed that hippocampal functional connectivity selectively increased with medial and superior temporal regions in the EX group but not the MED group over the course of the intervention. Interestingly, greater depression severity at baseline was associated with negative hippocampal functional connectivity with medial temporal and superior temporal regions. Taken together, these findings may point to exercise-related

"normalization" of hippocampal connectivity patterns with DMN regions in the context of depression, although this is speculative given the small sample size of this study. Nonetheless, these results are generally consistent with meta-analytic evidence of the aerobic-exercise related structural and functional changes in DMN regions (Li et al., 2017). In a meta-analysis of 14 prospective controlled studies (N=631), results revealed aerobic exercise-related increases in functional connectivity within the hippocampus, ACC, and PCC, as well as reduced atrophy in the medial temporal lobe and ACC.

Although increased hippocampal connectivity with DMN regions (rather than with ECN regions) was not our initial prediction, these findings are plausible, given that the DMN in depression and treatment for depression is still debated within the literature. One medication treatment study for depression (i.e., duloxetine) in middle aged adults (N=32) reported an increase in DMN connectivity from baseline to post-treatment (Fu et al., 2013). Another medication treatment study (i.e., venlafaxine) for late-life depression found treatment related increases intra-network coupling (i.e., DMN-MTG) but reduced inter-network coupling (DMN-IFG) in remitters vs. non-remitters (Karim et al., 2017). The exercise intervention literature in older adults suggests that exercise engagement (Voss et al., 2011) and higher fitness levels are each independently associated with increased DMN connectivity (Voss et al., 2016). Therefore, the current findings can fit with both exercise-related changes observed in non-depressed adults and medication treatment-related changes found in functional connectivity. Of note, previous functional connectivity studies largely used network-level connectivity measures as opposed to a hippocampal seed-based approach as was used in the present study.

3.3.6 Limitations

The availability of a range of valuable neurobiological, clinical, and cognitive data in this randomized pilot intervention study allowed for a rich characterization of exercise effects on behavioral and brain outcomes; however, the implications of these findings are first and foremost limited by the very small sample size. Generalizability of these findings is further complicated by the inclusion of polar age groups, with disproportionate enrollment of YA relative to OA, which was ultimately counterbalanced by greater attrition among YA relative to OA participants. Further, technical difficulties related to the MR scanner resulted in some participants being scanned on a 3T MR scanner, which introduced a number of possible neuroimaging-related confounds into the results (i.e., strength of magnet, variability in scanner drift, scanning parameters), making it difficult to accurately characterize exercise effects on brain outcomes, a primary aim of this study.

Further, there a number of limitations to the analytic methods used to process neuroimaging measures, as automated segmentation tools are subject to several sources of bias. A key limitation of voxel-based morphometry is that it does not provide absolute values of volume. The hippocampal subfield segmentation tool in Freesurfer version 6.0 is a novel segmentation tool and subject to significant error, particularly when using only a T1 image for segmentation instead of the combination of a T1 and T2 image. Additionally, exercise effects on functional connectivity are subject to several sources of methodological error and are difficult to interpret (e.g., state vs. trait effects, lack of clinical specificity).

3.3.7 Summary

Despite these limitations, findings from this 12-week pilot randomized controlled trial revealed that adding exercise to antidepressant medication treatment for depression resulted in more rapid and stable decline in depressive symptoms relative to medication treatment alone. Further, exercise had variable effects for cognitive functioning in younger versus older adults, resulting in cognitive benefits in attention and learning in younger but not in older adults. Notable effects of exercise on regional brain morphology was evidenced through associations found between improvements in fitness and increases in cortical thickness in prefrontal, anterior cingulate, and parahippocampal regions, all which showed reductions in cortical thickness with greater depression severity prior to the intervention. Intervention-related increases in cortical thickness in medial OFC and rostral ACC were additionally associated with improvements in executive functioning and learning and memory performance. Exercise-related changes in hippocampal (HC) functional connectivity patterns included increased connectivity with default mode network (DMN) regions, which not observed in response to medication treatment alone.

4.0 EXPERIMENT 2: PHYSICAL ACTIVITY ASSOCIATIONS WITH DEPRESSIVE SYMPTOMS AND COGNITIVE FUNCTION IN OLDER ADULTS WITH MILD COGNITIVE IMPAIRMENT

4.1 EXPERIMENT 2 METHODS

Data from Experiment 2 were used to test aims 1.2 and 2.2 of this proposal. Specifically, data from this study were leveraged to explore the association of objectively-measured daily activity levels with depression and cognitive trajectories in the context of a psychotherapy-based intervention augmented with exercise aimed to prevent depression and slow progression of cognitive decline in older adults with MCI. Intervention group differences in mood and cognitive outcomes were not of primary interest in the current study, given that the exercise intervention was not well controlled. In fact, participants in the exercise group complained about difficulty engaging in exercise, and adherence was not enforced or documented. Rather, it is possible that objective measures of physical activity across intervention groups may better capture physical activity associations with mood and cognitive outcomes.

4.1.1 Participants

Participants were part of the RECALL study (Dyadic Problem-Solving Therapy to Prevent MDD in Individuals with Mild Cognitive Impairment and their Caregivers) between

2010-2015, a 16-month (4-months + 1 year follow-up) randomized intervention testing the effects of PST and PST + Exercise on reducing depressive symptoms and preventing Major Depression in older adults with MCI. 94 participants (including patients and caregivers) were recruited for the intervention, 11 people withdrew consent prior to the intervention. 75 participants with MCI completed the intervention and the long-term follow-up visit, of which 18 participants were accompanied by a caregiver and 47 participants were not accompanied by a caregiver.

4.1.1.1 Inclusion Criteria:

1. Age > 60 years
2. New MCI Diagnosis (<1 month)
3. PHQ-9 Score >2 but <9
4. Adequate physical and sensory function to undergo neuropsychological assessment
5. If accompanied by a caregiver, caregiver must have normal cognitive function (3MS ≥80) and meet same psychiatric criteria including PHQ-9 <9

4.1.1.2 Exclusion Criteria:

1. CNS neurological disorder
2. History of Major Depression in the last 5 years
3. Substance Use Disorder in the last 5 years
4. Lifetime history of Bipolar Disorder of Schizophrenia

4.1.2 Intervention

Participants were randomized to one of three intervention groups: 1) Enhanced Usual Care, 2) 16-weeks of Problem-Solving Therapy (PST), and 3) 16-weeks of Problem-Solving Therapy + Exercise (90 minutes per week). Participants randomized to the two PST groups also received 2 PST booster sessions over a 12-month follow-up period post-intervention. Physical activity levels, depressive symptoms, and cognitive function were assessed at baseline, post-intervention, and at the 12-month follow-up visit. See Figure 1 for a timeline of the intervention and assessment schedule in Experiment 1.

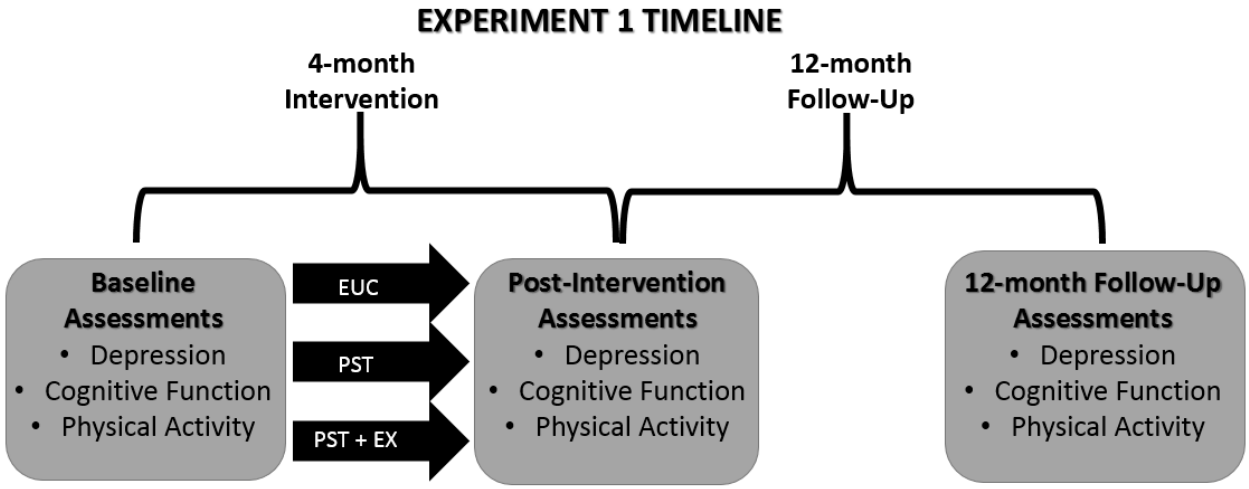

Figure 23. Timeline of Intervention of Assessment Schedule for Experiment 2

4.1.2.1 Enhanced Usual Care

16 participants were randomized to this group. These participants underwent all clinical and cognitive assessments, as well as physical activity monitoring at the same time-points as participants in other groups. This group did not undergo any intervention, but a study psychiatrist monitored the mental health treatment of participants in the EUC group throughout the study.

4.1.2.2 Problem-Solving Therapy (PST)

11 participants were randomized to this group. Participants were administered problem-solving therapy based on the PST manual developed by the Alexopoulos-Arean group (Arean et al., 1993; Nezu & Perri, 1989), but modified for those living with cognitive impairments (PST-cog). The conventional 12-week therapy format was also extended to 16-weeks to allow for skill acquisition and repetition given participants' memory deficits. For those participants accompanied by a caregiver, a caregiver-version of PST was administered based on a manual developed by Dr. Garand (Garand et al., 2014), but adapted to focus on supporting problem-solving skills of the participant with MCI rather than the caregiver, to promote maintenance and generalization of skills post-intervention. For both MCI participants and caregivers, 8 PST sessions (45-60 minutes each), were administered bi-weekly over 16 weeks on an individual basis in either the PCP office or home. Experienced research clinicians provided PST under the supervision of a licensed clinical psychologist. Booster sessions were also provided to all participants receiving PST at 3-months and 9-months post-intervention.

4.1.2.3 Problem-Solving Therapy + Exercise (PST+EX)

17 participants were randomized to this group. Participants and caregivers in this group were also administered PST as described above, but were additionally asked to engage in moderate-intensity aerobic exercise at home 3 times per week. Participants were also provided with a stretching band and instructed how to use it for stretching before and after exercise sessions. Unfortunately, exercise was only promoted and not enforced, and *adherence was not documented* in this study. As mentioned above, exercise augmentation was an ancillary aim in the study design, and therefore not well controlled in this pilot study. Study therapists reported

that participants assigned to the PST + Exercise group complained about difficulty maintaining an exercise routine.

4.1.3 Measures:

Screening measures:

Structured Clinical Interview for DSM-IV-TR Axis 1 Disorders (SCID-IV): The SCID-IV is a diagnostic manual including most information that would be diagnostically useful to assess the presence of current and past DSM-IV-TR Axis 1 disorders, including mood disorders, psychotic disorders, substance use disorders, anxiety disorders, somatoform disorders, and eating disorders (First, Spitzer, Gibbon M, & Williams, 2002). The SCID-IV was used to assess the following exclusionary criteria while screening participants for enrollment in this study: history of a Major Depressive Episode over the last 5 years, history of a substance use disorder over the last 5 years, and lifetime history of Bipolar Disorder and Schizophrenia.

Modified Mini-Mental State Examination (3MS): The 3MS is a widely used brief screening tool used to assess dementia. A score of < 80 on the 3MS is used as the cut-off to assess probable dementia (Teng & Chui, 1987). This measure was used to screen and exclude potential participants who may meet criteria for dementia.

Primary Measures

Physical Activity (Aims 1.2 & 2.2)

Physical activity levels were assessed using a Sensewear physical activity-monitoring device over a period of 1-week at 3 time points during the study: baseline (N=62), post-intervention (N=48), and 12-month follow-up (N=44). This device is worn on the upper left arm

by the triceps and records body temperature, movement, energy expenditure, and sleep efficiency. Participants were asked to wear the device for a period of 1 week except while showering or swimming. Physical activity measures collected using this device were processed using BodyMedia SenseWear software.

In highly sedentary samples, such as older adults with depression and MCI, there is no gold standard dose of physical activity engagement due to limited variability in activity levels and peak activity levels that typically fall below the threshold for 'moderate-intensity activity', as defined by American College of Sports Medicine and Center for Disease Control and Prevention Guidelines (i.e., 3.0 to 6.0 METs). Therefore, physical activity levels were examined in multiple ways in the present study (See Table XX): traditional indicators of physical activity and rest activity rhythms (i.e., markers of stability and variability in activity levels within and across days that device is worn).

Examination of rest-activity rhythms (RARs) may be a particularly valuable approach for detecting clinically meaningful variability in activity levels in older adults with MCI and depressive symptoms. Markers of RARs harness and combine measures of sleep and physical activity, both of which are critical for maintaining mental health and cognitive and brain health, particularly in late life. Moreover, disruptions in RARs have been previously applied to detecting early signs of depression and preventing depression in late-life (Smagula, 2015, Smagula et al., 2016), and have also been linked to age-related cognitive decline (Oosterman et al., 2009), preclinical Alzheimer's Disease (Musiek et al., 2018), elevated risk for MCI and dementia (Tranah et al., 2011), and poorer functional status and quality of life among individuals with dementia (Carvalho-Bos et al., 2007) .

Table 11. Summary of Physical Activity Measures used in Experiment 2

Physical Activity Measures
Average Daily Active Energy Expenditure (EE)
Average Daily metabolic equivalent (METs)
Average Daily Minutes of Physical Activity
Average Daily Number of Steps
Physical Activity Composite Score (Std. Avg. of: active EE, METs, min of PA, Steps)
IntraDaily Variability (IV)/Fragmentation of Rest-Activity Rhythms (IV)
Interdaily Stability (IS) of Rest-Activity Rhythms (IS)
Relative Amplitude (RA) of Rest-Activity Rhythms: normalized diff. between most active 10 hours and least active 5 hours (uninterrupted) within a day

Depressive Symptoms (Aim 1.2)

Depressive symptoms were assessed using the 9-item Patient Health Questionnaire (PHQ-9) (Kroenke, Spitzer, Williams, & Lowe, 2010) at baseline, post-intervention, and the 12-month follow-up visit. This is a brief screening tool used to assess severity of depressive symptoms. Given that this study was focused on subclinical levels of depression, participants scoring ≥2 but < 9 on the PHQ-9 were eligible to participate. The mean severity of depressive symptoms at baseline for all MCI participants was 6.05 (2.81).

Cognitive Function (Aim 2.2)

Cognitive functioning was assessed using two primary measures. These measures included the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Randolph, Tierney, Mohr, & Chase, 1998) and two subtests from the Delis-Kaplan Executive Function System (D-KEFS) (Delis, Kramer, Kaplan, & Holdnack, 2004) assessment: the Trail Making Test and the Color-Word Interference Test. Cognitive domains assessed included attention and processing speed, executive function, memory, visuospatial function, and verbal

fluency. All cognitive tasks and respective domains that will be included in the current study are listed in Table 10 below.

Attention and Processing Speed

Basic attention was assessed by the RBANS Digit Span subtest (forward span), an auditory digit repetition task. Attention and psychomotor speed (processing speed) was assessed using the RBANS Coding task, a speeded task in which participants were asked to match digits to symbols. Participants' performance on these two tests was combined to create an Attention Index score, which was used in data analyses, in addition to individual cognitive tasks.

Executive Function

Two primary executive functions were assessed in this study: response inhibition and set-shifting ability. Response inhibition was assessed using condition 3 of the DKEFS Color Word Interference Task, in which participants were asked to inhibit the automatic dominant response of reading while naming colors aloud. Set-shifting ability was assessed using two tasks; first, participants were asked to switch between reading words and inhibiting the automatic reading response to name colors on condition 4 of the DKEFS Color Word Interference Task. Second, participants were asked to draw a line while switching between connecting numbers and letters in a sequential order on condition 4 of the DKEFS Trail-Making Task.

Memory

Delayed verbal memory was assessed using the RBANS word-list recall and recognition tasks and RBANS story-recall task. In these tasks, participants are asked to freely recall words from a 10-word list learned 20-minutes earlier, recognize words from that 10-word list out of 20 of words, and freely recall a 2-sentence story that they learned 20-minutes earlier, respectively.

Delayed nonverbal memory was assessed by asking participants to reconstruct a geometric figure from memory that they copied 20-minutes earlier. Participants' performance on these 4 measures were combined using RBANS age-based norms to create a Delayed Memory Index score, which was used in data analyses, in addition to the individual cognitive tasks.

Visuospatial Function

Visuospatial function was assessed using two tasks. The RBANS Figure Copy subtest, in which participants were asked to copy a complex geometric figure, assesses visuospatial constructional ability. The RBANS line orientation task, in which participants were asked to determine the spatial orientation of line pairs, assesses spatial perception and orientation. Participants' performance on these two tasks were combined using RBANS age-based norms to create a Visuospatial Function Index, which were used in data analyses, in addition to individual subtest scores.

Table 12. Summary of cognitive measures and domains assessed in Experiment 2

Experiment 2	
Cognitive Domains	**Cognitive Measures**
Attention & Processing Speed	RBANS Attention Index RBANS Digit Span Forward Subtest RBANS Coding Subtest
Executive Function	DKEFS Color-Word Interference Conditions 3 & 4 DKEFS Trail Making Test Condition 4 (Set-Shifting)
Memory	RBANS Delayed Memory Index RBANS List Recall
Visuospatial Function	RBANS Figure Copy Subtest RBANS Line Orientation Subtest RBANS Modified Visuospatial Constructional Index
Language Skills	RBANS Language Index

4.1.4 Data Analysis:

Very similar to the first study, Repeated Measures ANOVA was used to examine changes in PA/RAR indices, depressive symptoms, and performance on cognitive measures, covarying for age, sex, education, and race, as appropriate. Further, t-tests were additionally used to test the presence of post-intervention group differences in depressive symptoms/cognitive function that were not present at baseline. If so, group differences at baseline were examined. Sensitivity analyses using regression models were conducted to examine the association of change in fitness and levels with change in depressive symptoms and change in cognitive performance.

4.1.5 Predictions

1) **Cross-Sectional Associations between PA/RARs and Depression/Cognition**

Greater amounts of PA, lower intradaily variability in RARs, and greater interdaily stability in RARs at baseline would be *negatively associated* with depression severity and *positively associated* with global cognitive functioning, executive functioning, and learning and memory at baseline in older adults with MCI and depression symptoms.

2) **Longitudinal Associations between PA and Change in Depression/Cognition**

A. Greater amounts of PA, lower intradaily variability in RARs, and greater interdaily stability in RARs at baseline would predict greater *reduction in* depression severity and *improvement* in cognitive functioning from pre- to post-intervention in older adults with MCI and depression symptoms.

B. Greater amounts of PA, lower intradaily variability in RARs, and greater interdaily stability in RARs at baseline would predict *greater improvement in cognitive functioning* (i.e., less decline) from baseline to the 12-month follow-up in older adults with MCI and depression symptoms.

3) **Covariance of PA with Depression and Cognition**

A. Greater increases in PA, reductions in intradaily variability in RARs, and increases in interdaily stability in RARs from pre- to post-intervention would be associated with a greater *reduction* in depression severity and *improvement* in cognitive functioning from pre- to post-intervention.

B. Greater *stability* (i.e., less decline) in amount of PA, intradaily variability in RARs, and interdaily stability in RARs from post-intervention to the 12-month follow-up would be associated with the following outcomes in older adults with MCI and depression symptoms:

i.) Greater *stability* in intervention-related changes in depression from post-intervention to the 12-month follow-up

iii.) Greater *stability* in cognitive functioning from post-intervention to 12-month follow-up in older adults with MCI and depression symptoms.

4.2 EXPERIMENT 2 RESULTS

4.2.1 Participant characteristics at Baseline

Prior to the intervention, all participants had a diagnosis of mild cognitive impairment and subclinical depressive symptoms (Baseline 3MS score = 92.66 (4.59); Baseline PHQ-9 score: 6.16 (2.95)). Mean age of the sample was 74.45 years (SD=8.703), including 66% women and 73% Caucasians. More than 75% of the sample had completed some level of post-secondary education (mean years of education = 15.34 (2.605)). Participants were highly sedentary at baseline based on objective PA monitoring (mean hours of PA per day: 1.17 (0.94); Range: 0.27 – 3.33). Participants wore the accelerometers for an average of 6.47 days (SD=1.14) at baseline. Number of hours of accelerometer data collected did not significantly differ across time points (F=2.291, p=0.109). Intervention groups differed with regard to PA levels at baseline, such that

those randomized to the PST+EX group had higher mean daily physical activity levels at baseline relative to the PST alone and usual care groups (Steps: F=8.236 p=0.001; Active Energy Expenditure: F=5.103 p=0.011; Hours of PA: F=4.432 p=0.019; 10-minute Bouts of PA: 3.911 p=0.029; Minutes spent in 10-minute bouts of PA: F=3.763 p=0.032). Intervention groups did not differ with regard to severity of depressive symptoms or cognitive performance at baseline (p > 0.10).

4.2.2 Associations of Demographic Factors (i.e., Education, Race, Sex) with PA/RARs, Depressive Symptoms, and Cognitive Functioning

Higher education attainment was associated with higher levels of daily physical activity at baseline (METs: r= 0.44, p=0.004; Active Energy Expenditure: r=0.34, p=0.03; Hours of PA: r=0.35, p=0.02, 10-minute Bouts of PA: 0.32, p=0.04) but was not associated with depressive symptom severity or cognitive performance at baseline, with the exception of an association with better performance for response inhibition (D-KEFS Color Word Interference Condition 3: r= 0.04, p=0.007). This sample included a higher proportion non-Caucasian participants than is observed in the general population (20% African American, 2% Asian, 2% Mixed Race). An examination of racial difference on behavioral measures at baseline revealed that non-Caucasian participants had lower intradaily variability (i.e., less fragmentation) in RARs (lnIV: t= 2.917, p=0.006), greater severity of depressive symptoms (PHQ-9: t= -2.684, p=0.01), and better performance on measures of global cognition (t= 2.126, p=0.04), verbal learning (RBANS List Learning: t= -2.582, p=0.007), and visuospatial functioning (RBANS Visuospatial Constructional Index: t= 2.558, p=0.04). Sex differences were also observed on several behavioral measures at baseline, such that male participants had higher levels of daily physical

activity (METs: t=-2.194, p=0.03; Active Energy Expenditure: t=-2.484, p=0.017), higher levels of depressive symptoms, (PHQ-9: t= 3.122, p=0.003), and better performance for global cognition (RBANS Total Index: t=2.231, p=0.031) and verbal learning (RBANS Immediate Memory Index: t=2.915, p=0.006) relative to female participants. See Table 11 for further details regarding participant characteristics at baseline.

Table 13. Participant Demographic Characteristics Experiment 2

Variable	Overall Sample Mean (N=44)	EUC	PST	PST+EX
Age	74.45 (8.70)	76.19 (9.54)	76.18 (6.26)	71.71 (8.98)
Years of Education	15.34 (2.61)	14.81 (2.71)	15.36 (2.58)	15.82 (2.58)
% Female	65.90%	75.00%	81.80%	47.10%
% Caucasian	75.00%	68.80%	81.80%	76.50%

4.2.3 Intervention Fidelity

Although it was not the primary aim of this study to examine intervention effects on depressive symptoms in this subsample (N=44) of the parent study (N=65), understanding intervention fidelity may help in interpreting key outcomes of the present study. Intervention group differences were found with regard to trajectory of change in depressive symptoms from baseline to the 1-year follow-up (F= 3.26, p=0.049, r^2=0.15), after covarying for age, sex, and race. The PST group showed the greatest decline in depressive symptoms from baseline to the 1-year follow-up. At the 1-year follow-up, depressive symptom severity was the lowest within the PST group, and was significantly different than the usual care group. The PST + EX group did not differ from either group at the 1-year follow-up. Group differences in depressive symptom

severity was non-significant at baseline and post-intervention. These results suggest that the PST intervention when implemented alone had long-term benefits (i.e., one year after completion of the intervention) for reduction in depressive symptoms relative to usual care; however, adding a prescription of exercise to the PST intervention did not have long-term benefits for reduction in depressive symptoms. In fact, physical activity levels did not increase during the intervention or after completion of the intervention in the PST+EX group relative to the PST alone or usual care groups (all PA and RAR indices: $p > 0.10$), suggestive of ineffective implementation of the PST+EX intervention (i.e., poor exercise adherence).

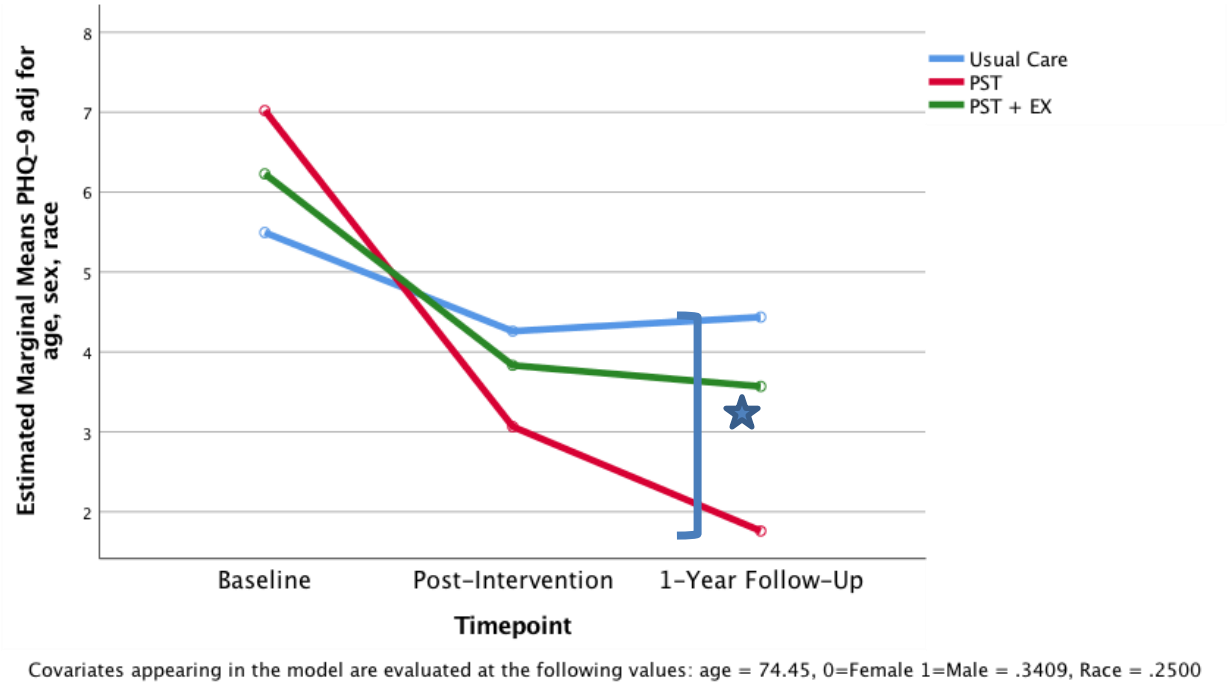

Figure 24 Group differences in Trajectory of Depressive Symptoms over the 16-month study across 3 timepoints.

4.2.4 Cross-Sectional Associations between PA/RARs and Depressive Symptoms and Cognitive Functioning at Baseline

Lower levels of physical activity was associated with greater severity of depressive symptoms at baseline across several indices of daily PA (METs: r= -0.31, p=0.05; Active Energy Expenditure: r= -0.33, p=0.03; Hours of PA: r= -0.36, p=0.02; 10-minute Bouts: r= -0.31, p=0.05; Minutes spent in 10-minute Bouts: r= -0.31 p=0.04). RARs indices were not associated with depression severity at baseline. However, lower intradaily variability in RARs was associated with cognitive functioning at baseline, specifically verbal learning (RBANS List

Learning raw score: r= -0.47, p=0.002). After adjusting for age, education, sex, and race, the effect size was reduced and the association became marginal (Beta= -0.264, p=0.093, r^2=0.05). Significant sex differences in verbal learning performance likely contributed to the reduction in effect size and statistical significance of the association (i.e., men performed better for verbal learning relative to women). The association between intradaily variability in RARs and verbal learning was also examined using new norms for RBANS performance in older adults, corrected for age, sex, gender, and race (Duff et al., 2017), which also yielded a marginal association (RBANS List Learning raw score: r=0.26, p=0.10).

In an exploratory analysis, high and low exercise groups were generated by dividing the participants based on the median number of minutes of PA engagement in 10-minute bouts (Median Minutes in 10-minute bouts = 21). This variable was specifically used to generate 'high' and 'low' exercise groups, because 10-minute bouts of MVPA are thought to reflect 'exercise' rather than simply reflecting brief periods of light-intensity PA that naturally occur throughout the day. Participants who engaged in at least 20-minutes of MVPA (across the duration that the accelerometer was worn: mean=6.47 days) performed better than the 'low' exercise group on measures of visuospatial constructional skills and executive functioning (i.e., set-shifting and response inhibition) at baseline (Modified Visuospatial Constructional Index: t=-2.20 p=0.03; D-KEFS Trail Making Task Condition 4 vs. 5: t= -4.26 p<0.001; D-KEFS Color Word Interference Condition 3: t= -2.44, p=0.02). 'High' and 'low' exercise groups did not differ on depressive symptom severity at baseline (See Table 12 for further details regarding cognitive measures).

Table 14. Cognitive Measures in Experiment 2

Timepoint	Measure	Overall Sample (N=44)	EUC (N=16)	PST (N=11)	PST+EX (N=17)
	Depression Outcomes				
Baseline	PHQ-9	6.16 (2.95)	5.75 (2.72)	7.18 (3.37)	5.88 (2.89)
Post-Intervention	PHQ-9	3.80 (2.17)	4.44 (2.42)	3.45 (1.75)	3.41 (2.15)
12-month Follow-Up	PHQ-9	3.43 (2.99)	4.56 (4.15)	2.09 (1.45)	3.24 (2.02)
Post-Intervention	Percent Change PHQ-9	28.39 (48.85)	12.7 (48.68)	48.30 (24.63)	30.28 (57.36)
12-month Follow-Up	Percent Change PHQ-9	-17.43 (145.81)	-2.04 (69.63)	12.03 (98.56)	-53.07 (214.38)
	Global Cognition				
Baseline	RBANS Total Index	94.93 (10.65)	93.67 (8.31)	97.91 (10.01)	94.12 (12.9)
Post-Intervention	RBANS Total Index	96.50 (12.31)	94.63 (11.28)	99.91 (12.43)	96.06 (13.4)
12-month Follow-Up	RBANS Total Index	97.79 (12.98)	94.4 (12.33)	100.4 (11.72)	99.24 (14.29)
	Attention				
Baseline	RBANS Attention Index	98.34 (16.50)	95.44 (16.84)	102.45 (17.28)	98.41 (16.09)
Post-Intervention	RBANS Attention Index	99.91 (16.99)	98.5 (19.03)	103.73 (14.19)	98.76 (17.22)
12-month Follow-Up	RBANS Attention Index	118.12 (137.81)	96.27 (16.4)	181.82 (270.21)	96.18 (15.42)
	Executive Functioning				
Baseline	D-KEFS Trails 4 vs. 5 Contrast Scaled Score	9.55 (3.22)	9.63 (3.90)	8.00 (3.00)	10.47 (2.35)
Post-Intervention	D-KEFS Trails 4 vs. 5 Contrast Scaled Score	8.57 (3.20)	8.56 (3.05)	8.64 (3.38)	8.53 (3.41)
12-month Follow-Up	D-KEFS Trails 4 vs. 5 Contrast Scaled Score	10.83 (13.81)	8.13 (3.70)	9.50 (2.22)	14 (21.35)
Baseline	D-KEFS Color Word Interference Condition 3	9.89 (4.26)	8.88 (3.78)	10.45 (5.03)	10.47 (4.24)
Post-Intervention	D-KEFS Color Word Interference Condition 3	10.11 (4.08)	8.88 (4.30)	11.00 (4.10)	10.71 (3.79)
12-month Follow-Up	D-KEFS Color Word Interference Condition 3	11.07 (3.79)	10.86 (3.55)	11.6 (4.62)	10.94 (3.67)
	Learning and Memory				
Baseline	RBANS Immediate Memory Index	96.43 (13.65)	99.25 (11.74)	99.82 (11.19)	91.59 (15.9)
Post-Intervention	RBANS Immediate Memory Index	101.86 (13.13)	102.88 (11.02)	107.64 (9.58)	97.18 (15.65)
12-month Follow-Up	RBANS Immediate Memory Index	105.31 (15.18)	105.53 (12.83)	109.40 (14.54)	102.71 (17.61)
Baseline	RBANS List Learning subtest Raw Score	23.86 (4.15)	24.44 (4.83)	24.55 (3.21)	22.88 (4.05)
Post-Intervention	RBANS List Learning subtest Raw Score	26.86 (3.64)	27.38 (3.59)	28.09 (2.74)	25.59 (3.97)
12-month Follow-Up	RBANS List Learning subtest Raw Score	26.90 (5.83)	27.33 (5.56)	27.00 (6.27)	26.47 (6.13)
Baseline	RBANS Delayed Memory Index	94.20 (11.95)	95.75 (11.54)	94.55 (10.96)	92.53 (13.36)

Post-Intervention	RBANS Delayed Memory Index	96.02 (12.09)	97.00 (11.68)	95.55 (16.21)	95.41 (9.97)
12-month Follow-Up	RBANS Delayed Memory Index	98.33 (14.02)	96.73 (12.94)	98.6 (13.33)	99.59 (15.92)
	Language Skills				
Baseline	RBANS Language Index	98.52 (9.48)	96.63 (7.57)	101.55 (12.67)	98.35 (8.8)
Post-Intervention	RBANS Language Index	97.75 (12.11)	94.25 (9.47)	102.45 (11.46)	98 (14.16)
12-month Follow-Up	RBANS Language Index	98.17 (10.63)	95.33 (8.10)	102.1 (13.13)	98.35 (10.87)
	Visuospatial Skills				
Baseline	RBANS Visuospatial Constructional Index	94.81 (15.26)	90.33 (14.19)	96.55 (12.80)	97.65 (17.41)
Post-Intervention	RBANS Visuospatial Constructional Index	92.5 (16.21)	88.81 (15.73)	90.73 (16.82)	97.12 (16.11)
12-month Follow-Up	RBANS Visuospatial Constructional Index	93.71 (18.22)	86.87 (16.07)	91.8 (17.3)	100.88 (18.85)

4.2.5 Changes in PA/RARs, Depressive Symptoms, and Cognitive Functioning from Baseline to Post-Intervention

Indices of PA and RARs did not change from baseline to post-intervention across all participants ($p > 0.10$ for all measures of PA and RARs). Therefore, our hypothesis that change in indices of physical activity would be associated with change in depressive symptoms was unable to be tested. Across all participants, a reduction in depressive symptoms was observed from baseline to post-intervention ($t= 4.731$ $p< 0.001$). Cognitive performance improved from baseline to post-intervention for verbal learning (RBANS Immediate Memory Index: $t= -3.132$ $p= 0.003$; RBANS List Learning raw score: $t=-6.625$ $p< 0.001$). A trend towards a decline in performance for executive functioning was observed based on one measure assessing psychomotor set-shifting ($t=1.938$ $p= 0.059$). Given racial differences on cognitive measures at baseline, racial differences in change in cognitive performance from baseline to post-intervention was assessed, and results revealed that improvement in verbal learning was found only in Caucasian participants (RBANS Immediate Memory Index: $t= -3.489$ $p= 0.001$; RBANS List

Learning raw score: t=-6.698 p< 0.001) but was not observed for non-Caucasian participants (p>0.10).

4.2.6 Changes in PA/RARs, Depressive Symptoms, and Cognitive Functioning from Post-Intervention to 1-year follow-up

Average number of steps declined across all participants from post-intervention to the 1-year follow-up (t= 2.421 p=0.021). There was a trend towards continued improvement in performance for verbal learning (RBANS Immediate Memory Index: t=-1.647 p=0.10), as well as a trend toward improvement in memory performance (RBANS Delayed Memory Index: t= -1.652 p= 0.10) and executive functioning (i.e., response inhibition) (D-KEFS Color Word Interference Condition 3: t= -1.926 p=0.061) from post-intervention to the 1-year follow-up . An examination of racial differences in change in cognitive performance from post-intervention to the 1-year follow-up revealed that only *non-Caucasian* participants showed improvement in cognitive performance during this follow-up period, within the domains of verbal learning (RBANS Immediate Memory Index: t= -2.414, p=0.042) and executive functioning (D-KEFS Color Word Interference Condition 3: t=-4.648, p= 0.002) and a trend towards improvement in memory performance (RBANS Delayed Memory Index: t= -1.955, p=0.086). Changes in cognitive performance from post-intervention to the 1-year follow-up were non-significant across domains for Caucasian participants (p>0.10).

4.2.7 Longitudinal associations between PA/RARs and Depressive Symptoms

Given that PA and RARs levels did not change during the intervention, longitudinal associations between physical activity levels at baseline and change in depressive symptoms and measures of cognitive functioning were explored. The rationale for this analysis was based on the assumption that accelerometry-based indices of physical activity may be a marker of broader health behavior patterns, which may in turn reflect overall health status and specifically relate to brain health (e.g., structural brain integrity, neurovascular health). As such, markers of PA and/or circadian activity patterns (i.e., RARs) at baseline may predict intervention adherence and responsiveness to the intervention (i.e., change in depressive symptoms and cognitive functioning). To test the predictive value of baseline PA/RARs indices for change in depressive symptoms and cognitive functioning, step-wise regression models were conducted predicting percent change in depressive symptoms from baseline to post-intervention, using individual PA and RAR indices as the independent variable (in separate models), and age, education, sex, race, and baseline depressive symptoms as covariates. The results revealed that *lower* intradaily variability in RARs at baseline (i.e., *less* fragmented RARs) was associated with *greater decline* in depressive symptoms from baseline to post-intervention (Beta= -0.34, p=0.046, r^2 =0.08). Likewise, *higher* intradaily variability in RARs at baseline was associated with *greater severity* of residual depressive symptoms post-intervention, after covarying for baseline depression severity, age, education, sex, and race (Beta = 0.52, p= 0.004, r^2 =0.18) (See Figure 2). Additionally, engagement in at least 20-minutes of MVPA within 10-minute bouts at baseline (i.e., 'high' exercise group) was predictive of greater improvement in memory performance from baseline to post-intervention (% Change in RBANS Delayed Memory Index: t=-2.022, p=0.05).

No other PA or RARs indices at baseline were predictive of change in depressive symptoms or cognitive functioning ($p > 0.10$). See Table 13 for further details regarding PA variables.

Table 15. Physical Activity Measures in Experiment 2

Timepoint	Measure	Overall Sample (N=44)	EUC (N=16)	PST (N=11)	PST+EX (N=17)
	Daily Overall Physical Activity				
Baseline	Steps	4076.52 (2679.70)	3270.12 (2972.61)	2350.27 (1201.77)	5756.05 (2128.72)
Post-Intervention	Steps	3999.00 (2705.77)	3316.53 (2898.08)	2633.15 (1260.52)	5525.09 (2566.29)
12-month Follow-Up	Steps	3609.06 (2562.82)	3161 .65 (2972.12)	2471 .64 (1855.05)	4655.51 (2338.34)
Baseline	Metabolic Equivalent (METs)	1.16 (0.19)	1.12 (0.20)	1.09 (0.12)	1.24 (0.19)
Post-Intervention	Metabolic Equivalent (METs)	1.17 (0.19)	1.16 (0.22)	1.15 (0.18)	1.2 (0.18)
12-month Follow-Up	Metabolic Equivalent (METs)	1.18 (0.19)	1.15 (0.18)	1.20 (0.25)	1.18 (0.17)
	Daily Moderate-to-Vigorous Physical Activity				
Baseline	Minutes of MVPA	46.33 (47.64)	33.70 (40.50)	23.41 (12.28)	70.2 (56.42)
Post-Intervention	Minutes of MVPA	49.00 (46.29)	45.92 (48.05)	35.35 (28.29)	60.56 (53.14)
12-month Follow-Up	Minutes of MVPA	48.99 (41.58)	42.28 (30.30)	46.81 (45.87)	54.97 (46.91)
Baseline	Active Energy Expenditure	997.13 (1067.57)	698.15 (839.02)	453.52 (253.32)	1563.11 (1279.82)
Post-Intervention	Active Energy Expenditure	979.61 (945.39)	836.25 (896.70)	667.99 (637.39)	1316.17 (1089.31)
12-month Follow-Up	Active Energy Expenditure	1403.93 (2123.67)	855.57 (870.84)	825.90 (780.10)	2176.47 (3017.19)
	Total Bouts of Moderate to Vigorous PA				
Baseline	Number of 10-minute Bouts	4.61 (8.44)	2.36 (5.51)	0.90 (0.88)	8.65 (11.06)
Post-Intervention	Number of 10-minute Bouts	4.68 (7.29)	3.38 (6.14)	2.64 (3.67)	7.24 (9.36)
12-month Follow-Up	Number of 10-minute Bouts	4.34 (6.86)	3.08 (4.60)	1.30 (1.95)	7.19 (9.06)
Baseline	Minutes of MVPA in 10-minute Bouts	82.73 (150.93)	47.93 (129.37)	12.10 (11.94)	152.94 (184)
Post-Intervention	Minutes of MVPA in 10-minute Bouts	92.68 (151.58)	69.63 (144.37)	40.55 (59.29)	148.12 (185.33)
12-month Follow-Up	Minutes of MVPA in 10-minute Bouts	80.45 (138.81)	44.83 (80.18)	21.80 (35.44)	143.81 (185.67)
	Rest Activity Rhythm Indices				
Baseline	Intradaily Variability in RARs	0.73 (0.24)	0.81 (0.32)	0.64 (0.15)	0.72 (0.20)
Post-Intervention	Intradaily Variability in RARs	0.70 (0.20)	0.76 (0.24)	0.64 (0.18)	0.68 (0.16)
12-month Follow-Up	Intradaily Variability in RARs	0.74 (0.20)	0.71 (0.28)	0.77 (0.11)	0.73 (0.18)
Baseline	Interdaily Stability in RARs	0.48 (0.18)	0.46 (0.18)	0.43 (0.22)	0.53 (0.13)
Post-Intervention	Interdaily Stability in RARs	0.5 (0.21)	0.47 (0.25)	0.48 (0.20)	0.53 (0.17)
12-month Follow-Up	Interdaily Stability in RARs	0.44 (0.19)	0.39 (0.20)	0.45 (0.22)	0.46 (0.16)
Baseline	Relative Amplitude of RARs	0.73 (0.22)	0.72 (0.27)	0.68 (0.23)	0.78 (0.16)
Post-Intervention	Relative Amplitude of RARs	0.71 (0.25)	0.67 (0.32)	0.69 (0.20)	0.77 (0.19)
12-month Follow-Up	Relative Amplitude of RARs	0.69 (0.23)	0.62 (0.26)	0.71 (0.28)	0.74 (0.17)

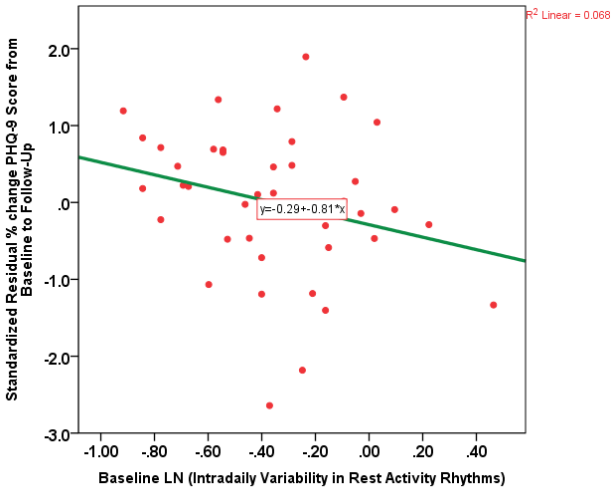

Figure 25. Negative association between Intradaily Variability in RARs at Baseline and Percent Change in Depression Severity from Baseline to Post-Intervention after adjusting for baseline depressive symptoms, age, education, sex, and race

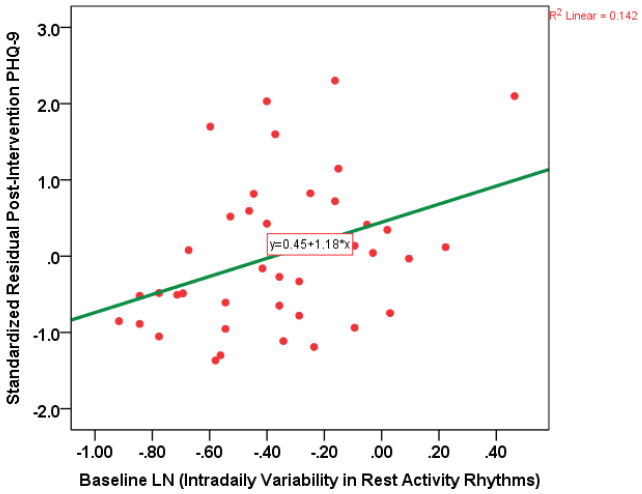

Figure 26. Positive Association between Intradaily Variability in RARs at Baseline and Depressive Symptoms Post-Intervention, after adjusting for baseline depressive symptoms, age, education, sex, and race.

4.2.8 Cross-Sectional Associations between PA/RAR Indices and Depressive Symptoms and Cognitive Functioning Post-Intervention and at 1-year follow-up

After completion of the intervention, higher interdaily stability in RARs was associated with better response inhibition (D-KEFS Color Word Interference Condition 3: r=0.34, p=0.02). However, adjusting for sex, education, and race resulted in this association becoming non-significant (Beta= 0.212, p=0.109, r^2=0.04). Significant associations of education and race with inhibition performance likely contributed to the association becoming non-significant. Interestingly, there was a trend such that race moderated the association between interdaily stability in RARs and response inhibition post-intervention (Race x lnIS.2: Beta= 0.47, p=0.069, r^2=0.05) (See Figure 27). Higher interdaily stability in RARs was strongly associated with better response inhibition in non-Caucasian participants (i.e., 82% African American) but not in

Caucasian participants. At the 1-year follow-up, *lower* intradaily variability in RARs was associated with *better* response inhibition after adjusting for sex, education, and race (Beta= -0.347, p=0.042, r^2=0.11) (See Figure 28). In summary, less fragmentation of daily RARs *and* greater stability of RARs across several days was associated with better executive functioning (i.e., response inhibition).

4.2.9 Cross-Sectional Associations between PA/RAR Indices and Depressive Symptoms and Cognitive Functioning Post-Intervention and at 1-year follow-up

After completion of the intervention, higher interdaily stability in RARs was associated with better response inhibition (D-KEFS Color Word Interference Condition 3: r=0.34, p=0.02). However, adjusting for sex, education, and race resulted in this association becoming non-significant (Beta= 0.212, p=0.109, r^2=0.04). Significant associations of education and race with inhibition performance likely contributed to the association becoming non-significant. Interestingly, there was a trend such that race moderated the association between interdaily stability in RARs and response inhibition post-intervention (Race x lnIS.2: Beta= 0.47, p=0.069, r^2=0.05) (See 27). Higher interdaily stability in RARs was strongly associated with better response inhibition in non-Caucasian participants (i.e., 82% African American) but not in Caucasian participants. At the 1-year follow-up, *lower* intradaily variability in RARs was associated with *better* response inhibition after adjusting for sex, education, and race (Beta= -0.347, p=0.042, r^2=0.11) (See Figure 28). In summary, less fragmentation of daily RARs *and* greater stability of RARs across several days was associated with better executive functioning (i.e., response inhibition).

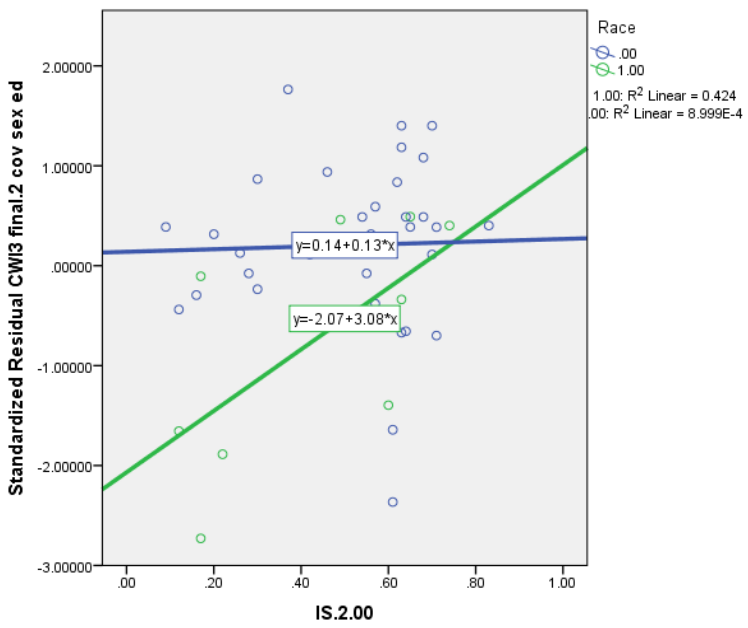

Figure 27. Race moderates the association between interdaily stability in rest activity rhythms and response inhibition post-intervention (Trend)

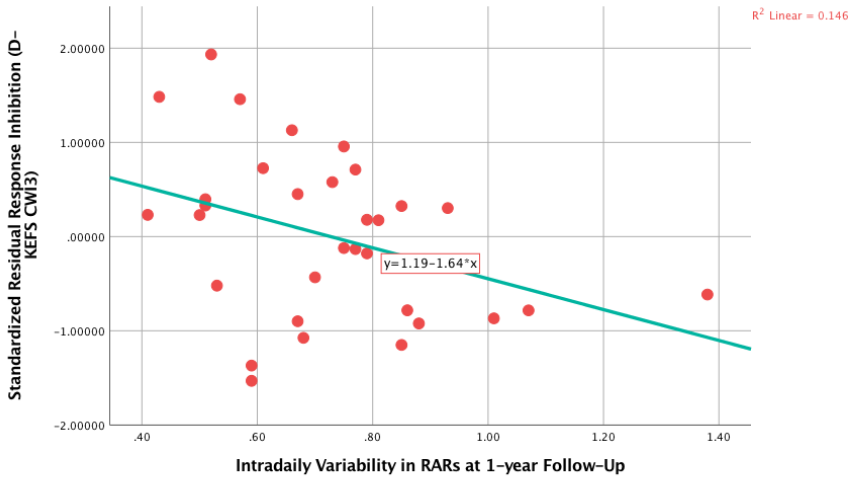

Figure 28. The association between Intradaily variability in RARs and response inhibition at the one-year follow-up

4.3 CONCLUSIONS

4.3.1 Intervention fidelity

The findings from the present study must be interpreted in the context of good intervention fidelity to the PST condition when implemented alone and poor intervention fidelity to the PST+exercise condition. Partially attributable to suboptimal intervention implementation, a key finding from the parent study is that the PST intervention when implemented alone, but not in combination with exercise, resulted in long-term benefits for reduction in subclinical levels of depressive symptoms (i.e., at 12-month follow-up) relative to enhanced usual care in older adults with MCI.

4.3.2 Depression Outcomes

An examination of MVPA/RARs associations with depressive symptoms across all participants (irrespective of intervention group) revealed that lower levels of MVPA were associated with greater severity of depressive symptoms at baseline. This finding is consistent with the strong reciprocal relationship between physical inactivity and depressive symptoms reported in the literature (Adamson & Motl, 2016). RARs indices were not directly related to depressive symptom severity at baseline. These findings suggest that depression severity is sensitive to the total amount of current daily MVPA engagement, which can be quantified using several conventional accelerometry measures (e.g., Hours of MVPA, Active Energy Expenditure, Minutes of PA in 10-minute bouts). In contrast, the RARs indices capture *regularity of patterns* of rest and activity (i.e., sensitive to patterns of PA and sleep) within and across days. We found lower intradaily variability in RARs prior to the intervention was longitudinally associated with greater decline in depressive symptom severity over the course of the 4-month intervention. The meaning or clinical significance of this longitudinal association remains ambiguous, as RARs indices have not yet been applied as predictors or outcomes in the context of depression treatment. Previous work suggests that RARs indices capture both *amount* and to some extent, *quality* of PA engagement and sleep (e.g., brief periods of low intensity PA vs. bouts of MVPA, frequent daytime napping, night-time awakenings) and may capture additional variance in health status beyond what is accounted for by specific metrics of MVPA and sleep (Smagula et al., 2015). In light of this, we speculate that variability in RARs likely reflects a set of longstanding premorbid health characteristics (e.g., PA, sleep & diet habits; cerebrovascular risk factors) that can potentially influence intervention engagement and responsiveness (i.e., change in depressive symptoms).

4.3.3 Cognitive Outcomes

Engagement in MVPA and variability in RARs were both associated with distinct aspects of cognitive functioning in older adults with MCI. MVPA engagement was not associated with measures of cognitive functioning when examined continuously; however, subgroup analysis at baseline revealed that the most active 50% of the sample (thresholded at median level of MVPA engagement in 10-minute bouts) performed better on measures of executive functioning and visuospatial skills relative to the least active 50% of the sample. Further, the most active 50% of the sample demonstrated improvement in memory performance over the course of the intervention, whereas the least active 50% of the sample did not show any improvement in memory performance. Less fragmentation of intradaily RARs was associated with better verbal learning at baseline and greater stability of RARs across days was associated with better executive functioning (i.e., inhibition) post-intervention, but both associations became marginal after adjustment for demographic covariates. Less fragmentation of intradaily RARs at the 12-month follow-up was also associated with better executive functioning, and remained significant after adjustment for demographic covariates. Given that MVPA and RARs indices did not change over the course of the study, cross-sectional associations observed between RARs indices and cognitive functioning at some time points but not others may seem puzzling; changes in these associations across time points is likely due to intervention-related changes in cognitive functioning (i.e., inhibition performance improved from post-intervention to the 12-month follow-up).

4.3.4 Racial differences in PA/RAR associations with Depression and Cognitive Outcomes

An interesting and unexpected finding in this study was racial differences observed in intervention-related changes in depressive symptoms and cognitive function, as well as racial differences in the association between RARs indices and cognitive functioning. Non-Caucasian participants, who were primarily African American, reported greater severity of depressive symptoms at baseline but demonstrated a much steeper decline in depressive symptoms (>100%) from baseline to post-intervention relative to Caucasian participants. Further, racial differences were observed in the timing of improvement in cognitive functioning, such that Caucasian participants exhibited improved performance in verbal learning from *baseline to post-intervention*, but non-Caucasian participants demonstrated improvements in executive functioning and verbal learning and memory from *post-intervention to the 12-month follow-up*. A deeper exploration of the data revealed that racial differences in timing of improvement in cognitive performance corresponded with a 'normalization' of group differences on those respective cognitive measures (i.e., racial differences in verbal learning performance at baseline were normalized by improvement exhibited in Caucasian participants). Although based on a small sample size, these racial differences in timing of cognitive changes may imply that cognitive domains that show 'deficits' (or relative weaknesses) may be more sensitive to intervention-related improvement. Further, racial differences were observed in the association of RARs indices with verbal learning at baseline and executive functioning post-intervention, such that there was a strong association between RARs indices and cognitive performance in non-Caucasian but not in Caucasian participants.

4.3.5 Implications

The findings from this study collectively highlight the web of reciprocal relationships between health behavior patterns, brain health, cognitive functioning, and depressive symptoms. The strength and directionality of these relationships also change over time, making it difficult to truly delineate "predictors" and "outcomes." In the present study, health behavior patterns were examined as 'predictors' of depression and cognitive 'outcomes', despite the bidirectional nature of these associations, with the primary motivation of characterizing the role of *modifiable* lifestyle factors in promoting cognitive and emotional health in late-life. Longitudinal associations observed between variability in RARs at baseline and change in depression severity, as well as between MVPA at baseline (i.e., median split groups of high vs. low MVPA) and change in memory performance, point to the long-term implications of health behavior patterns prior to an intervention for predicting intervention responsiveness. In light of these findings, it is important for future studies to consider premorbid health behaviors when examining treatment outcomes. Given that variability in RARs and MVPA at baseline was associated with intervention outcomes in this highly sedentary sample with limited variability in activity levels, stronger associations between pre-existing health behavior patterns and treatment outcomes will likely be detected in other populations.

4.3.6 Limitations

Several important limitations of this study must be considered in interpreting these results. First, small sample size was a key limitation given this was a pilot study and only included a subsample of the parent study. Further, the subsample included in this study included

an uneven distribution of participants across intervention groups, such that fewer participants from the group showing the greatest change in depressive symptoms (PST alone) were included relative to the other two groups (PST+EX and EUC) within the parent study. The participant sample was also subject to selection bias, as most participants were highly educated (mean years of education >15 years), which is not representative of the general older adult population diagnosed with MCI. Even greater selection bias may have been apparent in the African American subset of the sample, given that that the non-Caucasian subgroup (82% African American) performed better on several measures of cognitive function at baseline relative to Caucasian participants, which is not representative of racial differences observed in the general population of older adults with MCI. Further, due to recruitment challenges, the inclusion criteria for level of depressive symptoms required changed over time and resulted in a sample with low depressive symptom severity overall than might be expected in the general population with co-occurring MCI and depressive symptoms.

With regard to limitations concerning PA/RARs assessment, the level of 'objectivity' in accelerometry-based assessments of PA levels and patterns must be interpreted with caution, given that the one week that participants wear these devices at each time point of the study may not be truly representative of their overall levels and patterns of activity (i.e., due to situational factors and demand characteristics). Further, given the multitude of approaches available to analyze accelerometry-based measures of PA and RARs (e.g., total, mean, daily vs. total duration, non-parametric, extended cosine), associations observed across multiple indicators assessing similar aspects of PA/RARs should be weighted more heavily when interpreting findings. Finally, the limited cross-sectional and longitudinal variability in MVPA and RARs indices observed in this highly sedentary sample may underestimate associations observed

between MVPA/RARs indices and measures of depression and cognitive function.

As mentioned earlier, several overarching concerns regarding suboptimal implementation of the intervention must also be considered in interpreting these data, such as poor adherence to the exercise intervention in contrast to good adherence to the PST intervention when implemented alone. Moreover, study clinicians reported spending a disproportionate amount of time in therapy focused on problem-solving barriers to exercise adherence in the PST+EX group, which additionally resulted in suboptimal implementation of PST in in the PST+EX group. A key component of the parent study was the inclusion of dyads of older adults with MCI and their caregivers for participants who had caregivers available and willing to participate, and this key indicator of social support was not considered in the present study. Notably, the primary findings from the parent study suggest that social support may have a critical role in predicting primary treatment outcomes (i.e., change in depression) in this sample.

4.3.7 Summary

Despite these limitations, there are a number of notable strengths to this pilot study, namely the implementation of a novel combination of non-pharmacological interventions (PST and exercise) to reduce mental health symptom burden and slow cognitive decline in a population that is at high-risk for accelerated cognitive and functional decline (i.e., converting to dementia) and for developing Major Depression, all of which contribute to poor trajectories of brain health and quality of life in older adults. Further, the value of subtle changes in health behavior patterns (i.e., PA levels or RARs) has seldom been examined in this highly sedentary segment of the population for whom small increases in physical activity levels and regularity of RARs may have important implications for preventing or attenuating neurodegenerative

processes. To our knowledge, this is the first study to utilize RARs indices in the context of treatment for depressive symptoms, despite previous work demonstrating the high sensitivity of RARs for capturing behavioral manifestations of depression (Smagula et al., 2015). Moreover, the comparison of RARs indices and conventional accelerometry-based PA measures used may inform future studies regarding the distinct clinical implications of each measure and also highlight that using a combination of these measures may capture the greatest clinically-meaningful variance in PA levels in highly sedentary populations.

In conclusion, consistent with patterns observed in the general population, this sample of older adults with MCI and depressive symptom was highly sedentary. Across the overall sample, physical activity patterns did not change during or following a behavioral intervention aimed to reduce depressive symptoms and attenuate cognitive decline, even in the subgroup for which exercise was prescribed as a component of the intervention. Nonetheless, individual variability in several indicators of physical activity patterns, as assessed by engagement in MVPA and naturally occurring intra- and inter-daily variability in RARs, was related to cognitive performance and depressive symptom severity. Higher MVPA engagement was associated with lower depressive symptom severity at baseline and was predictive of greater improvement in memory performance over the course of the intervention. Lower intradaily variability in RARs at baseline was predictive of greater decline in depressive symptom severity over the course of the intervention. Further, less fragmentation of daily RARs and greater stability of RARs across days was related to better executive functioning, and this association was stronger for non-Caucasian (i.e., mostly African American) relative to Caucasian participants. In sum, MVPA engagement and RARs appear to be partially overlapping but distinct markers of health status that may each have unique implications for depression and neurocognitive function in late-life, and may both

help to better understand variability in intervention responsiveness in older adults with cognitive impairment and co-occurring depressive symptoms.

5.0 DISCUSSION

This dissertation aimed to characterize the effects of exercise on depression, cognitive function, and brain morphology and functional dynamics in older and younger adults by utilizing data from two randomized pilot intervention studies. The overarching goal of this project was to highlight the utility of exercise as a valuable and feasible behavioral intervention for attenuating co-occurring mood and cognitive symptoms, via its beneficial effects on brain health (i.e., reduced neuroinflammation, increased neurovasculature, proliferation of neurotrophic factors). Despite using only pilot data, two key innovations in this project allow for a novel contribution to the literature: 1) the exploration of neural mechanisms underlying the antidepressant effects of exercise by leveraging multiple distinct markers of brain morphology and examining exercise-related changes in intrinsic functional network dynamics, as well as 2) a comparison of the relevance of multiple objective markers of physical activity for attenuating depressive symptoms and cognitive decline in a highly sedentary older adult population with an elevated risk for developing Major Depression and Major Neurocognitive Disorder (i.e., dementia).

The two pilot studies included in this project were initially combined with the goal of examining exercise effects on depression and cognitive function in samples with varying levels of depression and cognitive dysfunction (i.e., clinical vs. subclinical depressive symptoms, MCI vs. cognitive symptoms of depression). Ultimately, it was difficult to draw cohesive conclusions across both studies due to marked differences in the study samples, study design, intervention

implementation, and primary outcome measures examined. Nonetheless, overarching themes across results from both pilot intervention studies will be highlighted.

5.1 EXERCISE/PA EFFECTS ON DEPRESSIVE SYMPTOMS

First, juxtaposing the results from these two studies reinforces subtle but important distinctions between various PA-related constructs, and the unique implications of various markers of PA for clinical and cognitive outcomes. For instance, regular engagement in supervised aerobic exercise may exert influences on cognitive and mood outcomes via changes in aerobic fitness. However, the broader literature suggests that exercise interventions in which depressed adults do not show improvements in fitness still achieve remission from depression (Stubbs et al., 2017), suggesting that exercise engagement may alleviate depression via direct and indirect pathways (e.g., increased motivation to remain active, increased social engagement). The notion of multiple pathways underlying PA-related benefits for depression is consistent with the results from Experiment 2, which highlight the value of regularity in patterns of PA (even at low-intensities), in addition to the role of engagement in MVPA, for alleviating depressive symptoms. These findings further relate to results from a large RCT(N=620) examining the effects of various doses of PA on depressive symptoms, which revealed that low-intensity but not moderate- or high-intensity PA predicted maintenance of intervention-related benefits in depressive symptom reduction 12-months following completion of the intervention (Helgadottir et al., 2017).

Two additional studies demonstrated potentially large, clinically meaningful benefits of exercise-augmentation to conventional depression treatments. In one pilot study, Gourgouvelis et al. (2018) showed that adding exercise to a combination of medication treatment and group

psychotherapy for depression resulted in a significantly greater reduction in depressive symptom severity and markedly better odds of remission from depression relative to no PA (PA group: 75% remission vs. no-PA: 25% remission). Further, a large RCT (N=121) involving treatment for late-life depression, in which exercise was an augmentation to medication treatment, revealed a similar pattern of findings as Experiment 1, such that exercise significantly benefited depression outcomes through more rapid symptom reduction, with selective benefits reported for affective rather than somatic symptoms of depression (Murri et al., 2018).

5.2 EXERCISE/PA ASSOCIATIONS WITH COGNITIVE FUNCTIONING, IN ADULTS WITH DEPRESSIVE SYMPTOMS

In both older adults with MCI and younger adults with Major Depression, exercise/PA-related benefits in performance on select cognitive domains were observed, including attention, learning, and memory. These exercise-related cognitive changes/associations were somewhat surprising, given the limited power to detect effects in these pilot studies, and in light of the mixed literature regarding cognitive benefits associated with depression treatment (Xu et al., 2011). Nonetheless, select cognitive benefits associated with exercise or PA are plausible in these two clinical sample with highly 'vulnerable' brains, given that exercise-related benefits for cognitive function have been observed in neurologically healthy younger and older adults (Committe, 2018).The implications of age differences in exercise effects on cognitive functioning observed in Experiment 1 remain ambiguous, when considered in the context of cognitive benefits of PA/RARs observed in more cognitively 'vulnerable' older adults (i.e., MCI diagnosis) in Experiment 2.

5.3 EXPERIMENT 1: EXERCISE EFFECTS ON BRAIN MORPHOLOGY IN ADULTS WITH MAJOR DEPRESSION

The novelty of Experiment 1 primarily stemmed from the inclusion of high-resolution brain MRI measures collected using a 7T MR scanner, which allowed for an exploration of exercise-related changes in microstructural brain outcomes (e.g., hippocampal subfields) that cannot be as clearly delineated using data collected from 3T MR scanners, which are most commonly used in mechanistic clinical intervention studies. Further, the availability both structural and functional MRI data allowed for a preliminary exploration of the augmentive effects of exercise on a range of brain health outcomes in the context of antidepressant treatment. First, we observed an unexpected decline in the right global hippocampal volume, as well as volume of right anterior hippocampal subfields in the MED group relative to the EX group. The meaning of these results remains unclear, given that hippocampal volumetric decline is inconsistent with brain changes that would expected in the context of effective pharmaceutical treatment for depression. However, the lack of hippocampal volumetric decline in the EX group partially maps onto findings reported in a meta-analysis of 14 studies examining aerobic exercise effects on hippocampal volume (N=737) suggesting that aerobic exercise may be protective against hippocampal volumetric decreases over time (Firth et al., 2018). Further, our null finding with regard to volumetric increases in the hippocampus is consistent with the only prior study to examine exercise effect on brain morphology in the context of depression treatment, which neglected to find exercise-related volumetric increases in the hippocampus (Krogh et al., 2014).

In contrast to the ambiguous findings regarding group differences in hippocampal volumetric changes, the most promising results in the present study with regard to exercise effects on brain morphology were observed in relation to estimates of *cortical thickness*, rather

than volume. First, reduced cortical thickness in the medial OFC, rostral ACC, and parahippocampal gyrus, was strongly associated with greater depression severity at baseline in this clinically depressed sample with a moderate range in depressive symptom severity (MADRS score range: 15-36). Importantly, the association between cortical thickness in PFC, ACC, and PHC and depression severity was independent of duration of current depressive episode and age of onset of first depressive episode, suggestive of specificity of the association to current depression severity (but could also be due to a third variable explaining variance in regional cortical thickness and depression severity). The selective association between cortical thickness in these regions and depression severity is striking, given that the medial OFC, rostral ACC, and PHC have consistently shown structural abnormalities in depressed relative to non-depressed adults (Gujral et al., 2017). In fact, structural abnormalities in the rostral ACC may be the most consistent regional structural abnormality associated with depression across the meta-analytic literature (Gujral et al., 2017). If reduced cortical thickness in these regions is a function of depression severity alone, one might expect to observe increases in cortical thickness in these regions as a function of decline in depression severity (or remission). However, this pattern was not observed in the current sample. Rather, an increase cortical thickness in the medial OFC, rostral ACC, and PHC was marginally associated with improvement in fitness, suggesting these regions that are sensitive to effects of depression also appear to be sensitive to improvements in aerobic fitness. Although we may theoretically predict a negative association between depression severity and cortical thickness in prefrontal, ACC, and PHC regions, and a positive association between improvement in fitness and cortical thickness in these regions, the co-occurrence of associations we *expect* to be related is seldom actually *observed,* particularly in the context of pilot studies. Although not statistically significant in this small sample, the strength of the

associations between change in fitness and change in cortical thickness in PFC, ACC, and PHC regions, in the expected direction, warrants further exploration in large-scale intervention studies.

5.4 EXPERIMENT 1: IMPROVEMENT IN FITNESS: ASSOCIATIONS WITH BRAIN-BEHAVIOR RELATIONSHIPS

This pilot intervention study was likely underpowered to detect neural mechanisms underlying the antidepressant effects of exercise. However, any associations found between exercise-related changes in markers of brain integrity and behavioral outcome measures may signal potential brain mechanisms associated with exercise related clinical or cognitive benefits, in the context of depression treatment. In the right medial OFC and rostral ACC, an increase in cortical thickness was associated improvement in cognitive performance on a measure of verbal learning, and an increase in cortical thickness in the medial OFC was additionally associated with improvement in performance on measures of executive functioning and memory. Given that improvement in fitness was also marginally associated with increases in cortical thickness in these regions, it is possible that morphological changes in the right medial OFC and rostral ACC may subserve exercise-related improvements in cognitive functioning observed during treatment for depression. To gain a more comprehensive understanding the role of these regions in the association between fitness and cognitive functioning in depressed adults, important next steps will be to examine exercise and/or fitness-related changes in functional connectivity within and between these regions, using seed-to-voxel and seed-to-seed analytic approaches.

5.5 EXPERIMENT 1: EXERCISE EFFECTS ON HIPPOCAMPAL FUNCTIONAL CONNECTIVITY IN ADULTS WITH MAJOR DEPRESSION

As a preliminary point of exploration, a simple hippocampal seed-based approach was utilized to examine intervention group differences post-intervention that were not present at baseline, with the aim of capturing variability in hippocampal functional connectivity patterns that is sensitive to exercise training as a component of treatment for depression. At baseline, the EX group demonstrated greater right hippocampal connectivity with ECN (i.e., inferior frontal gyrus, precentral gyrus) and DMN regions (i.e., posterior cingulate cortex) relative to the MED group. After completion of the intervention, both treatment groups demonstrated an increase in hippocampal connectivity with the supramarginal gyrus (SMG), which has been implicated in range of somatosensory and cognitive, and social-cognitive functions (i.e., visuospatial awareness, cognitive control, and expression of empathy) (Silani, Lamm et al., 2013). The meaning of increased hippocampal connectivity with the right SMG for clinical outcomes remains unclear, given the various cognitive and social-cognitive functions of the SMG. The EX group additionally demonstrated an increase in HC functional connectivity with medial temporal regions, known to be a part of the DMN. As mentioned earlier, the DMN is involved in self-referential processes and high DMN connectivity may relate to rumination, a prominent symptom of depression. The meta-analytic depression literature has largely demonstrated hyperconnectivity of DMN regions in depression (Kaiser et al., 2015), although there have been a number of inconsistencies in this literature. One meta-analysis in mid-life depression reported increased DMN connectivity was a predictive of treatment response (Pizzagalli, 2011). In the exercise literature, increased DMN connectivity has been observed as a function of exercise training (Voss et al., 2011), although this may to some extent be influenced by the age-related

increases in DMN connectivity, given the majority of mechanistic exercise trials have been conducted in older adults. In sum, based on the results of this targeted, apriori approach to examining exercise-related changes in intrinsic functional network dynamics, it is difficult to conclude the clinical meaning or relevance of these group differences in intervention-related changes in hippocampal functional connectivity patterns.

5.6 FEASIBILITY

Significant recruitment challenges were encountered in both pilot trials included in this dissertation; nonetheless, towards the end of the recruitment period, successful recruitment strategies were identified in both studies, which have been detailed in the results section for Experiment 1 and have been outlined in Gildengers et al. (2016) for Experiment 2. Inevitable challenges in the overall recruitment of older adults for clinical intervention studies must be considered, such as significant medical illness burden and heightened vulnerability to transportation challenges. These general barriers to recruitment, when coupled with cognitive impairment and depressive symptoms, in the context of possibly limited social and instrumental support structures, challenges to intervention recruitment and adherence are compounded. Nonetheless, the unexpectedly high intervention adherence rates observed in Experiment 1 (91%), in combination with meta-analytic evidence of non-significant dropout of depressed adults from exercise trials (Stubbs et al., 2015), suggests that study retention may be less of an issue if recruitment challenges can be overcome. Key limitations of each study have been detailed in earlier conclusions sections; however it is worth reiterating that the most striking limitation across both of these studies is the limited sample size.

5.7 FUTURE DIRECTIONS

With regard to Experiment 1, a further exploration of exercise- and fitness-related brain changes is warranted, given the strength of associations observed within the expected direction. A deeper exploration of exercise-related changes in functional connectivity measures is additionally needed, given that the simplistic hippocampal seed-based approach may not capture the most meaningful exercise-related changes in intrinsic connectivity patterns. Next steps in these analyses may include using an a broader eigenvector centrality approach (EVC) to explore intra- and inter-network coupling and de-coupling, consistent with the methods used in Karim et al. (2017)), as well as testing seed-to-voxel connectivity using alternative seed regions that were sensitive to depression and fitness-related changes and in this study (i.e., medial OFC, rostral ACC, and PHC).

5.8 BROADER IMPLICATIONS / SUMMARY

Results from this dissertation, albeit based on data from pilot intervention studies, reveal the important role of exercise/PA for a range of clinical, cognitive, and brain health outcomes. Across unique two clinical samples with varying degrees of depressive symptom burden and cognitive impairment, improvement in fitness, regularity of rest activity patterns, and engagement in exercise were each uniquely associated with depression and cognitive outcomes. Overarching conclusions from this dissertation highlight the widespread utility of exercise

interventions for alleviating clinical and subclinical levels of depression and cognitive decline, via *protective* effects on neural pathways that may be sensitive to the *deleterious* effects of depression and cognitive impairment.

BIBLIOGRAPHY

Arean, P. A., Perri, M. G., Nezu, A. M., Schein, R. L., Christopher, F., & Joseph, T. X. (1993). Comparative effectiveness of social problem-solving therapy and reminiscence therapy as treatments for depression in older adults. J Consult Clin Psychol, 61(6), 1003-1010.

Arkin, S. M. (2003). Student-led exercise sessions yield significant fitness gains for Alzheimer's patients. Am J Alzheimers Dis Other Demen, 18(3), 159-170.

Ashburner, J., & Friston, K. J. (2000). Voxel-based morphometry--the methods. Neuroimage, 11(6 Pt 1), 805-821. doi: 10.1006/nimg.2000.0582

Bailey, A. P., Hetrick, S. E., Rosenbaum, S., Purcell, R., & Parker, A. G. (2018). Treating depression with physical activity in adolescents and young adults: a systematic review and meta-analysis of randomised controlled trials. Psychol Med, 48(7), 1068-1083. doi: 10.1017/S0033291717002653

Barreto Pde, S., Demougeot, L., Pillard, F., Lapeyre-Mestre, M., & Rolland, Y. (2015). Exercise training for managing behavioral and psychological symptoms in people with dementia: A systematic review and meta-analysis. Ageing Res Rev, 24(Pt B), 274-285. doi: 10.1016/j.arr.2015.09.001

Benson, N., Hulac, D. M., & Kranzler, J. H. (2010). Independent examination of the Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV): what does the WAIS-IV measure? Psychol Assess, 22(1), 121-130. doi: 10.1037/a0017767

Benton, AL, Hamsher, SK, & AB, Sivan. (1982). Multilingual aplasia examination (2nd Edition). Iowa City, IA: AJA Associates.

Bherer, L., Erickson, K. I., & Liu-Ambrose, T. (2013). A review of the effects of physical activity and exercise on cognitive and brain functions in older adults. J Aging Res, 2013, 657508. doi: 10.1155/2013/657508

Blondell, Sarah J, Hammersley-Mather, Rachel, & Veerman, J Lennert. (2014). Does physical activity prevent cognitive decline and dementia?: A systematic review and meta-analysis of longitudinal studies. BMC public health, 14(1), 510.

Bora, E., Fornito, A., Pantelis, C., & Yucel, M. (2012). Gray matter abnormalities in Major Depressive Disorder: a meta-analysis of voxel based morphometry studies. J Affect Disord, 138(1-2), 9-18. doi: 10.1016/j.jad.2011.03.049

Bora, E., Harrison, B. J., Davey, C. G., Yucel, M., & Pantelis, C. (2012). Meta-analysis of volumetric abnormalities in cortico-striatal-pallidal-thalamic circuits in major depressive disorder. Psychol Med, 42(4), 671-681. doi: 10.1017/S0033291711001668

Bora, E., Harrison, B. J., Yucel, M., & Pantelis, C. (2013). Cognitive impairment in euthymic major depressive disorder: a meta-analysis. Psychol Med, 43(10), 2017-2026. doi: 10.1017/S0033291712002085

Brondino, N., Rocchetti, M., Fusar-Poli, L., Codrons, E., Correale, L., Vandoni, M., . . . Politi, P. (2017). A systematic review of cognitive effects of exercise in depression. Acta Psychiatr Scand, 135(4), 285-295. doi: 10.1111/acps.12690

Burdette, J. H., Laurienti, P. J., Espeland, M. A., Morgan, A., Telesford, Q., Vechlekar, C. D., . . . Rejeski, W. J. (2010). Using network science to evaluate exercise-associated brain changes in older adults. Front Aging Neurosci, 2, 23. doi: 10.3389/fnagi.2010.00023

Butters, M. A., Whyte, E. M., Nebes, R. D., Begley, A. E., Dew, M. A., Mulsant, B. H., . . . Becker, J. T. (2004). The nature and determinants of neuropsychological functioning in late-life depression. Arch Gen Psychiatry, 61(6), 587-595. doi: 10.1001/archpsyc.61.6.587

Colcombe, S. J., Erickson, K. I., Scalf, P. E., Kim, J. S., Prakash, R., McAuley, E., . . . Kramer, A. F. (2006). Aerobic exercise training increases brain volume in aging humans. J Gerontol A Biol Sci Med Sci, 61(11), 1166-1170.

Colcombe, Stanley, & Kramer, Arthur F. (2003). Fitness effects on the cognitive function of older adults a meta-analytic study. Psychological science, 14(2), 125-130.

Cole, J., Costafreda, S. G., McGuffin, P., & Fu, C. H. (2011). Hippocampal atrophy in first episode depression: a meta-analysis of magnetic resonance imaging studies. J Affect Disord, 134(1-3), 483-487. doi: 10.1016/j.jad.2011.05.057

Committe, Physical Activity Guidelines Advisory. (2018). Physical Activity Guidelines Advisory Committe Scientific Report, 2018. Washington, D.C. : Retrieved from https://health.gov/paguidelines/second-edition/report/pdf/09_F-3_Brain_Health.pdf.

Conn, V. S. (2010). Depressive symptom outcomes of physical activity interventions: meta-analysis findings. Ann Behav Med, 39(2), 128-138. doi: 10.1007/s12160-010-9172-x

Cooney, G. M., Dwan, K., Greig, C. A., Lawlor, D. A., Rimer, J., Waugh, F. R., . . . Mead, G. E. (2013). Exercise for depression. Cochrane Database Syst Rev, 9, CD004366. doi: 10.1002/14651858.CD004366.pub6

Delis, D. C., Kramer, J. H., Kaplan, E., & Holdnack, J. (2004). Reliability and validity of the Delis-Kaplan executive function system: An update. Journal of the International Neuropsychological Society, 10(2), 301-303. doi: 10.1017/S1355617704102191

Dill, V., Franco, A. R., & Pinho, M. S. (2015). Automated methods for hippocampus segmentation: the evolution and a review of the state of the art. Neuroinformatics, 13(2), 133-150. doi: 10.1007/s12021-014-9243-4

Diniz, B. S., Butters, M. A., Albert, S. M., Dew, M. A., & Reynolds, C. F., 3rd. (2013). Late-life depression and risk of vascular dementia and Alzheimer's disease: systematic review and meta-analysis of community-based cohort studies. Br J Psychiatry, 202(5), 329-335. doi: 10.1192/bjp.bp.112.118307

Drevets, W. C., Savitz, J., & Trimble, M. (2008). The subgenual anterior cingulate cortex in mood disorders. CNS Spectr, 13(8), 663-681.

Du, M. Y., Wu, Q. Z., Yue, Q., Li, J., Liao, Y., Kuang, W. H., . . . Gong, Q. Y. (2012). Voxelwise meta-analysis of gray matter reduction in major depressive disorder. Prog Neuropsychopharmacol Biol Psychiatry, 36(1), 11-16. doi: 10.1016/j.pnpbp.2011.09.014

Duman, R. S., & Monteggia, L. M. (2006). A neurotrophic model for stress-related mood disorders. Biol Psychiatry, 59(12), 1116-1127. doi: 10.1016/j.biopsych.2006.02.013

Erickson, K. I., Leckie, R. L., & Weinstein, A. M. (2014). Physical activity, fitness, and gray matter volume. Neurobiol Aging, 35 Suppl 2, S20-28. doi: 10.1016/j.neurobiolaging.2014.03.034

Erickson, K. I., Voss, M. W., Prakash, R. S., Basak, C., Szabo, A., Chaddock, L., . . . Kramer, A. F. (2011). Exercise training increases size of hippocampus and improves memory. Proc Natl Acad Sci U S A, 108(7), 3017-3022. doi: 10.1073/pnas.1015950108

First, MB, Spitzer, RL, Gibbon M, & Williams, JBW. (2002). Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Non-patient Edition (SCID-I/NP). New York: Biometrics Research, New York State Psychiatric Institute.

Firth, J., Stubbs, B., Vancampfort, D., Schuch, F., Lagopoulos, J., Rosenbaum, S., & Ward, P. B. (2018). Effect of aerobic exercise on hippocampal volume in humans: A systematic review and meta-analysis. Neuroimage, 166, 230-238. doi: 10.1016/j.neuroimage.2017.11.007

Flodin, P., Jonasson, L. S., Riklund, K., Nyberg, L., & Boraxbekk, C. J. (2017). Does Aerobic Exercise Influence Intrinsic Brain Activity? An Aerobic Exercise Intervention among Healthy Old Adults. Front Aging Neurosci, 9, 267. doi: 10.3389/fnagi.2017.00267

Fu, C. H., Steiner, H., & Costafreda, S. G. (2013). Predictive neural biomarkers of clinical response in depression: a meta-analysis of functional and structural neuroimaging studies of pharmacological and psychological therapies. Neurobiol Dis, 52, 75-83. doi: 10.1016/j.nbd.2012.05.008

Garand, L., Rinaldo, D. E., Alberth, M. M., Delany, J., Beasock, S. L., Lopez, O. L., . . . Dew, M. A. (2014). Effects of problem solving therapy on mental health outcomes in family caregivers of persons with a new diagnosis of mild cognitive impairment or early dementia: a randomized controlled trial. Am J Geriatr Psychiatry, 22(8), 771-781. doi: 10.1016/j.jagp.2013.07.007

Garza, A. A., Ha, T. G., Garcia, C., Chen, M. J., & Russo-Neustadt, A. A. (2004). Exercise, antidepressant treatment, and BDNF mRNA expression in the aging brain. Pharmacol Biochem Behav, 77(2), 209-220.

Gasquoine, P. G. (2013). Localization of function in anterior cingulate cortex: from psychosurgery to functional neuroimaging. Neurosci Biobehav Rev, 37(3), 340-348. doi: 10.1016/j.neubiorev.2013.01.002

Gildengers, A.G., Butters, M. A., Albert, S. M., Anderson, S.J., Dew, M.A., Erickson, K., & Reynolds, C. (2016). Design and Implementations of an intervention development study: Retaining Cognition while Avoiding Late-Life Depression. The American Journal of Geriatric Psychiatry, 24(6), 444-454.

Good, C. D., Johnsrude, I., Ashburner, J., Henson, R. N., Friston, K. J., & Frackowiak, R. S. (2001a). Cerebral asymmetry and the effects of sex and handedness on brain structure: a voxel-based morphometric analysis of 465 normal adult human brains. Neuroimage, 14(3), 685-700. doi: 10.1006/nimg.2001.0857

Good, C. D., Johnsrude, I. S., Ashburner, J., Henson, R. N., Friston, K. J., & Frackowiak, R. S. (2001b). A voxel-based morphometric study of ageing in 465 normal adult human brains. Neuroimage, 14(1 Pt 1), 21-36. doi: 10.1006/nimg.2001.0786

Gourgouvelis, J., Yielder, P., & Murphy, B. (2017). Exercise Promotes Neuroplasticity in Both Healthy and Depressed Brains: An fMRI Pilot Study. Neural Plast, 2017, 8305287. doi: 10.1155/2017/8305287

Greer, T. L., Grannemann, B. D., Chansard, M., Karim, A. I., & Trivedi, M. H. (2015). Dose-dependent changes in cognitive function with exercise augmentation for major depression: results from the TREAD study. Eur Neuropsychopharmacol, 25(2), 248-256. doi: 10.1016/j.euroneuro.2014.10.001

Groot, C., Hooghiemstra, A. M., Raijmakers, P. G., van Berckel, B. N., Scheltens, P., Scherder, E. J., . . . Ossenkoppele, R. (2016). The effect of physical activity on cognitive function in patients with dementia: A meta-analysis of randomized control trials. Ageing Res Rev, 25, 13-23. doi: 10.1016/j.arr.2015.11.005

Gujral, S., Aizenstein, H., Reynolds, C. F., 3rd, Butters, M. A., & Erickson, K. I. (2017). Exercise effects on depression: Possible neural mechanisms. Gen Hosp Psychiatry, 49, 2-10. doi: 10.1016/j.genhosppsych.2017.04.012

Heyn, P., Abreu, B. C., & Ottenbacher, K. J. (2004). The effects of exercise training on elderly persons with cognitive impairment and dementia: A meta-analysis. Archives of Physical Medicine and Rehabilitation, 85(10), 1694-1704. doi: 10.1016/j.apmr.2004.03.019

Hindin, S. B., & Zelinski, E. M. (2012). Extended Practice and Aerobic Exercise Interventions Benefit Untrained Cognitive Outcomes in Older Adults: A Meta-Analysis. Journal of the American Geriatrics Society, 60(1), 136-141. doi: 10.1111/j.1532-5415.2011.03761.x

Hoffman, B. M., Blumenthal, J. A., Babyak, M. A., Smith, P. J., Rogers, S. D., Doraiswamy, P. M., & Sherwood, A. (2008). Exercise fails to improve neurocognition in depressed middle-aged and older adults. Medicine and Science in Sports and Exercise, 40(7), 1344-1352. doi: 10.1249/MSS.0b013e31816b877c

Iwabuchi, S. J., Krishnadas, R., Li, C., Auer, D. P., Radua, J., & Palaniyappan, L. (2015). Localized connectivity in depression: a meta-analysis of resting state functional imaging studies. Neurosci Biobehav Rev, 51, 77-86. doi: 10.1016/j.neubiorev.2015.01.006

Jennings, J. R., Mendelson, D. N., Redfern, M. S., & Nebes, R. D. (2011). Detecting age differences in resistance to perceptual and motor interference. Exp Aging Res, 37(2), 179-197. doi: 10.1080/0361073X.2011.554512

Kaiser, R. H., Andrews-Hanna, J. R., Wager, T. D., & Pizzagalli, D. A. (2015). Large-Scale Network Dysfunction in Major Depressive Disorder: A Meta-analysis of Resting-State Functional Connectivity. JAMA Psychiatry, 72(6), 603-611. doi: 10.1001/jamapsychiatry.2015.0071

Karim, H. T., Andreescu, C., Tudorascu, D., Smagula, S. F., Butters, M. A., Karp, J. F., . . . Aizenstein, H. (2017). Intrinsic functional connectivity in late-life depression: trajectories over the course of pharmacotherapy in remitters and non-remitters. Molecular Psychiatry, 22, 450-457.

Kempermann, G., Kuhn, H. G., & Gage, F. H. (1998). Experience-induced neurogenesis in the senescent dentate gyrus. J Neurosci, 18(9), 3206-3212.

Kempton, M. J., Salvador, Z., Munafo, M. R., Geddes, J. R., Simmons, A., Frangou, S., & Williams, S. C. (2011). Structural neuroimaging studies in major depressive disorder. Meta-analysis and comparison with bipolar disorder. Arch Gen Psychiatry, 68(7), 675-690. doi: 10.1001/archgenpsychiatry.2011.60

Kennedy, K. M., & Raz, N. (2009). Aging white matter and cognition: differential effects of regional variations in diffusion properties on memory, executive functions, and speed. Neuropsychologia, 47(3), 916-927. doi: 10.1016/j.neuropsychologia.2009.01.001

Kheirbek, M. A., & Hen, R. (2011). Dorsal vs ventral hippocampal neurogenesis: implications for cognition and mood. Neuropsychopharmacology, 36(1), 373-374. doi: 10.1038/npp.2010.148

Koenig, A. M., DeLozier, I. J., Zmuda, M. D., Marron, M. M., Begley, A. E., Anderson, S. J., . . . Butters, M. A. (2015). Neuropsychological functioning in the acute and remitted States of late-life depression. J Alzheimers Dis, 45(1), 175-185. doi: 10.3233/JAD-148006

Koolschijn, P. C., van Haren, N. E., Lensvelt-Mulders, G. J., Hulshoff Pol, H. E., & Kahn, R. S. (2009). Brain volume abnormalities in major depressive disorder: a meta-analysis of magnetic resonance imaging studies. Hum Brain Mapp, 30(11), 3719-3735. doi: 10.1002/hbm.20801

Kroenke, K., Spitzer, R. L., Williams, J. B., & Lowe, B. (2010). The Patient Health Questionnaire Somatic, Anxiety, and Depressive Symptom Scales: a systematic review. Gen Hosp Psychiatry, 32(4), 345-359. doi: 10.1016/j.genhosppsych.2010.03.006

Krogh, J., Hjorthoj, C., Speyer, H., Gluud, C., & Nordentoft, M. (2017). Exercise for patients with major depression: a systematic review with meta-analysis and trial sequential analysis. BMJ Open, 7(9), e014820. doi: 10.1136/bmjopen-2016-014820

Krogh, J., Rostrup, E., Thomsen, C., Elfving, B., Videbech, P., & Nordentoft, M. (2014). The effect of exercise on hippocampal volume and neurotrophines in patients with major depression--a randomized clinical trial. J Affect Disord, 165, 24-30. doi: 10.1016/j.jad.2014.04.041

Kubesch, S., Bretschneider, V., Freudenmann, R., Weidenhammer, N., Lehmann, M., Spitzer, M., & Gron, G. (2003). Aerobic endurance exercise improves executive functions in depressed patients. J Clin Psychiatry, 64(9), 1005-1012.

Kvam, S., Kleppe, C. L., Nordhus, I. H., & Hovland, A. (2016). Exercise as a treatment for depression: A meta-analysis. J Affect Disord, 202, 67-86. doi: 10.1016/j.jad.2016.03.063

Lai, C. H. (2013). Gray matter volume in major depressive disorder: a meta-analysis of voxel-based morphometry studies. Psychiatry Res, 211(1), 37-46. doi: 10.1016/j.pscychresns.2012.06.006

Lam, L. C. W., Chau, R. C. M., Wong, B. M. L., Fung, A. W. T., Tam, C. W. C., Leung, G. T. Y., . . . Chan, W. M. (2012). A 1-Year Randomized Controlled Trial Comparing Mind Body Exercise (Tai Chi) With Stretching and Toning Exercise on Cognitive Function in Older Chinese Adults at Risk of Cognitive Decline. Journal of the American Medical Directors Association, 13(6). doi: Artn 568.E15

10.1016/J.Jamda.2012.03.008

Lee, R. S., Hermens, D. F., Porter, M. A., & Redoblado-Hodge, M. A. (2012). A meta-analysis of cognitive deficits in first-episode Major Depressive Disorder. J Affect Disord, 140(2), 113-124. doi: 10.1016/j.jad.2011.10.023

Li, M. Y., Huang, M. M., Li, S. Z., Tao, J., Zheng, G. H., & Chen, L. D. (2017). The effects of aerobic exercise on the structure and function of DMN-related brain regions: a systematic review. Int J Neurosci, 127(7), 634-649. doi: 10.1080/00207454.2016.1212855

MacRae, P. G., Asplund, L. A., Schnelle, J. F., Ouslander, J. G., Abrahamse, A., & Morris, C. (1996). A walking program for nursing home residents: effects on walk endurance, physical activity, mobility, and quality of life. Journal of the American Geriatrics Society, 44(2), 175-180.

Maier, W., Philipp, M., Heuser, I., Schlegel, S., Buller, R., & Wetzel, H. (1988). Improving depression severity assessment--I. Reliability, internal validity and sensitivity to change of three observer depression scales. J Psychiatr Res, 22(1), 3-12.

Malchow, B., Reich-Erkelenz, D., Oertel-Knochel, V., Keller, K., Hasan, A., Schmitt, A., . . . Falkai, P. (2013). The effects of physical exercise in schizophrenia and affective disorders. Eur Arch Psychiatry Clin Neurosci, 263(6), 451-467. doi: 10.1007/s00406-013-0423-2

McKinnon, M. C., Yucel, K., Nazarov, A., & MacQueen, G. M. (2009). A meta-analysis examining clinical predictors of hippocampal volume in patients with major depressive disorder. J Psychiatry Neurosci, 34(1), 41-54.

Montgomery, SA, & Asberg, M. (1979). A new depression scale designed to be sensitive to change. British Journal of Psychiatry, 134, 382-389.

Nebes, R. D., Butters, M. A., Mulsant, B. H., Pollock, B. G., Zmuda, M. D., Houck, P. R., & Reynolds, C. F., 3rd. (2000). Decreased working memory and processing speed mediate cognitive impairment in geriatric depression. Psychol Med, 30(3), 679-691.

Nezu, A. M., & Perri, M. G. (1989). Social problem-solving therapy for unipolar depression: an initial dismantling investigation. J Consult Clin Psychol, 57(3), 408-413.

Oertel-Knochel, V., Mehler, P., Thiel, C., Steinbrecher, K., Malchow, B., Tesky, V., . . . Hansel, F. (2014). Effects of aerobic exercise on cognitive performance and individual psychopathology in depressive and schizophrenia patients. European Archives of Psychiatry and Clinical Neuroscience, 264(7), 589-604. doi: 10.1007/s00406-014-0485-9

Phillips, C. L. (2017). Physical ActivityModulatesCommon Neuroplasticity Substrates in

Major Depressive and Bipolar Disorder. Neural Plast, 2017.

Pizzagalli, D. A. (2011). Frontocingulate dysfunction in depression: toward biomarkers of treatment response. Neuropsychopharmacology

36, 183-206.

Prehn, K., Lesemann, A., Krey, G., Witte, A. V., Kobe, T., Grittner, U., & Floel, A. (2017). Using resting-state fMRI to assess the effect of aerobic exercise on functional connectivity of the DLPFC in older overweight adults. Brain Cogn. doi: 10.1016/j.bandc.2017.08.006

Randolph, C., Tierney, M. C., Mohr, E., & Chase, T. N. (1998). The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): preliminary clinical validity. J Clin Exp Neuropsychol, 20(3), 310-319. doi: 10.1076/jcen.20.3.310.823

Rebar, A. L., Stanton, R., Geard, D., Short, C., Duncan, M. J., & Vandelanotte, C. (2015). A meta-meta-analysis of the effect of physical activity on depression and anxiety in non-clinical adult populations. Health Psychol Rev, 9(3), 366-378. doi: 10.1080/17437199.2015.1022901

Rethorst, C. D., Wipfli, B. M., & Landers, D. M. (2009). The antidepressive effects of exercise: a meta-analysis of randomized trials. Sports Med, 39(6), 491-511. doi: 10.2165/00007256-200939060-00004

Richard, E., Reitz, C., Honig, L. H., Schupf, N., Tang, M. X., Manly, J. J., . . . Luchsinger, J. A. (2013). Late-life depression, mild cognitive impairment, and dementia. JAMA Neurol, 70(3), 374-382. doi: 10.1001/jamaneurol.2013.603

Rock, P. L., Roiser, J. P., Riedel, W. J., & Blackwell, A. D. (2014). Cognitive impairment in depression: a systematic review and meta-analysis. Psychol Med, 44(10), 2029-2040. doi: 10.1017/S0033291713002535

Roig, M., Nordbrandt, S., Geertsen, S. S., & Nielsen, J. B. (2013). The effects of cardiovascular exercise on human memory: a review with meta-analysis. Neurosci Biobehav Rev, 37(8), 1645-1666. doi: 10.1016/j.neubiorev.2013.06.012

Rolland, Y., Pillard, F., Klapouszczak, A., Reynish, E., Thomas, D., Andrieu, S., . . . Vellas, B. (2007). Exercise program for nursing home residents with Alzheimer's disease: a 1-year randomized, controlled trial. J Am Geriatr Soc, 55(2), 158-165. doi: 10.1111/j.1532-5415.2007.01035.x

Rosenblat, J. D., Kakar, R., & McIntyre, R. S. (2016). The Cognitive Effects of Antidepressants in Major Depressive Disorder: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. Int J Neuropsychopharmacol, 19(2). doi: 10.1093/ijnp/pyv082

Russo-Neustadt, A. A., Beard, R. C., Huang, Y. M., & Cotman, C. W. (2000). Physical activity and antidepressant treatment potentiate the expression of specific brain-derived neurotrophic factor transcripts in the rat hippocampus. Neuroscience, 101(2), 305-312.

Sacher, J., Neumann, J., Funfstuck, T., Soliman, A., Villringer, A., & Schroeter, M. L. (2012). Mapping the depressed brain: a meta-analysis of structural and functional alterations in major depressive disorder. J Affect Disord, 140(2), 142-148. doi: 10.1016/j.jad.2011.08.001

Schmaal, L., Veltman, D. J., van Erp, T. G., Samann, P. G., Frodl, T., Jahanshad, N., . . . Hibar, D. P. (2015). Subcortical brain alterations in major depressive disorder: findings from the ENIGMA Major Depressive Disorder working group. Mol Psychiatry. doi: 10.1038/mp.2015.69

Schuch, F. B., Vancampfort, D., Richards, J., Rosenbaum, S., Ward, P. B., & Stubbs, B. (2016). Exercise as a treatment for depression: A meta-analysis adjusting for publication bias. J Psychiatr Res, 77, 42-51. doi: 10.1016/j.jpsychires.2016.02.023

Schuch, F. B., Vancampfort, D., Rosenbaum, S., Richards, J., Ward, P. B., Veronese, N., . . . Stubbs, B. (2016). Exercise for depression in older adults: a meta-analysis of randomized controlled trials adjusting for publication bias. Rev Bras Psiquiatr, 38(3), 247-254. doi: 10.1590/1516-4446-2016-1915

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., . . . Dunbar, G. C. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry, 59 Suppl 20, 22-33;quiz 34-57.

Sheline, Y. I., Barch, D. M., Garcia, K., Gersing, K., Pieper, C., Welsh-Bohmer, K., . . . Doraiswamy, P. M. (2006). Cognitive function in late life depression: relationships to depression severity, cerebrovascular risk factors and processing speed. Biol Psychiatry, 60(1), 58-65. doi: 10.1016/j.biopsych.2005.09.019

Silveira, H., Moraes, H., Oliveira, N., Coutinho, E. S., Laks, J., & Deslandes, A. (2013). Physical exercise and clinically depressed patients: a systematic review and meta-analysis. Neuropsychobiology, 67(2), 61-68. doi: 10.1159/000345160

Singh, M. K., & Gotlib, I. H. (2014). The neuroscience of depression: implications for assessment and intervention. Behav Res Ther, 62, 60-73. doi: 10.1016/j.brat.2014.08.008

Smith, J. C., Nielson, K. A., Woodard, J. L., Seidenberg, M., & Rao, S. M. (2013). Physical activity and brain function in older adults at increased risk for Alzheimer's disease. Brain Sci, 3(1), 54-83. doi: 10.3390/brainsci3010054

Smith, P. J., Blumenthal, J. A., Hoffman, B. M., Cooper, H., Strauman, T. A., Welsh-Bohmer, K., . . . Sherwood, A. (2010). Aerobic exercise and neurocognitive performance: a meta-analytic review of randomized controlled trials. Psychosom Med, 72(3), 239-252. doi: 10.1097/PSY.0b013e3181d14633

Smith, Patrick J, Blumenthal, James A, Hoffman, Benson M, Cooper, Harris, Strauman, Timothy A, Welsh-Bohmer, Kathleen, . . . Sherwood, Andrew. (2010). Aerobic exercise and neurocognitive performance: a meta-analytic review of randomized controlled trials. Psychosomatic medicine, 72(3), 239.

Smith, R., Chen, K. W., Baxter, L., Fort, C., & Lane, R. D. (2013). Antidepressant effects of sertraline associated with volume increases in dorsolateral prefrontal cortex. Journal of Affective Disorders, 146(3), 414-419. doi: 10.1016/j.jad.2012.07.029

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E., Johansen-Berg, H., . . . Matthews, P. M. (2004). Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage, 23 Suppl 1, S208-219. doi: 10.1016/j.neuroimage.2004.07.051

Smith, S. M., & Nichols, T. E. (2009). Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. Neuroimage, 44(1), 83-98. doi: 10.1016/j.neuroimage.2008.03.061

Spitzer, R. L., Williams, J. B., Kroenke, K., Linzer, M., deGruy, F. V., 3rd, Hahn, S. R., . . . Johnson, J. G. (1994). Utility of a new procedure for diagnosing mental disorders in primary care. The PRIME-MD 1000 study. JAMA, 272(22), 1749-1756.

Stillman, C. M., Cohen, J., Lehman, M. E., & Erickson, K. I. (2016). Mediators of Physical Activity on Neurocognitive Function: A Review at Multiple Levels of Analysis. Front Hum Neurosci, 10, 626. doi: 10.3389/fnhum.2016.00626

Stubbs, B., Vancampfort, D., Rosenbaum, S., Ward, P. B., Richards, J., Soundy, A., . . . Schuch, F. (2015). Dropout from exercise: randomized controlled trials among people with depression: A meta-analysis and meta regression. Journal of Affective Disorders, 190, 457-466.

Sun, M., Lanctot, K., Herrmann, N., & Gallagher, D. (2018). Exercise for Cognitive Symptoms in Depression: A Systematic Review of Interventional Studies. Can J Psychiatry, 63(2), 115-128. doi: 10.1177/0706743717738493

Tahmasian, M., Knight, D. C., Manoliu, A., Schwerthoffer, D., Scherr, M., Meng, C., . . . Sorg, C. (2013). Aberrant intrinsic connectivity of hippocampus and amygdala overlap in the fronto-insular and dorsomedial-prefrontal cortex in major depressive disorder. Front Hum Neurosci, 7, 639. doi: 10.3389/fnhum.2013.00639

Talukdar, T., Nikolaidis, A., Zwilling, C. E., Paul, E. J., Hillman, C. H., Cohen, N. J., . . . Barbey, A. K. (2017). Aerobic Fitness Explains Individual Differences in the Functional Brain Connectome of Healthy Young Adults. Cereb Cortex, 1-10. doi: 10.1093/cercor/bhx232

Teng, E. L., & Chui, H. C. (1987). The Modified Mini-Mental State (3MS) examination. J Clin Psychiatry, 48(8), 314-318.

Teri, L., Gibbons, L. E., McCurry, S. M., Logsdon, R. G., Buchner, D. M., Barlow, W. E., . . . Larson, E. B. (2003). Exercise plus behavioral management in patients with Alzheimer disease - A randomized controlled trial. Jama-Journal of the American Medical Association, 290(15), 2015-2022. doi: Doi 10.1001/Jama.290.15.2015

Thomas, S., Reading, J., & Shephard, R. J. (1992). Revision of the Physical-Activity Readiness Questionnaire (Par-Q). Canadian Journal of Sport Sciences-Revue Canadienne Des Sciences Du Sport, 17(4), 338-345.

Trivedi, M. H., & Greer, T. L. (2014). Cognitive dysfunction in unipolar depression: implications for treatment. J Affect Disord, 152-154, 19-27. doi: 10.1016/j.jad.2013.09.012

Vasques, P. E., Moraes, H., Silveira, H., Deslandes, A. C., & Laks, J. (2011). Acute exercise improves cognition in the depressed elderly: the effect of dual-tasks. Clinics (Sao Paulo), 66(9), 1553-1557.

Voelcker-Rehage, C., & Niemann, C. (2013a). Structural and functional brain changes related to different types of physical activity across the life span. Neuroscience and Biobehavioral Reviews, 37(9), 2268-2295. doi: 10.1016/j.neubiorev.2013.01.028

Voelcker-Rehage, C., & Niemann, C. (2013b). Structural and functional brain changes related to different types of physical activity across the life span. Neurosci Biobehav Rev, 37(9 Pt B), 2268-2295. doi: 10.1016/j.neubiorev.2013.01.028

Voss, M. W., Chaddock, L., Kim, J. S., Vanpatter, M., Pontifex, M. B., Raine, L. B., . . . Kramer, A. F. (2011). Aerobic fitness is associated with greater efficiency of the network underlying cognitive control in preadolescent children. Neuroscience, 199, 166-176. doi: 10.1016/j.neuroscience.2011.10.009

Voss, M. W., Erickson, K. I., Prakash, R. S., Chaddock, L., Malkowski, E., Alves, H., . . . Kramer, A. F. (2010). Functional connectivity: a source of variance in the association between cardiorespiratory fitness and cognition? Neuropsychologia, 48(5), 1394-1406. doi: 10.1016/j.neuropsychologia.2010.01.005

Voss, M. W., Prakash, R. S., Erickson, K. I., Basak, C., Chaddock, L., Kim, J. S., . . . Kramer, A. F. (2010). Plasticity of brain networks in a randomized intervention trial of exercise training in older adults. Front Aging Neurosci, 2. doi: 10.3389/fnagi.2010.00032

Voss, M. W., Vivar, C., Kramer, A. F., & van Praag, H. (2013). Bridging animal and human models of exercise-induced brain plasticity. Trends Cogn Sci, 17(10), 525-544. doi: 10.1016/j.tics.2013.08.001

Voss, Michelle W, Erickson, Kirk I, Prakash, Ruchika Shaurya, Chaddock, Laura, Kim, Jennifer S, Alves, Heloisa, . . . Mailey, Emily L. (2013). Neurobiological markers of exercise-related brain plasticity in older adults. Brain, behavior, and immunity, 28, 90-99.

Vu, N. Q., & Aizenstein, H. J. (2013). Depression in the elderly: brain correlates, neuropsychological findings, and role of vascular lesion load. Curr Opin Neurol, 26(6), 656-661. doi: 10.1097/WCO.0000000000000028

Wagner, G., Koch, K., Schachtzabel, C., Peikert, G., Schultz, C. C., Reichenbach, J. R., . . . Schlosser, R. G. (2013). Self-referential processing influences functional activation during cognitive control: an fMRI study. Soc Cogn Affect Neurosci, 8(7), 828-837. doi: 10.1093/scan/nss074

Wagner, S., Doering, B., Helmreich, I., Lieb, K., & Tadic, A. (2012). A meta-analysis of executive dysfunctions in unipolar major depressive disorder without psychotic symptoms and their changes during antidepressant treatment. Acta Psychiatrica Scandinavica, 125(4), 281-292. doi: 10.1111/j.1600-0447.2011.01762.x

Wagner, S., Helmreich, I., Lieb, K., & Tadic, A. (2012). A Meta-Analysis of Executive Dysfunctions in Unipolar Major Depressive Disorder (Mdd) without Psychotic Symptoms and Their Changes during Antidepressant Treatment. European Psychiatry, 27.

WHO. (2012). World Suicide Prevention Day.

Williams, C. L., & Tappen, R. M. (2008). Exercise training for depressed older adults with Alzheimer's disease. Aging Ment Health, 12(1), 72-80. doi: 10.1080/13607860701529932

Williams, L. M. (2016). Precision psychiatry: a neural circuit taxonomy for depression and anxiety. Lancet Psychiatry, 3(5), 472-480. doi: 10.1016/S2215-0366(15)00579-9

Zhang, Y., Brady, M., & Smith, S. (2001). Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. IEEE Trans Med Imaging, 20(1), 45-57. doi: 10.1109/42.906424

Zhao, Y. J., Du, M. Y., Huang, X. Q., Lui, S., Chen, Z. Q., Liu, J., . . . Gong, Q. Y. (2014). Brain grey matter abnormalities in medication-free patients with major depressive disorder: a meta-analysis. Psychol Med, 44(14), 2927-2937. doi: 10.1017/S0033291714000518

Zheng, G., Xia, R., Zhou, W., Tao, J., & Chen, L. (2016). Aerobic exercise ameliorates cognitive function in older adults with mild cognitive impairment: a systematic review and meta-analysis of randomised controlled trials. Br J Sports Med. doi: 10.1136/bjsports-2015-095699