

NEURAL PREDICTORS OF EXERCISE ADHERENCE IN OLDER ADULTS

by

Swathi Gujral

Bachelor of Science in Psychology, Indiana University, 2009

Submitted to the Graduate Faculty of

The Dietrich School of Arts and Sciences in partial fulfillment

of the requirements for the degree of

Master of Science

University of Pittsburgh

2015

UNIVERSITY OF PITTSBURGH
Dietrich School of Arts and Sciences

This thesis was presented

by

Swathi Gujral

It was defended on

December 9th, 2014

and approved by

Committee Member: Peter Gianoros, Professor, Department of Psychology

Committee Member: Anna Marsland, Associate Professor, Department of Psychology

Thesis Advisor: Kirk Erickson, Associate Professor, Department of Psychology

Copyright © by Swathi Gujral

2015

NEURAL PREDICTORS OF EXERCISE ADHERENCE IN OLDER ADULTS

Swathi Gujral, M.S.

University of Pittsburgh, 2015

Exercise is an important factor in maintaining physical and cognitive health throughout the lifespan. However, adherence to exercise regimens is poor with approximately 50% of older adults dropping out within 6 months, which makes it difficult to observe exercise-induced biological changes. Unfortunately, there are few known predictors for exercise adherence, but it is likely that a combination of social-cognitive factors, including self-efficacy, social support, personality traits, executive functions, and self-regulation all relate to exercise adherence. Importantly, all of these factors may rely upon the structural integrity of brain networks. In this study we tested whether grey matter volume prior to the initiation of an exercise intervention would predict adherence to the intervention. Participants included 159 adults aged 60-80 that were randomly assigned to either a moderate-intensity aerobic walking condition or a non-aerobic stretching and toning condition. Participants engaged in supervised exercise 3 times per week for 12 months. Structural magnetic resonance images were collected on individuals before randomization and used for analysis. An optimized voxel based morphometry (VBM) protocol was used to analyze gray matter volume using FSL. We used ordinary least squares regression models with bootstrapping using the Bootstrap Regression Analysis of Voxelwise Observations (BRAVO) toolbox to test the association between voxel-based grey matter volume and exercise adherence. We found a broad array of regions that significantly predicted exercise adherence

($p < .01$), including medial prefrontal cortex, superior parietal cortex, inferior temporal cortex, and cerebellum. Greater volume in these regions explained 20% of variance in adherence, above and beyond variance explained by self-efficacy. Our results suggest that greater gray matter volume predicts more successful adherence to a 12-month supervised exercise regimen.

TABLE OF CONTENTS

SPECIFIC AIMS	X
1.0 INTRODUCTION.....	1
1.1 BENEFITS OF PHYSICAL ACTIVITY	1
1.2 SOCIAL COGNITIVE PREDICTORS OF EXERCISE ADHERENCE.....	3
1.3 NEURAL EVIDENCE FOR SOCIAL COGNITIVE FACTORS PREDICTING EXERCISE ADHERENCE.....	5
1.3.1 The Social Cognitive Brain	5
1.3.2 Neural Substrates of Self-Efficacy and Meta-Cognition	7
1.3.3 Neural Substrates of Self-Regulation and Executive Function	8
1.3.4 Neural Substrates of Motivation.....	9
1.4 SUMMARY	10
2.0 METHODS	11
2.1 PARTICIPANTS	11
2.2 MEASURES	12
2.3 PROCEDURES.....	14
2.4 STATISTICAL ANALYSIS	15
2.4.1 MRI Data Analysis.....	15
2.4.2 Self-Efficacy Composite Score	17

2.4.3	Bootstrap Regression Models.....	17
2.4.4	Estimates of Effect Size	19
2.4.5	Dysjunction Analysis	19
2.4.6	Estimates of Percent Gray Matter Volume Predicting Adherence	20
3.0	RESULTS	21
3.1	SELF-EFFICACY PREDICTS EXERCISE ADHERENCE	21
3.2	GRAY MATTER VOLUME PREDICTS EXERCISE ADHERENCE.....	23
3.3	GRAY MATTER VOLUME PREDICTS EXERCISE ADHERENCE INDEPENDENT OF SELF-EFFICACY	23
3.4	GRAY MATTER VOLUME IS ASSOCIATED WITH SELF-EFFICACY: EXPLORATORY ANALYSIS.....	28
4.0	DISCUSSION	30
	BIBLIOGRAPHY.....	37

LIST OF TABLES

Table 1. Participant Characteristics	22
Table 2. Correlations between Self-Efficacy and Exercise Adherence	22
Table 3. Brain Regions predicting Exercise Adherence after controlling for Self-Efficacy	27
Table 4. Percent Gray Matter Voxels associated with Exercise Adherence.....	28

LIST OF FIGURES

Figure 1. Regression models testing gray matter volume association with adherence to the intervention	18
Figure 2. Cortical Grey Matter regions predicting Exercise Adherence	25
Figure 3. Dysjunction of regions predicting adherence with and without controlling for self-efficacy.....	26
Figure 4. Subcortical grey matter regions predicting exercise adherence	26
Figure 5. 3D view of grey matter regions associated with exercise adherence after controlling for self-efficacy.....	27
Figure 6. Cortical Grey Matter regions associated with Self-Efficacy	29
Figure 7. Subcortical Grey Matter regions associated with Self-Efficacy.....	29

SPECIFIC AIMS

Cognitive function and physical health progressively decline with age, but participation in physical activity promotes both physical and cognitive health in older adults (Colcombe & Kramer, 2003; Fagard, 2001). Yet, despite the known benefits of physical activity, older adults remain highly sedentary (Evenson, Buchner, & Morland, 2012). In exercise trials targeting older adults, approximately 50% drop out of structured exercise regimens within 6 months, making it difficult to observe exercise-induced biological changes (Conn, Minor, Burks, Rantz, & Pomeroy, 2003). This also limits the generalizability of outcomes from these exercise trials. Poor exercise adherence results in biased intervention samples, which in turn, distort findings regarding the protective effects of exercise on biological aging. Thus, understanding predictors of exercise adherence is the first step towards promoting exercise adherence in this physically and cognitively vulnerable population.

Research on exercise adherence has focused on contextual and psychological factors, with little emphasis on neurobiological factors. Social-cognitive theory is the most widely used framework for studying psychological motivations for exercise adherence, and proposes self-efficacy, social support, executive functions, and self-regulation as predictors of health behaviors (Young, Plotnikoff, Collins, Callister, & Morgan, 2014). Emerging evidence from structural equation modeling of longitudinal data suggests self-efficacy may be the central component by which other social cognitive factors relate to exercise adherence (Brassington, Atienza, Perczek,

DiLorenzo, & King, 2002; McAuley, Mailey, et al., 2011). Self-efficacy refers to one's beliefs about his or her capability to successfully perform a specified task and one's expectations regarding the outcome of the behavior (Bandura, 1997). Indices of exercise self-efficacy have been shown to be a consistent predictor of adherence to an exercise regimen (McAuley & Blissmer, 2000; McAuley et al., 2007). However, many studies *only* examine self-efficacy, ignoring contributions of other social-cognitive predictors (Anderson-Bill, Winett, Wojcik, & Williams, 2011; Resnick, Palmer, Jenkins, & Spellbring, 2000). In fact, self-efficacy explained only ~13% of variance in exercise adherence in older adults during a 1-year monitored exercise trial, thereby leaving a significant amount of unexplained variance (McAuley, Mailey, et al., 2011). Social-cognitive theory posits that several other social-cognitive processes are also important in exercise adherence (Ayotte, Margrett, & Hicks-Patrick, 2010; Young et al., 2014). Specifically, executive control and self-regulatory processes, (i.e., planning and goal-setting) are related to exercise adherence in older adults independent of self-efficacy (Hall, Fong, Epp, & Elias, 2008). In sum, exercise adherence in older adults remains poorly understood with a myriad of social-cognitive predictors all showing small to moderate relationships with adherence.

Social-cognitive factors predicting exercise, namely self-efficacy, self-regulatory strategies, and executive functions, all rely upon structural integrity of prefrontal and cingulate regions as assessed by volumetric methods (Amodio & Frith, 2006; Braver et al., 2014; Fleming, Weil, Nagy, Dolan, & Rees, 2010). Executive control and self-regulatory processes are supported by prefrontal circuitry (Heatherton & Wagner, 2011) and introspective awareness, and motivation have also been linked to prefrontal and cingulate regions (Amodio & Frith, 2006; Braver et al., 2014; Fleming, Huijgen, & Dolan, 2012). At least one study has also found that

greater whole-brain gray matter volume was related to higher falls self-efficacy scores in older women participating in an exercise trial (Davis, Marra, & Liu-Ambrose, 2011). Thus, the *objective* measurement of structural integrity of prefrontal and cingulate regions using volumetric methods may relate to exercise adherence in ways that cannot be captured by the broadly used *subjective* measures of self-efficacy in predicting exercise adherence.

Here I use structural MRI (sMRI) to examine whether gray matter volume in prefrontal and cingulate regions predicts adherence to a 1 year structured exercise regimen, and the extent to which gray matter volume in these regions is related to adherence independently of self-efficacy measures. To examine this, I used data from the Healthy Active Lifestyle Trial (HALT), a 1-year exercise intervention conducted at the University of Illinois, which randomized 159 adults aged 60 years and older to either a walking group or a stretching and toning group 3 times per week for 12 months. Data for the current study include structural MRI data, self-efficacy measures, and adherence for all participants in the trial. There are three primary aims and hypotheses:

Specific Aim 1: Examine whether the volume of the dorsal PFC and ventromedial PFC, as well as cingulate cortex, prior to the initiation of the intervention, predicts adherence.

Hypothesis: Greater gray matter volume in the prefrontal and cingulate regions will be associated with better adherence to the exercise regimen over the last 11 months of the intervention. Previous research has shown that reports of exercise self-efficacy prior to an intervention are typically overinflated therefore assessment of exercise self-efficacy shortly after the start of an intervention is thought to reflect a true ‘baseline’ level of exercise self-efficacy (McAuley, Mullen, et al., 2011).

Specific Aim 2: Examine whether PFC and cingulate cortex volume predict exercise adherence independent of self-efficacy.

Hypothesis: Volume in prefrontal and cingulate regions will predict exercise adherence even after using self-efficacy as a covariate.

Exploratory Aim 3: Examine whether gray matter volume in prefrontal and cingulate regions is associated with self-efficacy.

Hypothesis: Gray matter volume in the PFC and cingulate prior to the exercise intervention will be positively associated with exercise self-efficacy assessed 3-weeks after the start of the exercise intervention.

1.0 INTRODUCTION

Older adults comprise the most rapidly growing segment of the population, likely due to aging of the baby boomer generation and medical advances improving longevity. There was a 16% increase in the number of adults aged 65 and older in the United States from 2000-2010, and there is expected to be a 36% increase in the older adult population over the next decade (Aging, 2010). Despite great medical advances in the last century to help older adults maintain their health, aging is still associated with an increased risk for a number of chronic illnesses, including cardiovascular disease, diabetes, obesity, and cancer, depression, and dementia.

1.1 BENEFITS OF PHYSICAL ACTIVITY

Physical activity has beneficial effects on cardiovascular, immune, and neural functioning and helps in the prevention and management of many chronic medical conditions that commonly burden older adults (Vogel et al., 2009) ranging from cardiovascular disease and cancer, to depression and dementia. Awareness of the health benefits and importance of physical activity prompted the US federal government to set physical activity guidelines for all age groups (Services, 2008). Meta-analyses of physical activity interventions have shown that physical activity is beneficial for many cardiometabolic risk factors, including elevated blood pressure (Fagard, 2001), insulin resistance and glucose intolerance (Thompson et al., 2001; Umpierre et

al., 2011), elevated triglyceride concentrations, low high-density lipoprotein cholesterol (HDL-C) concentrations (Leon et al., 2000; Leon & Sanchez, 2001), and obesity (Villareal et al., 2006; Wing & Hill, 2001), as well as for certain types of cancer, including breast and prostate cancer (Vogel et al., 2009). A recent Cochrane review of 47 exercise trials also showed that exercise reduces risk for cardiac mortality and hospital admissions in those already having cardiovascular disease (Heran et al., 2011), and these benefits hold true for both younger and older adults (Menezes, Lavie, Milani, Arena, & Church, 2012). In addition to improving physical health, physical activity interventions have been consistently effective in improving mood (Bridle, Spanjers, Patel, Atherton, & Lamb, 2012; Conn, 2010) and cognitive and executive function in healthy older adults (Colcombe & Kramer, 2003; Erickson et al., 2011; Kramer et al., 1999) and those with cognitive impairment (Heyn, Abreu, & Ottenbacher, 2004; Lautenschlager et al., 2008). Although older adults are likely to benefit most from physical activity, as they have the greatest risk for the developing several chronic illnesses, older adults still appear to be more sedentary than all other segments of the US population (Evenson et al., 2012).

Several reviews of exercise interventions in older adults have shown that the elderly pose unique challenges for exercise interventions, such as having more physical and cognitive health burdens than younger adults, and lacking knowledge and having contrary beliefs about the benefits of exercise for aging populations (Baert, Gorus, Mets, Geerts, & Bautmans, 2011; Chao, Foy, & Farmer, 2000; Hui & Rubenstein, 2006; Schutzer & Graves, 2004). Interventions to promote physical activity among older adults have largely been ineffective in the long-term (Conn et al., 2003), and around 50% of older adults drop out of interventions within 6 months, prior to achieving any significant health-related goals (Dishman, 1994). Some reviews have also focused on environmental barriers for exercise among older adults, showing that older adults

who do not have access to recreational facilities and those who do not feel safe in their neighborhood report these as barriers to exercise (Baert et al., 2011; Schutzer & Graves, 2004).

1.2 SOCIAL COGNITIVE PREDICTORS OF EXERCISE ADHERENCE

Despite these barriers, there are individual differences in exercise adherence among older adults, and the social-cognitive theoretical framework is the most widely used model to explain these individual differences in exercise behavior (Brassington et al., 2002; Martin, Bowen, Dunbar-Jacob, & Perri, 2000; McAuley, 1993). Self-efficacy is a key concept of social cognitive theory that has consistently been associated with individual differences in exercise adherence (McAuley & Blissmer, 2000; McAuley et al., 2007; Sallis et al., 1986), as well as behavior change in other types of interventions, such as cigarette smoking, weight control, contraception, and alcohol abuse (Bandura, 1997; Luszczynska, Tryburcy, & Schwarzer, 2007). *Self-efficacy refers to one's beliefs about his or her capability to successfully perform a specified task and one's expectations regarding the outcome of the behavior* (Bandura, 1997). Self-efficacy is primarily informed by a history of performance accomplishments or mastery experiences, observation of others' mastery experiences, verbal persuasion, and affective and physiological states (Bandura, 1997). In the physical activity literature, efficacy expectations are theorized to influence adoption of physical activity and persistent effort to pursue physical activity (McAuley & Blissmer, 2000; McAuley, Mailey, et al., 2011). McAuley and colleagues have shown that self-efficacy may have the greatest effect on exercise behavior during times when adherence is most difficult, such as the start of an intervention or after finishing a structured exercise regimen (McAuley, 1992, 1993). Most recently in older adults, McAuley et al. (2011) showed that self-efficacy is a key predictor

of adherence to a 12-month exercise intervention, as well as a mediating pathway through which executive function and self-regulatory strategies predict adherence. In this study, self-efficacy explained ~13% of variance in adherence, a significant amount, but leaving much variance in adherence to be explained.

Other studies using social-cognitive theory to examine predictors of physical activity behavior have found that each social-cognitive construct, including self-efficacy, self-regulatory strategies, social support, and outcome expectations, independently explains unique variance in adherence (Anderson, Wojcik, Winett, & Williams, 2006; Anderson-Bill, Winett, Wojcik, & Williams, 2011; Anderson-Bill, Winett, Wojcik, & Winett, 2011; Park, Elavsky, & Koo, 2014; Resnick, 2001). Resnick et al. (2001) showed in a cross-sectional sample of older adults (N=191) that physical health, self-efficacy, and outcome expectations were directly associated with aerobic exercise behavior, whereas age and mental health were indirectly associated with exercise behavior through self-efficacy and outcome expectations. Anderson-Bill's group has also shown using a large sample (N=999) of participants in a web-health intervention that self-efficacy, self-regulation, and social support are each independently associated with pedometer-measured physical activity (Anderson-Bill, Winett, Wojcik, & Winett, 2011). Within the same sample, they also found that aging is associated with decreased physical activity self-efficacy levels, but increased levels of social support for physical activity and use of self-regulatory strategies to maintain physical activity (Anderson-Bill, Winett, Wojcik, & Williams, 2011). In a recent meta-analysis of 44 studies examining the contribution of social-cognitive models in predicting physical activity, Young et al. (2014) found that social-cognitive constructs collectively explained 31% of variance in physical activity. This meta-analysis also showed that age moderated the effect of social cognitive factors on physical activity, such that higher age was

associated with a stronger relationship between social-cognitive factors and physical activity. Importantly, this meta-analysis indicated that self-efficacy and self-regulatory strategies both showed consistent direct associations with physical activity, whereas social-support largely showed indirect associations, and outcome expectations only predicted physical activity in 20% of the studies. The current state of evidence on social-cognitive predictors of physical activity suggests that the social-cognitive model is a useful framework for understanding psychosocial predictors of exercise adherence.

Within the health-behavior literature, however, minimal attention has been given to understanding neurobiological predictors of exercise adherence. This is an important gap in the literature, given that objective measures of brain morphology may capture variance in exercise adherence collectively explained by social-cognitive factors, as well as tap into implicit influences on adherence (See Custers & Arts (2010) for Review of unconscious influences on goal-pursuit). Recent neuroimaging evidence regarding brain regions implicated in social-cognitive processing, and underlying specific social-cognitive and motivational constructs may help elucidate which brain regions may predict exercise adherence.

1.3 NEURAL EVIDENCE FOR SOCIAL COGNITIVE FACTORS PREDICTING EXERCISE ADHERENCE

1.3.1 The Social Cognitive Brain

The emerging field of Social-Cognitive Neuroscience has strived to identify functional brain networks that are implicated in social-cognitive processes using evidence from task-evoked

functional neuroimaging and resting-state functional connectivity studies. Social cognition in this literature broadly refers to perception and understanding oneself and others, and ways in which we use this knowledge to inform our attitudes and interpersonal behavior (Amodio & Frith, 2006). Functional neuroimaging studies have consistently associated social cognition with a network of regions including the medial PFC, anterior cingulate cortex, the temporal-parietal junction, the superior temporal sulcus, and the temporal poles (See Amodio & Frith, (2006) for Review). Although the specific roles of each of the regions within this network are poorly understood, substantial neuroimaging evidence suggests that the medial PFC is especially important in social-cognitive processing (Amodio & Frith, 2006; Cacioppo & Decety, 2011). Additionally, a recent meta-analysis found that there is significant overlap between regions implicated in the default mode network (DMN) in functional connectivity studies and regions activated in social cognitive tasks in task-evoked fMRI studies, including the mPFC, posterior cingulate, and lateral temporal-parietal regions. While the medial frontal, cingulate, and temporal-parietal regions may broadly support social cognitive processes, the mPFC may have a more important role in processes relevant to understanding oneself (Northoff et al., 2006; Philippi, Duff, Denburg, Tranel, & Rudrauf, 2012), which is relevant to understanding neural bases of self-efficacy. Philippi et al. (2012) showed that the medial PFC is critical to self-referential processing through a human lesion study including participants having focal damage to the medial PFC (See Northoff et al. (2006) for meta-analysis of fMRI studies on self-referential processing).

1.3.2 Neural Substrates of Self-Efficacy and Meta-Cognition

Only one cross-sectional study (N=79) has associated whole brain voxelwise gray matter volume with self-efficacy in older women participating in a physical activity intervention (Davis et al., 2011). Davis et al. (2011) examined self-efficacy using an Activities-Specific-Balance Confidence scale, and found that balance-related self-efficacy is positively related to gray matter volume, after accounting for age, global cognition, functional capacity, physical activity, and systolic blood pressure. This study provided preliminary evidence for an association between grey matter and self-efficacy.

While we have a poor understanding of the brain regions that support self-efficacy, a burgeoning area of cognitive neuroscience has examined neural substrates of a closely related construct, metacognition. Metacognition involves a two-component introspective process, whereby an individual is aware of one's cognitive ability and self-monitors in order to improve performance on a specific behavioral task (Flavell, 1979). Metacognition and self-efficacy both relate confidence in one's capabilities to performance on a specific task, although metacognitive processes have been more researched in the context of cognitive task performance rather than health-behaviors. Metacognitive ability, which refers to the relationship between one's confidence in their cognitive ability and actual accuracy, has been related to gray matter volume in the anterior PFC/frontopolar cortex in two recent studies (Fleming et al., 2010; McCurdy et al., 2013). Both Fleming et al. (2010) and McCurdy et al. (2013) asked individuals to rate their confidence in their response to a perceptual visual task, and then correlated participant confidence with accuracy for each response. They found that the ability to accurately predict one's performance was associated with aPFC volume. Although metacognition is a more global construct and has a more complex relationship with behavior and performance relative to self-

efficacy, both constructs tap into introspective awareness; thus initial evidence for aPFC volume covariation with metacognition supports the plausibility that aPFC volume may also be linked to self-efficacy.

1.3.3 Neural Substrates of Self-Regulation and Executive Function

Self-regulation refers to the processes involved in regulating one's behavior in order to initiate and maintain a goal-behavior (Heatherton & Wagner, 2011). Self-regulation is largely influenced by executive functions, including response inhibition, cognitive flexibility, and planning. Functional neuroimaging evidence on neural substrates of self-regulation largely suggests a top-down pathway from prefrontal regions associated with self-control (i.e. dorsolateral PFC and orbitofrontal cortex) and subcortical regions associated with reward incentives (i.e. striatum) and emotional valence (i.e. amygdala) (See Heatherton & Wagner (2011) for Review). Structural neuroimaging evidence also supports the role of prefrontal regions in executive function, namely ventromedial PFC (vmPFC), ventrolateral PFC (vlPFC), and dorsolateral PFC (dlPFC) (Burzynska et al., 2012; Smolker, Depue, Reineberg, Orr, & Banich, 2014). Burzynska et al. (2012) showed that cortical thickness in lateral prefrontal and parietal regions was correlated with executive performance as measured by the Wisconsin Card Sorting Task, and that that this relationship was stronger for older adults (N=56) relative to younger adults (N=73). Smolker & Depue (2014) showed that gray matter volume and cortical folding within the dlPFC, vlPFC, and vmPFC in younger adults predicted both executive function and specifically set-shifting and updating-performance.

1.3.4 Neural Substrates of Motivation

Although the social-cognitive literature does not explicitly incorporate the construct of motivation, the key social-cognitive constructs of self-efficacy and self-regulation are conceptually embedded within the broader concept of motivation within the neurocognitive literature. Motivation has been described as processes that drive goal-directed behaviors aimed at obtaining a reward or avoiding punishment (Carver, 2006; Pessoa, 2009). Recent studies support the notion that motivational processes influence executive control (Braver et al., 2014; Crocker et al., 2013). Recent methodological approaches have sought to integrate what were previously proposed as distinct neural substrates of motivation and cognition, to more holistically understand the close interconnections between motivational and executive control processes (Braver et al., 2014; Crocker et al., 2013; Pessoa, 2009; Pessoa & Engelmann, 2010). In a recent review of these disparate literatures, Braver et al. (2014) proposes that the lateral PFC, anterior cingulate, and striatum may serve as core regions implicated in the interaction between motivation and executive function. Pessoa & Engelman (2010) also propose that both the fronto-parietal attention network and cortical and subcortical valuation networks (including orbitofrontal cortex, anterior insula, mPFC, posterior cingulate cortex, striatum, nucleus accumbens, and amygdala) likely operate through an integrated process to produce goal-directed behavior. While recent efforts to theorize and test the complex relationships between social, cognitive, and motivational processes reflect only the preliminary stage of understanding goal-directed behavior, this evidence collectively suggests that there are complex neural substrates underlying goal-directed behavior; these neural substrates may also vary based on the type of goal-directed behavior and its respective cognitive demands.

1.4 SUMMARY

Adherence to exercise regimens is low among older adult populations despite its broad benefits to physical and mental health (Chao et al., 2000; Martin et al., 2000; Schutzer & Graves, 2004). In addition to environmental and physical and cognitive health barriers to exercise, a number of psychosocial factors predict exercise adherence. Social-Cognitive Theory offers a useful framework for understanding exercise behavior; within this model self-efficacy has been shown to be the most consistent predictor of adherence (Young et al., 2014). Additionally, a number of other social-cognitive factors have also shown to predict adherence, including self-regulatory strategies, social-support, and outcome expectations. Recent neural evidence from the fields of social neuroscience, cognitive neuroscience, and motivation neuroscience suggest that these social-cognitive predictors of adherence are supported by neural substrates in the medial and lateral prefrontal cortex, cingulate cortex, and possibly temporal-parietal regions. Thus, understanding neural predictors of adherence may capture the collective variance in adherence explained by social-cognitive factors, but also tap into the non-trivial amount of unexplained variance in adherence (~70%) after accounting for social-cognitive factors.

2.0 METHODS

2.1 PARTICIPANTS

One hundred and fifty-nine participants between the ages of 60 and 81 (mean age = 66.6 years; standard deviation = 5.6 years) were recruited to participate in a 1-year randomized exercise intervention examining the effects of aerobic fitness training on brain and cognitive health. Subjects were recruited through community advertisements and physician referrals. Potential subjects were initially screened over the phone for inclusion and exclusion criteria (see below for details). Upon passing the initial phone screening, subjects were invited to a group orientation to receive study details and ask questions regarding the program. Three subsequent baseline sessions were performed after the group orientation. The current study focused on the cross-sectional baseline data from participants that had high-resolution magnetic resonance imaging (MRI) data and completed the self-efficacy questionnaires described below.

Investigations of the full sample and sub-samples of this trial have been described in several studies (e.g. (Erickson et al., 2009; Erickson et al., 2011; Prakash et al., 2011; Voss et al., 2013)).

Inclusion criteria

Individuals were required to be 60+ years of age to participate in the intervention, capable to perform physical exercise, have physician consent to perform physical exercise,

successfully complete the VO_2 max test (described below), and have a sedentary lifestyle at the baseline assessment. A sedentary lifestyle was defined as participating in no more than one 20-minute physical activity per week for the past 6 months, as assessed by the Physical Activity Scale for the Elderly (PASE) (Washburn, Smith, Jette, & Janney, 1993). The sedentary lifestyle requirement for this intervention reduces the potential confound that individuals with more active lifestyles prior to the intervention may have higher adherence rates during the intervention.

Exclusion criteria

Individuals with cognitive impairment as assessed by the modified Mini Mental Status Examination, clinical depression (as measured by the Geriatric Depression Scale (Sheikh, 1986), or poor vision were excluded from the intervention study. Also, participants that did not meet safety criteria for participating in an MRI study were excluded from the intervention. These criteria include no previous history of head trauma, head or neck surgery, diabetes, neuropsychiatric or neurological conditions including brain tumors, or having any ferrous metallic implants that could cause injury due to the magnetic field.

2.2 MEASURES

Demographics. A brief questionnaire assessed basic demographic information including participants' age, gender, and education.

Self-efficacy. Participant's perceptions of their ability to adhere to an exercise regimen, in the face of barriers, and to accumulate physical activity were assessed using the three self-efficacy scales described below. These self-efficacy scales are the most commonly used measures of self-

efficacy in the physical activity literature (McAuley et al., 2007; McAuley, Mullen, et al., 2011). All self-efficacy scales were administered to participants at the end of the third week of the exercise intervention to ensure accurate assessments of efficacy judgments.

Exercise Self-Efficacy Scale: 8-item scale that assesses individuals' belief that they can exercise at moderate intensities three times per week for 40+ minutes at 1-week increments over the next 8-week period. This scale is scored on a 100-point percentage scale comprised of 10-point increments, ranging from 0% (not at all confident) to 100% (highly confident) (McAuley, 1993). A total scale score is derived by summing the responses to each item and dividing by the total number of items in the scale. This measure has been used widely in the social cognitive literature in understanding physical activity and has demonstrated outstanding internal consistency ($\alpha = .99$) (e.g., (Duncan & McAuley, 1993; McAuley, Jerome, Elavsky, Marquez, & Ramsey, 2003).

Barriers Self-Efficacy Scale: 13-item scale used to assess individuals' perceived capabilities to exercise three times per week for 40 minutes over the next two months in the face of commonly identified barriers to participation. This scale is scored on a 100-point percentage scale comprised of 10-point increments, ranging from 0% (not at all confident) to 100% (highly confident). Responses to each item are summed, and divided by the total number of items to achieve an overall efficacy strength score ranging from 0 to 100. This scale has good internal consistency ($\alpha \geq .93$) (McAuley, 1992).

Lifestyle Self-Efficacy Scale: 12-item scale used to assess individuals' confidence in their ability to accumulate 30 min of physical activity on 5 or more days of the week for incremental monthly periods. The scale is scored on a 100-point percentage scale comprised of 10-point increments, 0–100 scale, ranging from 0% (not at all confident) to 100% (highly confident).

Responses to each item are summed, and divided by the total number of items to achieve an overall efficacy strength score ranging from 0 to 100. The internal consistency among items in this scale was good ($\alpha \geq .95$) (McAuley et al., 2009).

Exercise adherence. Adherence reflects the percentage of attendance to exercise classes over the last 11 months of the program. Attendance data were recorded each day by staff, aggregated, and divided by the total possible number of sessions to calculate exercise adherence.

Structural magnetic resonance imaging (MRI). MRI scanning was conducted within one month of the start of the intervention. All participants underwent structural MRI scanning on a 3 Tesla Siemens Allegra scanner. High-resolution (1.3 mm \times 1.3 mm \times 1.3 mm) T1-weighted brain images were acquired using a 3D magnetization-prepared rapid gradient echo imaging protocol with 144 contiguous slices collected in an ascending fashion.

2.3 PROCEDURES

Participants came to the lab for a 2-hour baseline MRI session within one month prior to the start of the intervention trial. Structural MR images were collected during this session. As a part of the intervention, participants came in to the lab 3 times a week for 40-minute sessions to either walk or participate in stretching and toning (control condition). In the walking condition, participants started off by walking for 10 min and increased walking duration by 5-min increments on a weekly basis until a duration of 40 min was achieved at week 7. Participants walked for 40 min per session for the remainder of the program. In the stretching condition, participants engaged in

four muscle-toning exercises using dumbbells or resistance bands, two exercises designed to improve balance, one yoga sequence, and one exercise of their choice. To keep participants interested, a new group of exercises was introduced every 3 weeks. Three weeks after the start of the intervention, participants were asked to complete exercise self-efficacy questionnaires. Participants then continued to participate in the intervention for 11 more months, at which time total adherence was determined for the last 11 months of the intervention. This adherence value was used for all analyses described below.

2.4 STATISTICAL ANALYSIS

2.4.1 MRI Data Analysis

MR data was analyzed to determine the extent to which gray matter volume predicts exercise adherence and the extent to which gray matter volume predicts self-efficacy. MR data was processed using tools in the FMRIB Software Library (Image Analysis Group, FMRIB, Oxford, UK; <http://www.fmrib.ox.ac.uk/fsl/>; (Smith et al., 2004)). An optimized voxel based morphometry (VBM) protocol was used to analyze structural MRI data (FSL-VBM). An advantage of VBM is that it permits a whole-brain volumetric analysis in a semi-automated manner, making it easy to replicate for researchers with different levels of familiarity with neuroanatomy. 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 and 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, we limited our 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. On the other hand, VBM has shown to be a reliable method for analyzing gray matter data from healthy older adults (Colcombe & Kramer, 2003; Good et al., 2001a) and provides estimates that are similar to manual tracing in this population (Kennedy et al., 2009).

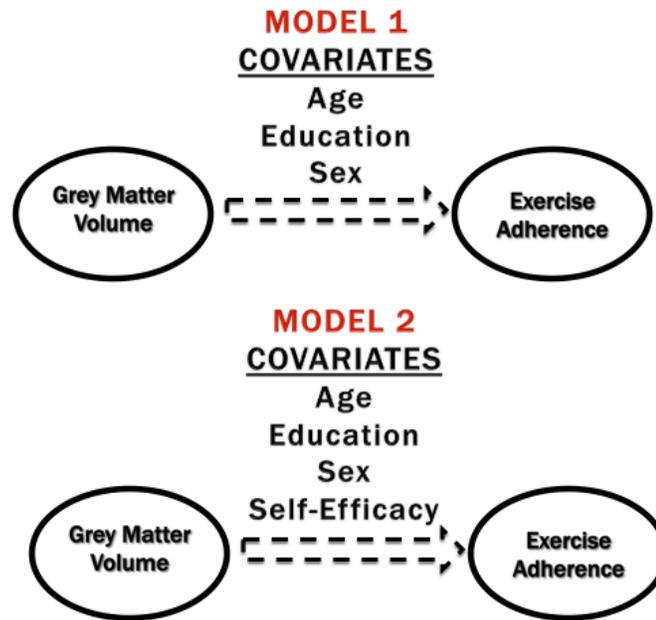
All images were processed using the following steps: (1) non-brain matter was removed using the brain extraction technique in FSL (Smith & Nichols, 2009). (2) All brain-extracted images were visually inspected for any residual non-brain matter, and any residual matter was then manually removed from the image (3) Next, these brain-extracted images were segmented in to gray matter, white matter, and cerebrospinal fluid basis using FSL's automated segmentation technique (Zhang, Brady, & Smith, 2001) (3) Next, the partial volume estimate maps of gray matter were registered to the Montreal Neurological Institute template (Jenkinson & Smith, 2001) and followed by non-linear registration (Andersson, 2007) to a study-specific template created from those 159 participants with both MRI and self-efficacy data. (4) each voxel of each registered gray matter image was modulated by applying the Jacobian determinant from the transformation matrix (Good et al., 2001b). 5) These modulated images were then concatenated into a 4D image, which was then smoothed using a 3 mm Gaussian kernel. Statistical analyses were then conducted on these segmented, registered, modulated, and smoothed gray matter images.

2.4.2 Self-Efficacy Composite Score

A composite self-efficacy score was created by standardizing and then averaging the self-efficacy scores from each of the three self-efficacy scales: exercise self-efficacy, barriers self-efficacy, and lifestyle self-efficacy. This composite score was the final self-efficacy variable included in the ordinary least squares regression models.

2.4.3 Bootstrap Regression Models

After obtaining the final voxel-wise partial volume estimates (PVE) of gray matter, I tested the association between gray matter volume and exercise adherence in older adults using the bootstrap regression tool within the Bootstrap Regression Analysis of Voxelwise Observations (BRAVO) toolbox (Preacher & Hayes, 2008). Documentation and tutorials for this toolbox are available at <https://sites.google.com/site/bravotoolbox>. First, I tested whether voxel-wise values of gray matter volume (PVE) would predict exercise adherence after adjusting for age, gender, and education. Second, I tested whether voxel-wise values of gray matter volume (PVE) would predict exercise adherence after adjusting for self-efficacy, in addition to adjusting for age, gender, and education. These regression models are illustrated below:



Model 1: Exercise Adherence = Bo + B1Demographic factors + B2Gray Matter Volume

Model 2: Exercise Adherence = Bo + B1.1Demographic factors + B3Self-Efficacy + B2.2Gray Matter Volume + e

Figure 1. Regression models testing gray matter volume association with adherence to the intervention

I tested the significance of the association between gray matter volume and exercise adherence with and without controlling for self-efficacy using the bootstrap permutation test approach (Manly, 1997; Preacher & Hayes, 2008). For each regression model, 500 permutation tests were performed per voxel, and in each permutation test, the values in the variable vectors (covariates, gray matter volume, and exercise adherence) were independently scrambled. The significance of the association was determined by comparing the distribution of bootstrapped values with the distribution of the original values using a bias-corrected and accelerated method (DiCiccio & Efron, 1996) at a one-tailed criterion of α of 0.025. Next, clusters of gray matter

voxels were identified showing significant associations with exercise adherence while controlling for multiple comparisons engendered by voxelwise testing using the False-Discovery Rate method (FDR) (Genovese, Lazar, & Nichols, 2002). The FDR approach used the p-value distributions from our bootstrap regression models to calculate a q-value of 0.038. Thus, the significance threshold for all subsequent analyses was set as $p_{\text{FDR}} < 0.038$.

2.4.4 Estimates of Effect Size

Average GM partial volume estimate values from any significant regions from the above analysis were extracted and included in a regression model in SPSS 21.0 in order to estimate the approximate effect size (R^2) of the relationship between gray matter volume and exercise adherence.

2.4.5 Dysjunction Analysis

A disjunction analysis was conducted in order to distinguish which gray matter regions predicted exercise adherence with and without covarying for self-efficacy. Separate masks were created using gray matter regions associated with adherence with and without controlling for self-efficacy. The mask of gray matter regions directly associated with adherence was subtracted from the mask of gray matter regions associated with adherence without controlling for self-efficacy, resulting in a third mask of gray matter regions associated with adherence likely via self-efficacy. This disjunction allowed for a visual comparison of regions predictive of adherence independent of self-efficacy and regions where gray matter associations with adherence may be

explained by self-efficacy (although we cannot statistically confirm mediation with this analytic approach).

2.4.6 Estimates of Percent Gray Matter Volume Predicting Adherence

The total number of gray matter voxels in the brain was estimated using the study-specific gray matter template created by averaging the gray matter maps of all participants (N=159). This allowed for a quantification of % volume related to adherence relative to the total amount of grey matter voxels in the brain, and within each lobe. This also provided a more tangible, concrete way to understand the extent and specificity of the relationship between grey matter volume and adherence within broad brain regions. It additionally afforded a common metric with which to compare the extent of grey matter associations with adherence before and after covarying for self-efficacy. To estimate the total number of grey matter voxels within each broad brain region, the MNI atlas within FSL was used to create separate masks for the frontal, temporal, parietal, and occipital lobes, as well as cerebellum. The percentage of significant voxels predictive of adherence within each brain region was then calculated.

3.0 RESULTS

3.1 SELF-EFFICACY PREDICTS EXERCISE ADHERENCE

Characteristics of the 159 participants are shown in Table 1. As reported in previous studies using this sample (McAuley, Mailey, et al., 2011), exercise self-efficacy ratings on each of the three self-efficacy scales were independently associated with adherence (all p 's < 0.05). See Table 2 for correlations between covariates (age and education), self-efficacy scales, and adherence. The association between self-efficacy and adherence did not vary by gender, and number of years of education attained was not significantly associated with exercise adherence or the self-efficacy scales (all p 's > 0.05). Age was modestly correlated with exercise adherence ($r=0.16$, $p < 0.05$), such that older participants had higher attendance rates during the intervention. After accounting for variance in adherence associated with age, gender, and education in a linear regression model, a composite score of the 3 self-efficacy scales explained 6% of the variance in adherence (Adjusted R^2 Covariates: 0.017 Adjusted R^2 change Self-efficacy= 0.056 Beta= 0.25 $p = 0.002$). The association between self-efficacy and adherence did not differ by intervention group (walking vs. stretching) (Self-efficacy x Group interaction Beta = -0.08 $p = 0.54$).

Table 1. Participant Characteristics

	Mean	Standard Deviation
Age (Years)	66.7	5.7
Years of Education	15.8	2.9
Exercise Self-Efficacy	84.1%	18.2%
Barriers Self-Efficacy	72.7%	19.8%
Lifestyle Self-Efficacy	79.0%	21.5%
Attendance	74.9%	17.4%

Table 2. Correlations between Self-Efficacy and Exercise Adherence

	1	2	3	4	5	6
1. Age	--	-0.09	-0.04	-0.1	0.01	0.16*
2. Years of Education		--	-0.08	-0.09	-0.07	-0.09
3. Exercise Self-efficacy			--	0.45**	0.59**	0.22**
4. Barriers Self-Efficacy				--	0.46**	0.22**
5. Lifestyle Self-Efficacy					--	0.17*
6. Attendance						--

* $p < 0.05$ ** $p < 0.01$

3.2 GRAY MATTER VOLUME PREDICTS EXERCISE ADHERENCE

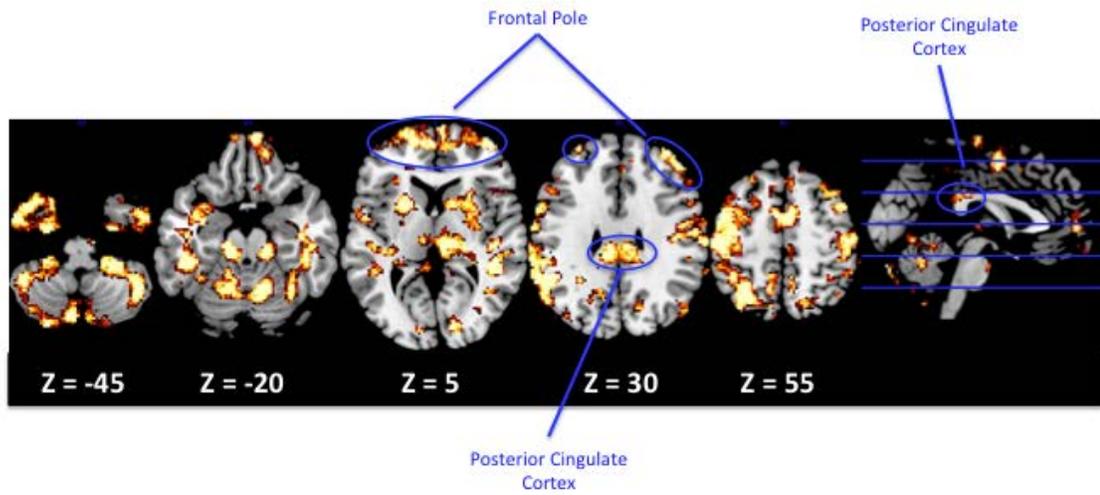
We used whole-brain voxelwise regression models with bootstrapping in the BRAVO Matlab toolbox to test our hypothesis that volume in prefrontal and cingulate regions would predict exercise adherence. Consistent with our hypothesis, a voxelwise bootstrapped regression model predicting adherence, while adjusting for age, education, and gender, showed that volume in the lateral and medial frontopolar cortex (aPFC), dorsal PFC, and posterior cingulate cortex predicted exercise adherence ($pFDR < .038$). Gray matter volume was also predictive of adherence in a broad array of other regions, including the motor cortex, basal ganglia, thalamus, superior parietal cortex, inferior temporal cortex, and cerebellum (See Figures 3.1 and 3.2). A whole-brain voxel-wise analysis showed that, on average, ~22% of gray matter voxels were significantly associated with adherence.

3.3 GRAY MATTER VOLUME PREDICTS EXERCISE ADHERENCE INDEPENDENT OF SELF-EFFICACY

A second voxelwise bootstrapped regression analysis was conducted, adding self-efficacy as a separate covariate to the model. After accounting for the relationship between self-efficacy and adherence, the association between aPFC and dorsal PFC volume and adherence remained

significant ($pFDR < 0.038$); however, posterior cingulate volume no longer predicted adherence ($pFDR > 0.038$). Pallidum volume also no longer predicted adherence after adjusting for self-efficacy. Volume in other regions predicting adherence remained significant after adjusting for self-efficacy, although the percentage of gray matter volume within each region predictive of adherence declined significantly after covarying for self-efficacy. These areas include the primary and supplementary motor cortex, inferior temporal cortex, superior parietal cortex, thalamus, putamen, and the cerebellum. Most of these associations were bilateral (See Table 3 below). Within the gray matter regions predictive of adherence, 33% volume predicted adherence independent of self-efficacy (See Table 4). After extracting PVE, voxel-wise estimates of gray matter volume averaged across voxels that were significantly associated with adherence, explained approximately 19% of variance in adherence above and beyond variance explained by age, education, gender, and self-efficacy (R^2 Covariates: 0.017, R^2 change Self-Efficacy: 0.056, R^2 change PVE gray matter: 0.19, R^2 overall: 0.265). See Figures 3.1-3.4 for a visual comparison of gray matter regions associated with adherence with and without adjusting for self-efficacy.

MODEL 1: WITHOUT CONTROLLING FOR SELF-EFFICACY



MODEL 2: AFTER CONTROLLING FOR SELF-EFFICACY

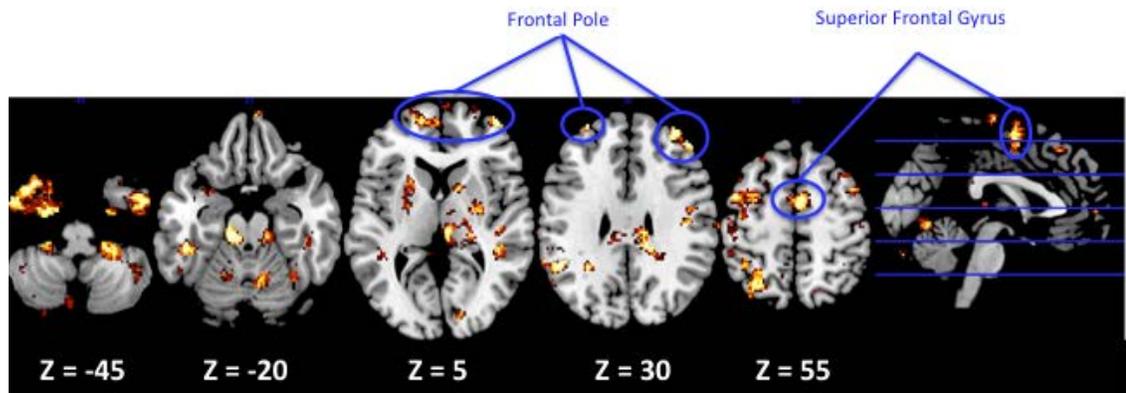
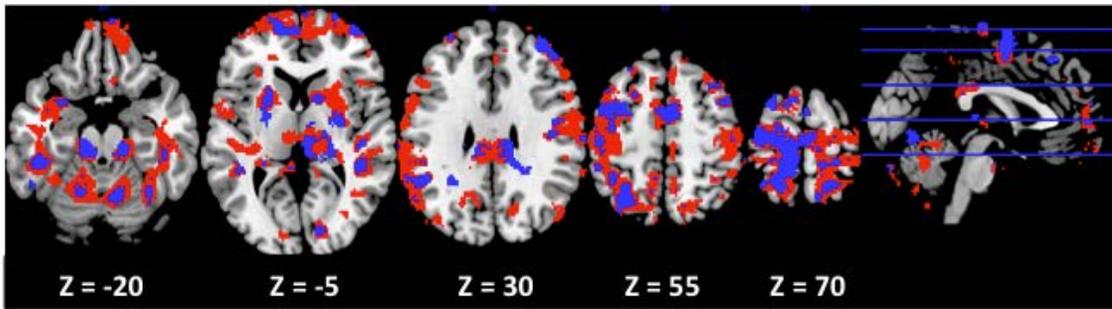


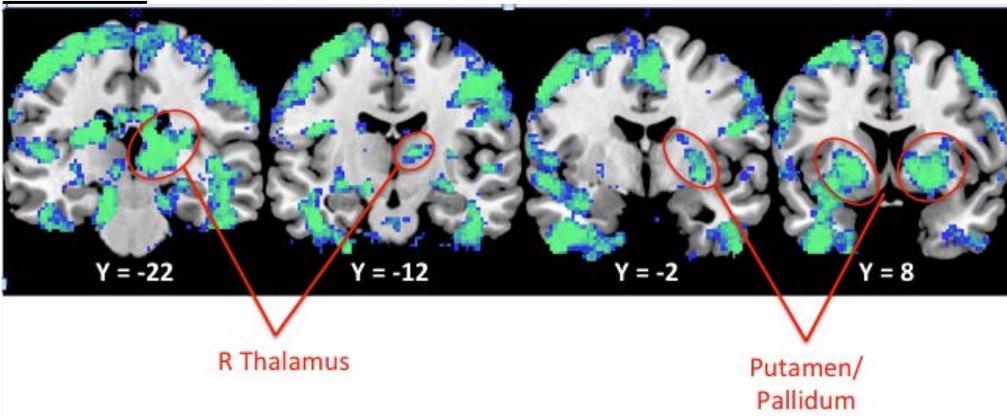
Figure 2. Cortical Grey Matter regions predicting Exercise Adherence



RED = regions predictive of adherence BEFORE adjusting for self-efficacy
BLUE = regions predictive of adherence independent of self-efficacy

Figure 3. Dysjunction of regions predicting adherence with and without controlling for self-efficacy

MODEL 1: WITHOUT CONTROLLING FOR SELF-EFFICACY



MODEL 2: AFTER CONTROLLING FOR SELF-EFFICACY

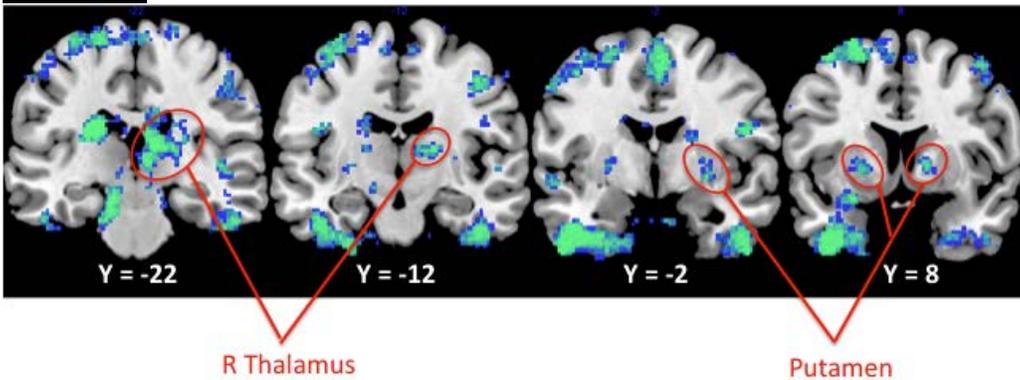


Figure 4. Subcortical grey matter regions predicting exercise adherence

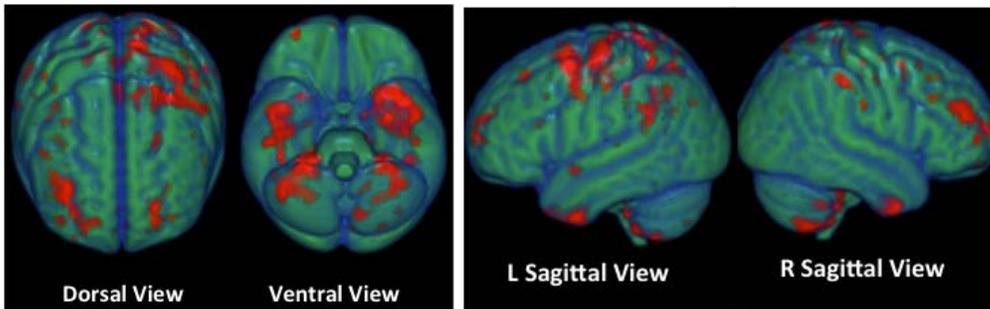


Figure 5. 3D view of grey matter regions associated with exercise adherence after controlling for self-efficacy

Table 3. Brain Regions predicting Exercise Adherence after controlling for Self-Efficacy

Regions	Cluster size (voxels)	X	Y	Z
<i>Frontal Cortex</i>				
L Superior frontal gyrus	3360	-10	-28	70
R Frontal pole	794	34	46	28
L Frontal pole	394	-20	68	18
R Middle frontal gyrus	47	42	26	50
<i>Temporal Cortex</i>				
Bilateral inferior temporal gyrus/temporal pole	1980	-36	6	-36
R Middle/superior temporal gyrus	235	46	-40	-2
<i>Parietal Cortex</i>				
R Supramarginal gyrus	114	60	-36	50
L Supramarginal gyrus/angular gyrus	451	-54	-48	32
R Superior parietal lobule	284	16	-56	70
<i>Subcortical regions</i>				
L putamen/pallidum	747	-16	-44	12
R putamen/pallidum	145	28	-2	-4
R Thalamus	1271	14	-38	28
<i>Bilateral cerebellum</i>	5404	-12	-18	-6

Table 4. Percent Gray Matter Voxels associated with Exercise Adherence

	Without controlling for SE	After controlling for SE
% Total Gray Matter Voxels	21.90%	7.30%
% Frontal cortex	23.40%	7.40%
% Temporal cortex	20.10%	11.20%
% Parietal cortex	27.50%	6.20%
% Occipital Cortex	7.90%	2.40%
% Cerebellum	31.90%	8.90%

3.4 GRAY MATTER VOLUME IS ASSOCIATED WITH SELF-EFFICACY:

EXPLORATORY ANALYSIS

A third voxelwise bootstrapped regression analysis was conducted to test the association between gray matter volume and self-efficacy, after adjusting for age, gender, and education. Volume in a broad array of cortical and subcortical regions was associated with self-efficacy, including the aPFC, cingulate cortex, insular cortex, motor cortex, temporal and parietal cortex, thalamus, amygdala, pallidum, and putamen ($p_{FDR} < 0.038$). There was significant overlap between regions associated with self-efficacy and those predictive of adherence. Cortical gray matter regions continued to show a significant association with self-efficacy even when using the conservative threshold, although the percentage of gray matter volume associated with self-efficacy within each region declined with the more stringent threshold for significance.

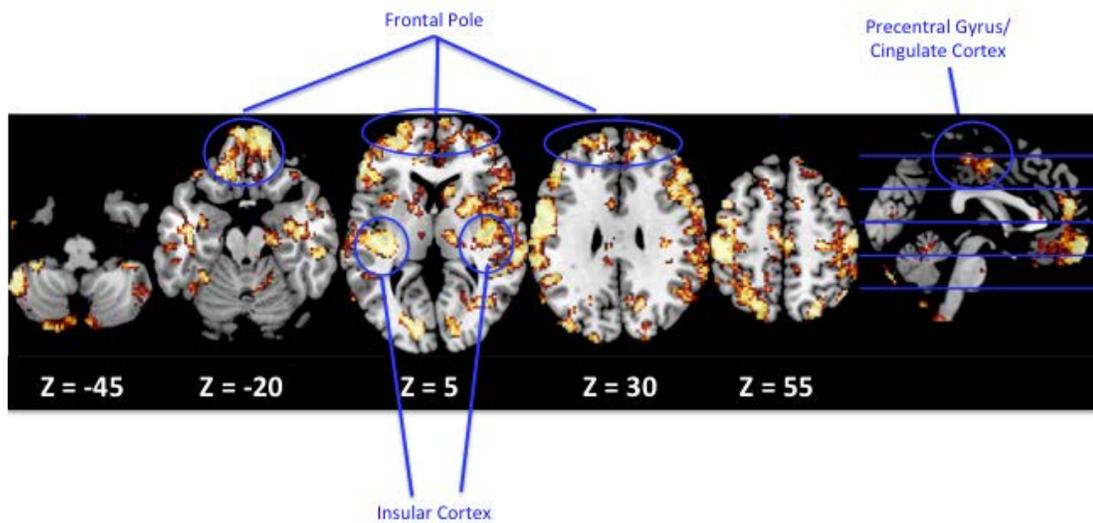


Figure 6. Cortical Grey Matter regions associated with Self-Efficacy

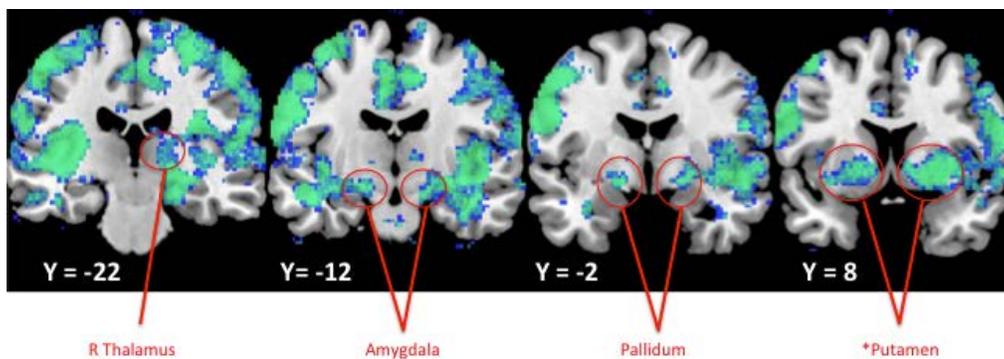


Figure 7. Subcortical Grey Matter regions associated with Self-Efficacy

4.0 DISCUSSION

I predicted that gray matter volume in prefrontal and cingulate regions would predict adherence to a 12-month exercise intervention in older adults. Consistent with this prediction, greater gray matter volume in lateral and medial aPFC, dlPFC, and supplementary motor cortex, as well as posterior cingulate cortex, were predictive of better adherence to the intervention, irrespective of intervention group. In addition to prefrontal and cingulate regions, greater gray matter volume in motor cortex, superior parietal cortex, inferior temporal cortex, right thalamus, bilateral putamen and pallidum, and cerebellum was also predictive of better adherence to the intervention. Volume in this broad array of frontal, temporal, parietal, and subcortical regions remained predictive of adherence even after controlling for self-efficacy.

The exercise literature collectively suggests that adherence is influenced by a number of social, cognitive, and motivational factors (Young et al., 2014). These factors, including self-efficacy, self-regulatory strategies, executive functions, outcome expectations, and perceived social support, may be supported by several, partially overlapping neural networks. Understanding the neural substrates supporting these predictors of adherence may help explain the breadth of gray matter regions found to be predictive of adherence in this study.

Given that self-efficacy is a key predictor of exercise adherence, gray matter associations with self-efficacy were examined. Gray matter integrity was associated with self-efficacy in prefrontal, temporal, parietal, cingulate, and insular cortex, as well as several subcortical

structures: the thalamus, amygdala, pallidum, and putamen. Many of these regions overlapped with regions predictive of adherence. Also, gray matter integrity in medial regions showed greater associations with self-efficacy relative to adherence. These findings are in concert with evidence from a meta-analysis of functional neuroimaging studies that identified cortical midline structures as important for self-referential processing (Northoff et al., 2006). Gray matter associations with self-efficacy have only been shown in one prior study of older women participating in a physical activity intervention (Davis et al., 2011), and the authors did not describe regions specifically related to self-efficacy. However, metacognition, a construct conceptually related to self-efficacy, has been linked to a broad array of similar regions as found in the present study, using structural MRI, functional connectivity, and lesion methods (Baird, Smallwood, Gorgolewski, & Margulies, 2013; Fleming et al., 2010; McCurdy et al., 2013; Philippi et al., 2012). Self-efficacy and metacognition both tap into introspective awareness, as well as confidence in one's capabilities regarding performance on a specific behavior. Moreover, both constructs are useful for performance monitoring in order to pursue a goal.

Prefrontal and limbic regions predictive of adherence in this study have also been implicated in self-regulation, another important predictor of exercise adherence. In a recent meta-analysis, Young (2014) found that self-regulation may even be a more consistent predictor of physical activity relative to self-efficacy. Self-regulation refers to having a goal intention and using a set of strategies to work towards that goal; these include planning, goal-setting, self-monitoring, and preventing relapse. Successful implementation of these self-regulatory strategies relies on executive functions, as described by Miyake et al. (2000): response inhibition, mental set-shifting, and information updating and monitoring. Although the neural substrates for self-regulation were not specifically examined in this study, prior evidence has established that

prefrontal regions are critical for executing these regulatory processes (See Heatherton et al. (2011) for review). Structural MRI studies suggest that the DLPFC and ventral PFC are critical for executive function (Smolker et al., 2014). Functional MRI studies largely suggest a top-down control pathway from prefrontal regions associated with self-control (i.e. dorsolateral PFC and orbitofrontal cortex) to subcortical regions associated with reward incentives (i.e. striatum) and emotional valence (i.e. amygdala) (Burzynska et al., 2012; Heatherton & Wagner, 2011; Smolker et al., 2014).

The present study, along with prior evidence from the social and cognitive neuroscience literatures, suggests that a complex network of prefrontal, motor, striatal, and temporal, and parietal regions support the pursuit of complex behavioral goals. These findings are in concert with recent theoretical efforts to integrate executive and motivational processes into a single paradigm for understanding complex goal-directed behavior (Braver et al., 2014; Pessoa & Engelmann, 2010). Pessoa & Engelman (2010) proposed that the fronto-parietal attention network and cortical and subcortical motivational networks (including orbitofrontal cortex, anterior insula, mPFC, posterior cingulate cortex, striatum, nucleus accumbens, and amygdala) likely operate in an interactive manner to initiate, maintain, and ultimately achieve goals. An unexpected association also emerged between grey matter integrity in the cerebellum and adherence in the present study, with 30% volume in the cerebellum predicting adherence. This finding is consistent with evidence from a recent meta-analysis of 350 functional neuroimaging studies showing that the cerebellum is implicated in metacognitive processing that involves high levels of abstraction (Van Overwalle, Baetens, Marien, & Vandekerckhove, 2014).

Regions in which grey matter integrity predicted adherence independent of self-efficacy were also explored, given that self-efficacy is presently the most studied predictor of exercise

adherence (Young et al., 2014). This examination tested the functional utility of using objective neuroimaging methods to understand exercise adherence, and indeed demonstrated that structural MRI methods help us to learn about adherence in ways that cannot be captured by subjective self-efficacy ratings. Most gray matter regions initially predicting adherence remained significant after controlling for self-efficacy. However, controlling for self-efficacy reduced the percentage of gray matter predicting adherence from 22% to 7% across the whole-brain. Interestingly, a disjunction of regions predicting adherence before and after controlling for self-efficacy revealed that volume in medial regions of the frontopolar cortex no longer predicted adherence after controlling for self-efficacy. This is consistent with the proposed role of medial aPFC as central to metacognition, which closely maps on self-efficacy (Baird et al., 2013). Lateral regions of the frontopolar cortex remained predictive of adherence after controlling for self-efficacy. This disjunction analysis overall suggested that gray matter associations with adherence may partially rely on associations with self-efficacy, as well as uniquely predict adherence independent of self-efficacy. However, the statistical approach used in the present study cannot confirm the extent to which self-efficacy truly mediates the relationship between gray matter volume in these regions and adherence.

The broader implications of this study include its contribution to the emerging field of neuroimaging research using the ‘brain as a predictor’ approach to understanding real-world behavioral phenomenon (Berkman & Falk, 2013). The aim of this new methodological approach is to leverage objective measures of neural structure and function using neuroimaging to predict long-term, ecologically valid outcomes that extend beyond laboratory testing. The advent of neuroimaging technology affords the possibility to link objective neurobiological markers to behavior in a variety of domains, including cognitive function, health, economic decision-

making, and clinical and neurological outcomes (Berkman & Falk, 2013). Berkman and colleagues have outlined guidelines for using this methodological approach to understand real-world outcomes. An important assumption underlying this approach is that neural markers serve as objective summary measures of psychological constructs and behavioral outcomes. Using this approach, the present study aimed to tap into neural substrates of exercise adherence and self-efficacy.

The findings from the present study have shown that older adults with greater grey matter volume in regions relevant to self-efficacy and self-regulation demonstrate better adherence to a yearlong exercise intervention. Importantly, these associations may be heightened in this elderly sample, given that older adults are known to have greater gray matter atrophy and greater variability in exercise adherence (Conn et al., 2003; Resnick & Nigg, 2003) The implications of these grey matter associations may also extend beyond exercise adherence, to include the adoption and maintenance of other healthy lifestyle behaviors that are protective against physical and cognitive health decline. In turn, grey matter integrity in these regions may broadly influence quality of life in older adults.

Understanding the relationship between gray matter volume prior to the intervention and exercise adherence is also the first step to understanding individual differences in exercise-induced improvements in gray matter volume (reduction in atrophy). The next step will be to examine the extent to which regions predictive of adherence show intervention-induced volumetric changes. This will help us to understand whether this relationship between brain health and adherence impacts exercise-induced improvements in gray matter as a function of poor adherence. To address this, interventions can be tailored to focus on improving self-efficacy during the initial phases of the intervention and target improving self-regulatory skills, such as

planning and goal setting. On the other hand, individuals with greater gray matter atrophy in these regions may show similar levels of improvement in brain health as those with less atrophy. This could indicate that those with poorer brain health have ‘more to gain’ from the exercise intervention, relative to those with better brain health, who may show a ‘ceiling effect’. Future research can also expand on this study by examining the relationship between gray matter volume and adherence after controlling for additional psychological predictors of adherence (i.e. self-regulatory strategies, executive functions). This will help to distinguish which brain regions are implicated in each psychological factor, as well as to understand the extent of overlap between regions implicated in each psychological factor. Future studies can also statistically examine the extent to which self-efficacy and other psychological factors mediate the relationship between gray matter volume and exercise adherence.

Limitations

There are several limitations to the present study. This is the first examination of the neural substrates predicting exercise adherence, therefore regions specifically predictive of adherence relative to those supporting behavioral goal-pursuit more generally cannot be distinguished from this study. Also, a comprehensive explanation for grey matter regions predictive of exercise adherence is yet to be determined; this study did not include adequate measures to test several possible explanations for these associations. Next, this was a 12-month intervention, and it is unclear whether these same effects would occur for shorter or longer trials or trials of a different type, duration, or intensity (e.g., resistance training). This study was also conducted using a mostly Caucasian sample of highly educated healthy older adults from a small Midwestern town; therefore, these results may not be easily generalizable to more culturally diverse, younger, and clinical populations. There are a number of additional limitations related to

the MRI analysis methods used in this study. First, voxel-based morphometry only provides estimates of tissue type, and thus in drawing conclusions from our data, it must be taken into account that the data is probabilistic rather than absolute. Also, using VBM techniques, brain images are forced into registered space prior to assessing volumetric maps, limiting the accuracy of these volumetric findings. Estimates using VBM are also not on a cellular level, so it is difficult to ascertain true “volume” from this segmentation technique. Nonetheless, VBM has been used as a standard method for estimating gray matter volume in a number of studies, and allows for examining relationships between gray matter volume and outcomes on a voxel-wise basis. Finally, estimates of effect size are difficult to ascertain using bootstrap regression methods with neuroimaging data; therefore, extracting values into SPSS only allows for a rough approximation of effect size.

In summary, I found that gray matter volume in a broad array of prefrontal, cingulate, temporal, parietal, subcortical, and cerebellar regions predicted exercise adherence in older adults. Most of these associations remained after accounting for the relationship between self-efficacy and adherence. Gray matter regions associated with self-efficacy were similarly widespread across cortical and subcortical regions, with significant overlap with regions predictive of adherence. These findings provide preliminary support for neural substrates underlying exercise adherence, as well as self-efficacy. Future research will need to expand on these findings by examining neural substrates of other social-cognitive factors, as well exploring how these associations impact exercise-related improvements in brain health.

BIBLIOGRAPHY

- Aging, A. o. (2010). A Profile of Older Americans: 2010., from U.S. Department of Health and Human Services.http://www.aoa.gov/AoARoot/Aging_Statistics/Census_Population/census2010/Index.aspx
- Amodio, D. M., & Frith, C. D. (2006). Meeting of minds: the medial frontal cortex and social cognition. *Nat Rev Neurosci*, 7(4), 268-277. doi: 10.1038/nrn1884
- Anderson, E. S., Wojcik, J. R., Winett, R. A., & Williams, D. M. (2006). Social-cognitive determinants of physical activity: the influence of social support, self-efficacy, outcome expectations, and self-regulation among participants in a church-based health promotion study. *Health Psychol*, 25(4), 510-520. doi: 10.1037/0278-6133.25.4.510
- Anderson-Bill, E. S., Winett, R. A., Wojcik, J. R., & Williams, D. M. (2011). Aging and the social cognitive determinants of physical activity behavior and behavior change: evidence from the guide to health trial. *J Aging Res*, 2011, 505928. doi: 10.4061/2011/505928
- Anderson-Bill, E. S., Winett, R. A., Wojcik, J. R., & Winett, S. G. (2011). Web-based guide to health: relationship of theoretical variables to change in physical activity, nutrition and weight at 16-months. *J Med Internet Res*, 13(1), e27. doi: 10.2196/jmir.1614
- Andersson, J., Jenkinson, M., Smith, S. (2007). Non-linear optimisation, aka spatial normalisation., from <http://www.fmrib.ox.ac.uk/analysis/techrep>
- Ashburner, J., & Friston, K. J. (2000). Voxel-based morphometry--the methods. *Neuroimage*, 11(6 Pt 1), 805-821. doi: 10.1006/nimg.2000.0582
- Ayotte, B. J., Margrett, J. A., & Hicks-Patrick, J. (2010). Physical activity in middle-aged and young-old adults: the roles of self-efficacy, barriers, outcome expectancies, self-regulatory behaviors and social support. *J Health Psychol*, 15(2), 173-185. doi: 10.1177/1359105309342283
- Baert, V., Gorus, E., Mets, T., Geerts, C., & Bautmans, I. (2011). Motivators and barriers for physical activity in the oldest old: a systematic review. *Ageing Res Rev*, 10(4), 464-474. doi: 10.1016/j.arr.2011.04.001
- Baird, B., Smallwood, J., Gorgolewski, K. J., & Margulies, D. S. (2013). Medial and Lateral Networks in Anterior Prefrontal Cortex Support Metacognitive Ability for Memory and

- Perception. *Journal of Neuroscience*, 33(42), 16657-16665. doi: Doi 10.1523/Jneurosci.0786-13.2013
- Bandura, A. (1997). The anatomy of stages of change. *Am J Health Promot*, 12(1), 8-10.
- Berkman, E. T., & Falk, E. B. (2013). Beyond Brain Mapping: Using Neural Measures to Predict Real-World Outcomes. *Current Directions in Psychological Science*, 22(1), 45-50. doi: Doi 10.1177/0963721412469394
- Brassington, G. S., Atienza, A. A., Perczek, R. E., DiLorenzo, T. M., & King, A. C. (2002). Intervention-related cognitive versus social mediators of exercise adherence in the elderly. *Am J Prev Med*, 23(2 Suppl), 80-86.
- Braver, T. S., Krug, M. K., Chiew, K. S., Kool, W., Westbrook, J. A., Clement, N. J., . . . group, M. (2014). Mechanisms of motivation-cognition interaction: challenges and opportunities. *Cogn Affect Behav Neurosci*, 14(2), 443-472. doi: 10.3758/s13415-014-0300-0
- Bridle, C., Spanjers, K., Patel, S., Atherton, N. M., & Lamb, S. E. (2012). Effect of exercise on depression severity in older people: systematic review and meta-analysis of randomised controlled trials. *Br J Psychiatry*, 201(3), 180-185. doi: 10.1192/bjp.bp.111.095174
- Burzynska, A. Z., Nagel, I. E., Preuschhof, C., Gluth, S., Backman, L., Li, S. C., . . . Heekeren, H. R. (2012). Cortical thickness is linked to executive functioning in adulthood and aging. *Hum Brain Mapp*, 33(7), 1607-1620. doi: 10.1002/hbm.21311
- Cacioppo, J. T., & Decety, J. (2011). Social neuroscience: challenges and opportunities in the study of complex behavior. *Ann N Y Acad Sci*, 1224, 162-173. doi: 10.1111/j.1749-6632.2010.05858.x
- Carver, C. S. (2006). Approach, avoidance, and the self-regulation of affect and action. *Motivation and Emotion*, 30(2), 105-110. doi: Doi 10.1007/S11031-006-9044-7
- Chao, D., Foy, C. G., & Farmer, D. (2000). Exercise adherence among older adults: challenges and strategies. *Control Clin Trials*, 21(5 Suppl), 212S-217S.
- Colcombe, S., & Kramer, A. F. (2003). Fitness effects on the cognitive function of older adults: a meta-analytic study. *Psychol Sci*, 14(2), 125-130.
- 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
- Conn, V. S., Minor, M. A., Burks, K. J., Rantz, M. J., & Pomeroy, S. H. (2003). Integrative review of physical activity intervention research with aging adults. *J Am Geriatr Soc*, 51(8), 1159-1168.
- Crocker, L. D., Heller, W., Warren, S. L., O'Hare, A. J., Infantolino, Z. P., & Miller, G. A. (2013). Relationships among cognition, emotion, and motivation: implications for

- intervention and neuroplasticity in psychopathology. *Frontiers in Human Neuroscience*, 7. doi: Artn 261 Doi 10.3389/Fnhum.2013.00261
- Custers, R., & Aarts, H. (2010). The unconscious will: how the pursuit of goals operates outside of conscious awareness. *Science*, 329(5987), 47-50. doi: 10.1126/science.1188595
- Davis, J. C., Marra, C. A., & Liu-Ambrose, T. Y. (2011). Falls-related self-efficacy is independently associated with quality-adjusted life years in older women. *Age Ageing*, 40(3), 340-346. doi: 10.1093/ageing/afr019
- DiCiccio, T. J., & Efron, B. (1996). Bootstrap confidence intervals. *Statistical Science*, 11, 189-228.
- Dishman, R. (1994). Introduction: consensus, problems, and prospects. *Human Kinetics* (pp. 1-27). Champaign, IL.
- Duncan, T. E., & McAuley, E. (1993). Social support and efficacy cognitions in exercise adherence: a latent growth curve analysis. *J Behav Med*, 16(2), 199-218.
- Erickson, K. I., Prakash, R. S., Voss, M. W., Chaddock, L., Hu, L., Morris, K. S., . . . Kramer, A. F. (2009). Aerobic fitness is associated with hippocampal volume in elderly humans. *Hippocampus*, 19(10), 1030-1039. doi: 10.1002/hipo.20547
- 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
- Evenson, K. R., Buchner, D. M., & Morland, K. B. (2012). Objective measurement of physical activity and sedentary behavior among US adults aged 60 years or older. *Prev Chronic Dis*, 9, E26.
- Fagard, R. H. (2001). Exercise characteristics and the blood pressure response to dynamic physical training. *Med Sci Sports Exerc*, 33(6 Suppl), S484-492; discussion S493-484.
- Flavell, J. (1979). Metacognition and cognitive monitoring: A new area of cognitive-developmental inquiry. *American Psychologist*, 34(10), 906.
- Fleming, S. M., Huijgen, J., & Dolan, R. J. (2012). Prefrontal contributions to metacognition in perceptual decision making. *J Neurosci*, 32(18), 6117-6125. doi: 10.1523/JNEUROSCI.6489-11.2012
- Fleming, S. M., Weil, R. S., Nagy, Z., Dolan, R. J., & Rees, G. (2010). Relating introspective accuracy to individual differences in brain structure. *Science*, 329(5998), 1541-1543. doi: 10.1126/science.1191883
- Genovese, C. R., Lazar, N. A., & Nichols, T. (2002). Thresholding of statistical maps in functional neuroimaging using the false discovery rate. *Neuroimage*, 15(4), 870-878. doi: Doi 10.1006/Nimg.2001.1037

- 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
- Hall, P. A., Fong, G. T., Epp, L. J., & Elias, L. J. (2008). Executive function moderates the intention-behavior link for physical activity and dietary behavior. *Psychol Health*, 23(3), 309-326. doi: 10.1080/14768320701212099
- Heatherston, T. F., & Wagner, D. D. (2011). Cognitive neuroscience of self-regulation failure. *Trends Cogn Sci*, 15(3), 132-139. doi: 10.1016/j.tics.2010.12.005
- Heran, B. S., Chen, J. M., Ebrahim, S., Moxham, T., Oldridge, N., Rees, K., . . . Taylor, R. S. (2011). Exercise-based cardiac rehabilitation for coronary heart disease. *Cochrane Database Syst Rev*(7), CD001800. doi: 10.1002/14651858.CD001800.pub2
- 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. *Arch Phys Med Rehabil*, 85(10), 1694-1704.
- Hui, E. K., & Rubenstein, L. Z. (2006). Promoting physical activity and exercise in older adults. *J Am Med Dir Assoc*, 7(5), 310-314. doi: 10.1016/j.jamda.2006.03.006
- Jenkinson, M., & Smith, S. (2001). A global optimisation method for robust affine registration of brain images. *Med Image Anal*, 5(2), 143-156.
- Kennedy, K. M., Erickson, K. I., Rodrigue, K. M., Voss, M. W., Colcombe, S. J., Kramer, A. F., . . . Raz, N. (2009). Age-related differences in regional brain volumes: a comparison of optimized voxel-based morphometry to manual volumetry. *Neurobiol Aging*, 30(10), 1657-1676. doi: 10.1016/j.neurobiolaging.2007.12.020
- Kramer, A. F., Hahn, S., Cohen, N. J., Banich, M. T., McAuley, E., Harrison, C. R., . . . Colcombe, A. (1999). Ageing, fitness and neurocognitive function. *Nature*, 400(6743), 418-419. doi: 10.1038/22682
- Lautenschlager, N. T., Cox, K. L., Flicker, L., Foster, J. K., van Bockxmeer, F. M., Xiao, J., . . . Almeida, O. P. (2008). Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. *JAMA*, 300(9), 1027-1037. doi: 10.1001/jama.300.9.1027
- Leon, A. S., Rice, T., Mandel, S., Despres, J. P., Bergeron, J., Gagnon, J., . . . Bouchard, C. (2000). Blood lipid response to 20 weeks of supervised exercise in a large biracial population: the HERITAGE Family Study. *Metabolism*, 49(4), 513-520.

- Leon, A. S., & Sanchez, O. A. (2001). Response of blood lipids to exercise training alone or combined with dietary intervention. *Med Sci Sports Exerc*, 33(6 Suppl), S502-515; discussion S528-509.
- Luszczynska, A., Tryburcy, M., & Schwarzer, R. (2007). Improving fruit and vegetable consumption: a self-efficacy intervention compared with a combined self-efficacy and planning intervention. *Health Educ Res*, 22(5), 630-638. doi: 10.1093/her/cyl133
- Manly, B. (1997). *Randomization, bootstrap, and monte carlo methods in biology* (Vol. 2nd ed.). London: Chapman & Hall.
- Martin, K. A., Bowen, D. J., Dunbar-Jacob, J., & Perri, M. G. (2000). Who will adhere? Key issues in the study and prediction of adherence in randomized controlled trials. *Control Clin Trials*, 21(5 Suppl), 195S-199S.
- McAuley, E. (1992). The role of efficacy cognitions in the prediction of exercise behavior in middle-aged adults. *J Behav Med*, 15(1), 65-88.
- McAuley, E. (1993). Self-efficacy and the maintenance of exercise participation in older adults. *J Behav Med*, 16(1), 103-113.
- McAuley, E., & Blissmer, B. (2000). Self-efficacy determinants and consequences of physical activity. *Exerc Sport Sci Rev*, 28(2), 85-88.
- McAuley, E., Hall, K. S., Motl, R. W., White, S. M., Wojcicki, T. R., Hu, L., & Doerksen, S. E. (2009). Trajectory of declines in physical activity in community-dwelling older women: social cognitive influences. *J Gerontol B Psychol Sci Soc Sci*, 64(5), 543-550. doi: 10.1093/geronb/gbp049
- McAuley, E., Jerome, G. J., Elavsky, S., Marquez, D. X., & Ramsey, S. N. (2003). Predicting long-term maintenance of physical activity in older adults. *Prev Med*, 37(2), 110-118.
- McAuley, E., Mailey, E. L., Mullen, S. P., Szabo, A. N., Wojcicki, T. R., White, S. M., . . . Kramer, A. F. (2011). Growth trajectories of exercise self-efficacy in older adults: influence of measures and initial status. *Health Psychol*, 30(1), 75-83. doi: 10.1037/a0021567
- McAuley, E., Morris, K. S., Motl, R. W., Hu, L., Konopack, J. F., & Elavsky, S. (2007). Long-term follow-up of physical activity behavior in older adults. *Health Psychol*, 26(3), 375-380. doi: 10.1037/0278-6133.26.3.375
- McAuley, E., Mullen, S. P., Szabo, A. N., White, S. M., Wojcicki, T. R., Mailey, E. L., . . . Kramer, A. F. (2011). Self-regulatory processes and exercise adherence in older adults: executive function and self-efficacy effects. *Am J Prev Med*, 41(3), 284-290. doi: 10.1016/j.amepre.2011.04.014

- McCurdy, L. Y., Maniscalco, B., Metcalfe, J., Liu, K. Y., de Lange, F. P., & Lau, H. (2013). Anatomical coupling between distinct metacognitive systems for memory and visual perception. *J Neurosci*, 33(5), 1897-1906. doi: 10.1523/JNEUROSCI.1890-12.2013
- Menezes, A. R., Lavie, C. J., Milani, R. V., Arena, R. A., & Church, T. S. (2012). Cardiac rehabilitation and exercise therapy in the elderly: Should we invest in the aged? *J Geriatr Cardiol*, 9(1), 68-75. doi: 10.3724/SP.J.1263.2012.00068
- Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D. (2000). The unity and diversity of executive functions and their contributions to complex "Frontal Lobe" tasks: a latent variable analysis. *Cogn Psychol*, 41(1), 49-100. doi: 10.1006/cogp.1999.0734
- Northoff, G., Heinzl, A., Greck, M., Bennpohl, F., Dobrowolny, H., & Panksepp, J. (2006). Self-referential processing in our brain - A meta-analysis of imaging studies on the self. *Neuroimage*, 31(1), 440-457. doi: Doi 10.1016/J.Neuroimage.2005.12.002
- Park, C. H., Elavsky, S., & Koo, K. M. (2014). Factors influencing physical activity in older adults. *J Exerc Rehabil*, 10(1), 45-52. doi: 10.12965/jer.140089
- Pessoa, L. (2009). How do emotion and motivation direct executive control? *Trends Cogn Sci*, 13(4), 160-166. doi: Doi 10.1016/J.Tics.2009.01.006
- Pessoa, L., & Engelmann, J. B. (2010). Embedding reward signals into perceptio nand cognition. *Frontiers in Neuroscience*, 4.
- Philippi, C. L., Duff, M. C., Denburg, N. L., Tranel, D., & Rudrauf, D. (2012). Medial PFC Damage Abolishes the Self-reference Effect. *Journal of Cognitive Neuroscience*, 24(2), 475-481.
- Prakash, R. S., Voss, M. W., Erickson, K. I., Lewis, J. M., Chaddock, L., Malkowski, E., . . . Kramer, A. F. (2011). Cardiorespiratory fitness and attentional control in the aging brain. *Frontiers in Human Neuroscience*, 4, 229. doi: 10.3389/fnhum.2010.00229
- Preacher, K. J., & Hayes, A. F. (2008). Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. *Behavior Research Methods*, 40(3), 879-891. doi: Doi 10.3758/Brm.40.3.879
- Resnick, B. (2001). Testing a model of exercise behavior in older adults. *Res Nurs Health*, 24(2), 83-92.
- Resnick, B., & Nigg, C. (2003). Testing a theoretical model of exercise behavior for older adults. *Nurs Res*, 52(2), 80-88.
- Resnick, B., Palmer, M. H., Jenkins, L. S., & Spellbring, A. M. (2000). Path analysis of efficacy expectations and exercise behaviour in older adults. *J Adv Nurs*, 31(6), 1309-1315.

- Sallis, J. F., Haskell, W. L., Fortmann, S. P., Vranizan, K. M., Taylor, C. B., & Solomon, D. S. (1986). Predictors of adoption and maintenance of physical activity in a community sample. *Prev Med*, 15(4), 331-341.
- Schutzer, K. A., & Graves, B. S. (2004). Barriers and motivations to exercise in older adults. *Prev Med*, 39(5), 1056-1061. doi: 10.1016/j.yjpm.2004.04.003
- Services, U. S. D. o. H. H. (2008). 2008 Physical Activity Guidelines for Americans. from U.S. Department of Health & Human Services
Office of Disease Prevention and Health Promotion
- Sheikh, J. I., Yesavage, J.A. (1986). Geriatric depression scale (GDS): Recent evidence and development of a shorter version. In T. L. Brink (Ed.), *Clinical Gerontology: A Guide to Assessment and Intervention* (pp. 165-173). New York: The Haworth Press.
- 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
- Smolker, H. R., Depue, B. E., Reineberg, A. E., Orr, J. M., & Banich, M. T. (2014). Individual differences in regional prefrontal gray matter morphometry and fractional anisotropy are associated with different constructs of executive function. *Brain Struct Funct*. doi: 10.1007/s00429-014-0723-y
- Thompson, P. D., Crouse, S. F., Goodpaster, B., Kelley, D., Moyna, N., & Pescatello, L. (2001). The acute versus the chronic response to exercise. *Med Sci Sports Exerc*, 33(6 Suppl), S438-445; discussion S452-433.
- Umpierre, D., Ribeiro, P. A., Kramer, C. K., Leitao, C. B., Zucatti, A. T., Azevedo, M. J., . . . Schaan, B. D. (2011). Physical activity advice only or structured exercise training and association with HbA1c levels in type 2 diabetes: a systematic review and meta-analysis. *JAMA*, 305(17), 1790-1799. doi: 10.1001/jama.2011.576
- Van Overwalle, F., Baetens, K., Marien, P., & Vandekerckhove, M. (2014). Social cognition and the cerebellum: a meta-analysis of over 350 fMRI studies. *Neuroimage*, 86, 554-572. doi: 10.1016/j.neuroimage.2013.09.033
- Villareal, D. T., Miller, B. V., 3rd, Banks, M., Fontana, L., Sinacore, D. R., & Klein, S. (2006). Effect of lifestyle intervention on metabolic coronary heart disease risk factors in obese older adults. *Am J Clin Nutr*, 84(6), 1317-1323.

- Vogel, T., Brechat, P. H., Lepretre, P. M., Kaltenbach, G., Berthel, M., & Lonsdorfer, J. (2009). Health benefits of physical activity in older patients: a review. *Int J Clin Pract*, 63(2), 303-320. doi: 10.1111/j.1742-1241.2008.01957.x
- Voss, M. W., Erickson, K. I., Prakash, R. S., Chaddock, L., Kim, J. S., Alves, H., . . . Kramer, A. F. (2013). Neurobiological markers of exercise-related brain plasticity in older adults. *Brain Behav Immun*, 28, 90-99. doi: 10.1016/j.bbi.2012.10.021
- Washburn, R. A., Smith, K. W., Jette, A. M., & Janney, C. A. (1993). The Physical Activity Scale for the Elderly (PASE): development and evaluation. *J Clin Epidemiol*, 46(2), 153-162.
- Wing, R. R., & Hill, J. O. (2001). Successful weight loss maintenance. *Annu Rev Nutr*, 21, 323-341. doi: 10.1146/annurev.nutr.21.1.323
- Young, M. D., Plotnikoff, R. C., Collins, C. E., Callister, R., & Morgan, P. J. (2014). Social cognitive theory and physical activity: a systematic review and meta-analysis. *Obes Rev*, 15(12), 983-995. doi: 10.1111/obr.12225
- 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