Biomarkers and Neuropsychological Change: A Pilot Study of Three Months of the interactive Physical and Cognitive Exercise System (iPACES™) for Older Adults

By

Jessica Stark

****

Senior Thesis

A thesis presented in partial fulfillment
of the requirements for the degree of
Bachelor of Science
Department of Psychology
Neuroscience Program

UNION COLLEGE

Schenectady, New York

March 2017

ABSTRACT

STARK, JESSICA. Biomarkers and Neuropsychological Change: A Pilot Study of Three Months of the interactive Physical and Cognitive Exercise System (iPACES™) for Older Adults.

Department of Psychology, March 2017.

ADVISOR: Professor Cay Anderson-Hanley

The current pilot study of the interactive Physical and Cognitive Exercise System (iPACES™) examined the relationship between biomarkers and cognitive change over three months of neuroexergaming, wherein older adults pedaled and steered along a virtual bike path to complete a list of errands (Memory Lane™). Executive function and saliva were measured at baseline, mid (6-week), and three months. Results revealed moderate to large correlations between executive function and salivary biomarkers cortisol, BDNF, and IGF1. These findings suggest that neuroexergaming interventions such as iPACES™ may impact both cognitive and neurobiological pathways and perhaps could be an effective way to promote healthy aging in the increasing older adult population.

TABLE OF CONTENTS

INTRODUCTION

Over the past few decades, there has been a dramatic increase in the older adult population in the United States. With this increase comes a bigger focus on the health problems of this group. A large problem facing older adults is their decrease in cognitive ability. One of the causes behind this is dementia. Dementia is an umbrella term referring to the loss of memory. The most common form of dementia is Alzheimer's disease (AD), which accounts for 60-80% of cases ("Types of Dementia", 2017). If a patient is still able to live independently despite his or her diminished memory, then he or she is considered to have Mild Cognitive Impairment (MCI). If he or she is unable to live independently, this person is classified as having dementia (Prince, Guerchet, & Prima, 2015). The chances of developing dementia increases with age, with incidence doubling every 6 years after age 60 (Prince, Guerchet, & Prima, 2015). Currently, dementia cases worldwide are estimated to be 47.47 million and the incidence of dementia is predicted to reach 75.63 million by 2030 (Prince, Guerchet, & Prima, 2015). These numbers have led to a new focus in research on the prevention and delay of dementia and cognitive decline as well as the biological mechanisms behind these two aging disorders.

Literature on Exercise, Exergaming and Cognition in Older Adults:

Cognitive decline in the aging is a major concern and leads to significant personal and societal costs, and studies that have examined the role of exercise in prevention and amelioration and have found significant benefits (e.g., Colcombe et al., 2003). One meta-analysis that explored eighteen studies involving sedentary, healthy older adults found a significant improvement in cognition, largely in executive functioning, as a result of exercise intervention (Colcombe et al, 2003). A different review investigated both healthy and

1

cognitively impaired adults that underwent exercise interventions (Uffelen et al., 2008). Using 23 studies, 15 with healthy patients and eight with patients who had begun to experience cognitive decline, the review revealed that five of each type of study found improvements in information processing, executive function, and memory. However, at this point in time, the researchers concluded that more trials were needed to prove the effects of exercise and cognition in the healthy older adult population (Uffelen et al, 2008).

However, a more recent meta-analysis on cardiovascular activity and memory found mixed results (Roig et al., 2013). Of the 22 studies explored, acute exercise bouts only had a moderate affect on short-term memory, whereas long-term exercise only had a small effect on short-term memory. For long-term memory, acute exercise demonstrated large to moderate effects, while long-term exercise had no effect (Roig et al., 2013). Yet, the populations used in these studies were of all ages. Thus, it is possible that long-term memory might improve after an exercise intervention for older adults.

Other work has explored physical activity levels across participants' lives to see if activity intensity earlier in life could have an effect on the benefits of exercise (Middleton et al., 2010). In one study, researchers assessed women over 65 years old who self reported their physical activity across their lifespan (Middleton et al., 2010). Statistical analyses demonstrated that women who were active in their teenage years were less likely to experience cognitive decline as older adults (Middleton et al., 2010). Additionally, if they were inactive during their teenage years and then became active later in life, then this chance also decreased but not significantly. However, the participants' level of physical activity in older adulthood was not significantly associated with their chance of cognitive impairment in older adulthood (Middleton et al., 2010). This study conflicts with other research that claims

that exercise intervention in sedentary older adults improves cognition (Colcombe et al., 2003). However, it is possible that the positive effects reported for sedentary older adults might only be present in those who were physically active earlier in life. It is also possible that exercise may be less effective for older adult women.

Different research has demonstrated that that the positive effects of exercise in older adult populations can occur quite quickly (Segal et al., 2012). For example, an acute exercise intervention had older adults bike for just six minutes at 70% of their maximum oxygen capacity level, and results demonstrated that both healthy older adults and older adults with MCI had enhanced past memories (Segal et al., 2012). Therefore, there may be therapeutic and positive benefits to consistent and long-term exercise if there are already benefits after just six minutes.

Despite the multitude of research that has demonstrated the benefits of exercise, only a small proportion of older adults engage in traditional exercise, so recent research has focused on the cognitive benefits of exergaming, which incorporates videogame play or virtual scenery to increase motivation for exercise (Anderson-Hanley et al., 2012; Bamidis et al., 2014; Chao, Scherer, & Montgomery, 2014; Maillot, Perrot, & Hartley, 2012). Exergaming is an important option to consider because of its potential to replicate the benefits of traditional exercise while keeping a high motivation because of its video game nature.

Evidence of the positive effects of exergaming is supported by a recent literature review that explored the use of Nintendo Wii exergames for older adults (Chao et al., 2015). Twenty-two studies were explored, with findings demonstrating that Wii exergames significantly improved physical functioning, decreased depressive symptoms, and improved

socialization and motivation to exercise (Chao et al., 2015). Thus, exergaming could not only have physical effects, but also cognitive effects on emotion and motivation. These mentioned benefits would enhance the quality of life for older adults, further suggesting that exergames might be a very good option for exercise interventions, especially because it is often difficult to motivate older adults to engage in physical exercise. These studies provide evidence that exergaming interventions are beneficial for older adult populations, but unfortunately do not give insight into whether they are necessarily better than traditional exercise interventions.

Fortunately, research has compared Nintendo Wii exergames to traditional exercise to assess whether an exergaming intervention would be more effective than a traditional exercise intervention (Maillot, Perrot, & Hartley, 2012). Those in the exergame group improved their game performance, overall physical functioning, executive functioning, and processing speed significantly over the study's time course when compared to the control group involved in traditional physical exercise (Maillot, Perrot, & Hartley, 2012). These findings suggest that exergaming might have benefits that exceed traditional exercise.

Additionally, another similar study that did not involve Nintendo Wii exergames compared exergaming to traditional exercise as well (Anderson-Hanley et al., 2012). The investigators studied the differences between stationary biking along a virtual path (called "cybercycling") verses stationary biking with no virtual path. Results provided that older adults that cyber cycled had superior cognitive functioning compared to those who completed traditional exercise, further demonstrating that exergaming may have an added benefit over conventional exercise (Anderson-Hanley et al, 2012).

Researching the effects of combining both cognitive and physical exercise is important because recent meta-analysis research has revealed that computerized cognitive

training alone does not significantly benefit older adult executive functioning (Lampit, Hallock &Valenzuela, 2014). In this meta-analysis, 52 studies were assessed that included any computerized tasks or video games with a cognitive component (Lampit, Hallock &Valenzuela, 2014). Because so many studies were included, these findings strongly suggest that mental training alone might not have a significant enough benefit for clinicians to encourage older adults to engage in these mental exercises. However, other evidence has suggested that cognitive training, specifically cognitive computer tasks, do have cognitive benefits for other adults, thereby creating a need for additional research that will provide further evidence for the efficacy of mental exercise interventions (Corbett et al., 2015).

Literature on Exercise, Exergaming, and Plasticity in Older Adults:

However, in the effort to prevent and delay cognitive impairment, other research has investigated neuronal mechanisms behind the benefits reported after exergaming and traditional exercise interventions (Bamidis et al., 2014; Hotting & Roder, 2012; Voss et al., 2010). For instance, many studies have explored both humans and animals to assess the effect of exercise on cognition and neuronal plasticity, or the ability for the human brain to change and adapt (Bamidis et al., 2014; Hotting & Roder, 2012). Neuronal plasticity is important for older adults because it allows them to be able to take on new and challenging tasks. A recent review that investigated studies that conducted exercise interventions with adults suggested that exercise might have the ability to trigger processes that may increase neuroplasticity (Hotting & Roder, 2012). The researchers also noted that some of the studies explored demonstrated that combing physical and cognitive exercise could enhance both physical and mental outcomes. The researchers also reported that in order to have the

neuronal benefits, a person must increase the exercise intensity and maintain it (Hotting & Roder, 2012).

Other research has explored the possible neuronal effects of combining mental and physical exercise in older adults (Bamidis et al., 2014). For instance, one study stated that it is possible that connections between neurons, and not loss of neurons, are the reason for cognitive deficits (Bamidis et al., 2014). Yet, if neuronal processes are plastic, then these neuronal connections might have the ability to be more efficient if structured, intense exercise training is given, which might even lead to improvement in areas separate from the cognitive tasks at hand (Bamidis et al., 2014).

Multiple studies have shown that even the adult brain has the ability to adapt via neurogenesis when given new and challenging physical or mental demands (As referenced in Bamidis et al., 2014). However, global connectivity among brain regions, which allows the brain to function more efficiently, declines with age (As referenced in Bamidis et al., 2014). Therefore, an exergaming intervention might potentially help older adults regain this global connectivity because exergaming would likely be something new and challenging for an older adult. This connectivity is important because research has shown that those with MCI may be more likely to convert to AD if they exhibit decreased connectivity among brain regions (As referenced in Bamidis et al., 2014).

Additional research has explored the effect that exercise has on plasticity and connectivity in older adults (Voss et al., 2010). For instance, one study conducted a one-year walking exercise intervention in older adults to assess whether functional connectivity networks in the brain would change in advantageous ways (Voss et al., 2010). Results demonstrated that these exercise-induced increases in functional connectivity were associated

with better executive functioning (Voss et al., 2010). However, we only know that these two things are associated. The neurobiological mechanism by which this occurs is still unclear. Therefore, research is needed to further clarify these mechanisms, which may be through increases in biomarkers such as Brain-Derived Neurotrophic Factor (BDNF), Insulin-Like Growth Factor 1, and Cortisol.

Literature on Brain-Derived Neurotrophic Factor

One neurobiological mechanism that may be mediating the relationship between exercise and increases in cognition is Brain Derived Neurotrophic Factor (BDNF; Coelho et al., 2013; Leckie et al., 2014; Szuhany, Bugatti & Otto, 2014; Vaughan et al., 2014). BDNF is a neurotrophin, which is a substance in the brain that maintains the growth and survival of neurons. One recent meta-analysis assessed 29 studies where BDNF levels were measured during either single bout or long-term exercise interventions for adults of all ages (Szuhany, Bugatti & Otto, 2014). The analysis of these studies showed that there were moderate increases in BDNF after single bouts of exercising, but significantly larger increases post-exercising when participants were exercising regularly. In contrast, when participants were at rest, BDNF levels for long-term exercise interventions were only marginally higher than BDNF levels for single bout exercise studies (Szuhany, Bugatti, &Otto, 2014). The researchers also found that the effect of exercise on BDNF levels was not as profound in females (Szuhany, Bugatti, &Otto, 2014). This meta-analysis provides that there is fairly strong evidence that BDNF levels might increase after exercise, and that these increases may be more significant if a person is exercising regularly.

BDNF levels have been linked with memory impairment as well (Bekinschtein, Cammarota & Medina, 2014; Erickson, Miller, & Roekcklein, 2012). For instance, BDNF

protein levels have been associated with hippocampal atrophy (Erickson, Miller, & Roekcklein, 2012). The hippocampus is one of the main brain areas involved in memory, and one of the predominant explanations for hippocampal atrophy in the aging population is a single nucleotide polymorphism on the BDNF gene (Erickson, Miller, & Roekcklein, 2012). This means that there is one misplaced amino acid on this gene. Decreases in autobiographical memory, or past memories about oneself, have been associated with this polymorphism (Erickson, Miller, & Roekcklein, 2012). Additionally, research has suggested that lower BDNF levels are associated with AD, also lending the possible explanation that lower BDNF levels may be a result of neurons dying (Erikson, Miller, & Roecklein, 2012).

Overall, research has demonstrated that lower levels of BDNF might be related to problems with hippocampal functioning and therefore memory problems in aging populations (Erickson, Miller & Roecklein, 2012). Yet, exercise can potentially increase BDNF levels and reduce hippocampal atrophy (Erickson, Miller & Roecklein, 2012). Research on both humans and animals has shown that when BDNF is increased during aerobic exercise, hippocampal atrophy is decreased, and memory and symptoms of depression improve (Erikson, Miller & Roecklein, 2012). This makes exercise interventions an appealing option for both healthy older adults as well as older adults with MCI or AD.

This previously mentioned BDNF polymorphism has also been associated with mental illnesses such as anxiety (Chen et al., 2006). For instance, when mice were genetically altered to have this polymorphism, they had defective secretion of BDNF from their neurons (Chen et al., 2006). Also, when mice with the homozygous phenotype for this gene were placed under high stress situations, they had more anxiety-related behaviors than those who were not homozygous for this polymorphism. These findings suggest that this

mutation in the BDNF gene might be related to anxiety disorders because of its potential effect on the genetic predisposition of anxiety behaviors (Chen et al., 2006).

Additional research has explored the relationship between BDNF levels, stress, and anxiety (Suliman, Hemmings & Seedat, 2013). One meta-analysis revealed that BDNF was significantly lower in those with anxiety disorders, but that this effect was dependent on the type of anxiety disorder as well as the source of BDNF protein (Suliman, Hemmings, & Seedat, 2013). BDNF is an important biomarker to investigate because it is believed that increases in BDNF can counteract the negative effects of stress hormones on hippocampus volume. This makes low levels of BDNF particularly troublesome in a person with anxiety because if his or her BDNF proteins cannot help reduce the stress hormones that come with these anxious feelings, this may result in reduced hippocampus volume and cognitive functioning (Suliman, Hemmings & Seedat, 2013). If we can increase BDNF through exercise, then this could be a potential way to counteract these deleterious effects, which may or may not be especially effective for those with anxiety.

The relationship between BDNF and exercise has been explored in non-clinical older adult populations as well (Coelho et al., 2013; Leckie et al., 2014; Ruiz et al., 2015; Vaughan et al., 2014). For example, one recent review explored studies that investigated the effects of physical exercise on peripheral BDNF levels in elderly populations (Coelho et al., 2013). The majority of the studies assessed found significantly higher BDNF levels during exercise. The exercise protocols varied from acute exercise to long-term exercise, and had different aerobic and strength training paradigms. The researchers could not provide a definite recommendation as to what exercise would be most beneficial, but posited that moderate physical activity would be the most likely to help increase peripheral BDNF levels (Coelho et

al., 2013). Therefore, more research is needed in this area to further explain what type exercise would be most beneficial.

Fortunately, a different study implemented a 1-year aerobic exercise intervention for older adults to assess its effects on BDNF levels (Leckie et al., 2014). The researchers suggested that BDNF might be mediating increases in executive functioning after aerobic exercise interventions (Leckie et al., 2014). This study had participants in a moderate-intensity walking intervention with a stretching control group. Results demonstrated that serum BDNF mediated the increased accuracy in task switching (an executive functioning task), but that these changes were only significant for those over the age of 71. Additionally, further statistical analyses demonstrated that BDNF only increased in the walking group for those over 65 years old (Leckie et al., 2014). These findings suggest that BDNF may only be related to increases in cognition in those that are over 65 years old. Interestingly, a different study found that an eight-week exercise intervention did not have effects on either cognition or serum BDNF for those who were above 90 years old (Ruiz et al., 2015). This suggests that exercise interventions may only help cognitive outcomes in an older-adult age group of around 65-90.

A different study conducted a 16-week exercise intervention with only women that underwent a cardiovascular, strength, and motor fitness training program (Vaughan et al., 2014). Those who completed the intervention performed significantly better on measures of executive functioning such as Trail-making and Stroop, and also had increases in plasma BDNF (Vaughan et al., 2014). Because BDNF is known to be involved in neurogenesis and plasticity, these researchers also suggested that BDNF might be the mechanism by which these increases in executive functioning were occurring (Vaughan et al., 2014). This research

provides evidence that BDNF might mediate increases in cognition in older women who are exercising, but contrasts research that indicates that exercise intervention might not be as effective for women (Colcombe et al., 2003).

Additional research has investigated the role of BDNF in exercise-induced plasticity in older adult populations (Voss et al., 2013). One study had older adult participants undergo a one-year aerobic exercise intervention and found that BDNF did not significantly change across the one-year intervention (Voss et al., 2013). However, the researchers did find increased functional connectivity between brain regions that was mediated by changes in BDNF (Voss et al., 2013). Therefore, the changes in BDNF that occur following a one-year aerobic exercise intervention might be able to induce functional connectivity and therefore enhanced brain functioning in older adults.

BDNF is also a particularly important neurotrophin to explore because research has suggested that it is one of the key players in learning and memory, particularly for long-term memory storage (Bekinschtein et al., 2008; Bekinschtein, Cammarota & Medina, 2014). Long-term memory is especially significant to preserve in older adults because the ability to form long-term memories declines with normal aging (Bekinschtein et al., 2008). Thus, biomarkers like BDNF and other neurotrophins are an important option to explore because they can help us assess healthy aging. A recent review defined one of the hallmarks of healthy aging as cognitive functioning, which can be divided into memory, processing speed, and executive functioning (Lara et al., 2015). Therefore, it is the hope that assessing biomarkers like BDNF might give insight into why there are increases or decreases in these areas of cognitive functioning in the aging population.

Literature on IGF1

However, BDNF is not the only neurotrophin that might have a role in healthy aging and cognitive functioning in older adults. Research has suggested that both BDNF as well as insulin-like growth factor 1 (IGF1), also a neurotrophin involved in the growth and survival of neurons, have the potential to induce plasticity enhancing pathways (Lista & Sorrentino, 2010). These increases in plasticity could be mediating the increases in cognitive functioning that are observed after exercise intervention (Lista & Sorrentino, 2010). As reported in Lista & Sorrentino (2010), many studies have reported that BDNF and IGF1 among others might be the mechanism behind the positive benefits of exercise that prevent cognitive decline because of these neurotrophins' role in neurogenesis (Lista & Sorrentino, 2010). Yet, these mechanisms need to be further explored to specifically confirm their responsibility in how exercise might prevent cognitive decline (Lista & Sorrentino, 2010). Therefore, IGF1 appears to be critical to explore in older-adult exercise interventions.

Recent research has explored these neurotrophin's relationship to aerobic exercise (Maass et al., 2016). For example, one recent three-month exercise intervention assessed both IGF1 and BDNF in older adults that were assigned to either an aerobic exercise or stretching group (Maass et al., 2016). The researchers reported that IGF1 changes were positively correlated with hippocampal volume changes that they considered to be involved in the hippocampus-dependent memory changes (Maass et al., 2016). Yet, these changes occurred independently of exercise. There were no associations between the aerobic exercise group and the control group when considering increases in IGF1 or BDNF (Maass et al., 2016). These results indicate that there is conflicting evidence as to whether exercise intervention itself would help improve memory in older adults, and whether or not a three-month exercise intervention could increase neurotrophic factors IGF1 and BDNF. However, because other studies have

shown that there are differences between exergaming and traditional exercise, it is possible that IGF1 and BDNF may have different outcomes in a neuroexergaming intervention (Anderson-Hanley et al., 2012).

Other studies have specifically explored IGF1's relationship to cognition (Aleman & Aleman-Torres, 2009). One meta-analysis investigated studies that assessed the relationship between IGF1 and cognition in human participants throughout their lifespan (Aleman &Aleman-Torres, 2009). Eleven of the 13 studies assessed found positive associations between cognition and IGF1 for both men and women, eight of which used older adult participants (Aleman & Aleman-Torres, 2009). The researchers reported that previous work has demonstrated that serum IGF-1 is a significant player in neuronal growth, survival, and function throughout the lifespan and therefore may be an important biomarker to assess in cognitive impairment that is associated with natural or pathological aging (Aleman & Torres-Aleman, 2009). Results also suggested that IGF1 could be the mechanism by which exercise acts in a neuroprotective way, which is supplemented by research demonstrating that mice with IGF1 deficiencies do not have increased cognition after exercise (Trejo et al., 2008). This study suggests that IGF1 may be related to increases in cognition, but only provides limited information on the role of exercise.

However, many other studies have explored how IGF1 could mediate the effects of exercise on cognition (Brown, Peiffer, & Martins, 2013). One literature review discussed whether physical exercise could decrease risk of AD (Brown, Peiffer, & Martins, 2013). Like other research, they discovered there might be a certain threshold of intensity where older adults obtain more benefit from exercising (Coelho et al., 2013; Hotting and Roder, 2012). The researchers explored biomarkers associated with AD as well, finding that decreased

levels of IGF-1 expression were associated with AD neuropathology (Brown, Peiffer, & Martins, 2013). Thus, results suggested that IGF1 might be the mechanism behind physical activity's improvement of AD pathology (Brown, Peiffer, &Martins, 2013). Animal research added to these findings by demonstrating that infusion of IGF1 into the brains of exercising adult rats increased hippocampal neurogenesis levels while blocking IGF1 had the opposite effect (Brown, Peiffer, &Martins, 2013; Lista et al., 2010). The researchers also proposed a possible synergistic relationship between IGF1 and BDNF signaling because research has shown that blocking IGF-1 prevents the induction of BDNF in the hippocampus following exercise (Brown, Peiffer, &Martins, 2013). Therefore, it seems that increases in both of these neurotrophic factors during exercise could prevent AD.

Further evidence for IGF1's role in cognition and aging has been explored in longitudinal research. One recent study explored the association between cognition and serum IGF1 across an 8-year time span with participants 40-80 years old (Tumati et al, 2016). Results demonstrated that those in the top quintile of IGF-1 had lower levels of cognition at 8-year follow up (Tumati et al., 2016). This result contrasts others, which generally demonstrate that increases in IGF1 are associated with increases in cognitive functioning (Brown, Peiffer, & Martins, 2013; Lista & Sorrentino, 2010; Aleman & Aleman-Torres, 2009). This study also showed that the association between IGF1 and cognition persists for older adults. These findings overall suggest that high IGF-1 levels are associated with poorer long-term cognition (Tumati et al., 2016). Therefore, it may be that the amount of IGF1 needed for optimal cognitive functioning is a bell curve, where both too much and too little are associated with poorer cognition. Similar results have been reported elsewhere, such that both high and low IGF1 have been related to increased mortality rates (Lara et al., 2015).

Literature on Cortisol

In contrast, research has indicated that lower amounts of cortisol are associated with optimal cognitive functioning (Hayes et al., 2015; Lara et al., 2013). Cortisol is a significant biomarker to study in older adults because it has been proposed as a biomarker of healthy aging (Lara et al., 2015). For instance, one study explored the relationship of serum cortisol concentrations in participants with mild cognitive impairment, dementia, and a control group of cognitively healthy older adults (Lara et al., 2013). These serum cortisol concentrations were taken in the morning, and a DNA sample was taken in order to assess APOE genotypes in these groups because the APOE genotype has been associated with an increased risk of obtaining AD (Lara et al., 2013). Results demonstrated that serum cortisol concentration was significantly lower in the control group when compared to both the MCI and the dementia group, but no significant differences were found in serum cortisol levels between the MCI and the dementia group (Lara et al., 2013). In addition to this, the researchers did not find a significant relationship between the participants' levels of cortisol when compared to their APOE genotype (Lara et al., 2013) Therefore, increased concentrations of cortisol are related to both MCI and dementia but not APOE genotype, but further research must be done to fully assess the relationship between cortisol increases and AD (Lara et al., 2013).

Another study also investigated cortisol levels in relation to MCI and dementia (Popp et al., 2014). The researchers assessed whether plasma and cerebrospinal fluid (CSF) levels of cortisol were associated with the progression of MCI and AD (Popp et al., 2014). This hypothesis resulted from previous studies finding that increases in cortisol consistently appear in AD patients (Popp et al., 2014). Results demonstrated that participants with AD and MCI related to AD had significantly increased CSF cortisol concentrations when

compared to participants with MCI unrelated to AD as well as healthy older adults (Popp et al., 2014). These comparatively higher levels of CSF cortisol were associated with a faster progression of AD and therefore a faster progression of cognitive decline (Popp et al., 2014). Thus, these findings suggest that high cortisol in older adults are associated with declines in cognition functioning.

Additional research has demonstrated that cortisol may have a role in healthy aging (Geerlings et al., 2015). For instance, one study assessed both morning and evening cortisol levels in healthy older adults to investigate the relationship between cortisol levels, brain matter volumes, and cognition (Geerlings et al., 2015). The researchers found that older adults with higher cortisol in the evening had smaller total brain volume, especially gray matter volume, as well as deficits in many domains of cognitive functioning (Geerlings et al., 2015). In contrast, those with higher levels of morning cortisol had higher volumes of white matter as well as superior speed of processing and executive functioning capacities (Geerlings et al., 2015). These results demonstrate that high evening cortisol is associated with broader deficits in cognitive functioning whereas high morning cortisol is associated with better cognitive functioning in more specific areas associated with white matter volume (Geerlings et al., 2015). Thus, cortisol levels in older adults are associated with brain volume and level of cognitive functioning, but high levels of cortisol imply different things at different times of the day.

Other research has revealed that cortisol levels are associated with mental health in older adults (Hek et al., 2012). One study assessed whether older adults with anxiety disorders had different patterns of cortisol release than those without anxiety disorders (Hek et al., 2012). The researchers found that older adults with anxiety disorders had lower cortisol

awakening responses than those without anxiety disorders, suggesting that chronic anxiety might have led to abnormal cortisol release (Hek et al., 2012). Research on healthy older adults implies that these higher cortisol levels in the morning are beneficial to executive functioning, implying that older adults with anxiety may be especially at risk for cognitive deficit because of their lower levels of morning cortisol (Geerlings et al., 2012).

However, previous research has shown that we can change cortisol levels through aerobic exercise (Hayes et al., 2015). For instance, a meta-analysis of 21 studies involving acute bouts of aerobic exercise and measurements of salivary cortisol levels found that levels of salivary cortisol during aerobic exercise increased consistently (Hayes et al., 2015). However, this meta-analysis was done on adult participants, not specifically older adult participants, and did not have consistent time of day that cortisol was assessed (Hayes et al., 2015). This study demonstrates that cortisol can increase after aerobic exercise, but the varying time of day that these samples were taken means that these results should be taken with caution.

Yet, a different study exploring cortisol levels and exercise found slightly different results when exclusively exploring an older adult population (Heaney et al., 2013). The researchers took cortisol samples in the morning for all participants, and found that cortisol levels decreased immediately after exercise and 1 hour after exercise (Heaney et al., 2013). These cortisol levels should not have been affected by the increases in cortisol observed after waking, since the exercise occurred about three hours after the participant woke up (Heaney et al., 2013). Therefore, further research is needed to explore whether exercise for older adults could decrease cortisol levels that are associated with global deficits in cognitive functioning as well as gray matter volume (Geerlings et al., 2015). Cortisol is clearly a

critical hormone to explore when considering older adult cognition because cortisol levels have relationships with level of cognitive functioning, anxiety, aerobic exercise, as well as MCI and AD.

Expectations and Hypotheses:

The majority of the previous work that has focused on biomarkers of plasticity and cognition has not explored these biomarkers under the context of a neuroexergaming intervention. Thus, this current gap in the literature will be addressed by exploring BDNF, IGF1, and cortisol's relationship to executive functioning and memory measures in this three-month neuroexergaming intervention. This study will contribute to the gap in neuroexergaming literature and therefore make a necessary contribution to the field of healthy aging.

Based on previous research, it is expected that:

1. Executive functioning (EF) will improve over the 3-month intervention.

2. BDNF levels will increase over the 3-month intervention, and there will be positive correlations between change in BDNF and EF measures.

3. IGF1 levels will increase over the 3-month intervention and there will be positive correlations between change in IGF1 and EF measures.

4. Cortisol levels will decrease over the 3-month intervention and there will be negative correlations between change in cortisol and EF measures.

5. Scores on the Brunnel Mood Scale related to "Tension" and "Depression" will decrease.

METHODS

The current pilot study examined the interactive Physical and Cognitive Exercise System (iPACES™), a "neuroexergame" which synthesizes exergaming with mental exercises specifically designed to maximize cognitive benefits while exercising, which has been found to impact executive functioning following single bout use in the lab (Anderson-Hanley et al., 2016). The present study addresses barriers to longer-term exercise and takes this novel neuroexergame into the home by providing under-desk peddlers and tablets to run the Memory Lane™ exergame for participants to use. Participants pedal and use a controller to steer along a virtual bike path where a list of errand locations are presented, which they learn and recall when presented with forced choice/forks in the road. The mental challenge is amplified when participants complete the list of errands and have to retrace their pathway home, recalling the errand locations in reverse order.

The present quasi-experimental study with A-B design was approved by the Union College IRB, and all participants provided informed consent as well as Demographic, Exercise History, Physical Activity and Readiness self-reports. Participants in the study (n=31) were co-residing pairs and single older adults who were trained to use the iPACES 3-5x/week. Participants were recruited from Shaker Pointe Retirement Community, Schaffer Heights Retirement Community, and in the local Capital Region. Participants were excluded if they were below 50 years of age, could not read a computer screen, had inadequate hearing and speech to be tested, believed they could not pedal and under-desk elliptical, were already exercising at recommended levels (45 minutes of aerobic exercise 5-7x/week), or were not available for regular exercise participation for 3-5x/week for 14 weeks. Mean age was 76.1 years (SD = 10.4) and mean education was 16.6 years (SD = 2.5). There were 18 females and

13 males. At first, participants played game-only for two weeks, followed by 12 weeks of iPACES, with cognitive assessments before and after each of these two-week windows (these short-term comparisons are reported elsewhere; VanBrakle, 2015). Participants were then encouraged to continue using the iPACES to complete longer-term exercise of three months. Roughly half (N=17) completed the full trial, which is typical of older adult exercise protocols. Of these long-term exercisers, saliva samples for pre, mid (6 week) and 3 month evaluations were available for seven participants. The cognitive assessments focused on executive function and included ratio scores for Stroop (A/C), Digit Span (B/F), and Color Trails (1/2). These three measures of executive functioning were given at all five time points, which where baseline, two weeks, four weeks, six weeks, and fourteen weeks. The Brunnel Mood Scale was given at baseline, 2-week, and 14-week time points to assess changes in mood across the intervention. Saliva samples were collected by passive drool method and processed by enzyme-linked immunosorbent assays (ELISA) probing for BDNF, IGF1, and cortisol. Pearson correlations were computed using the post-pre change scores for cognitive measures and biomarkers to compare differences from baseline to the 6-week and 14-week time points.

RESULTS

Results demonstrated that among seven completers who exercised using the iPACES™ Memory Lane™ exergame, a moderate positive correlation was found between IGF1 and executive function (Digits Backwards ratio) after 6 weeks and 14 weeks (r = .76 and .45, respectively). Similarly, at 6 weeks, there was a moderate positive correlation between BDNF and executive function (Stroop ratio; r = .47), while a moderate negative correlation was found between cortisol and executive function (Stroop ratio; r = -.43). Differences in scores on the Brunnel Mood Scale were not significant, as all but one participant rated their negative moods as zero at all three time points (Table 1). Of the seven completers with saliva samples available, executive function increased between baseline and six weeks for Color Trails, and executive function scores improved from baseline to fourteen weeks for Stroop C and Digit Span Backward (Table 3). On average, participants' scores on the Montreal Cognitive Assessment (MoCA) increased 0.43 points out of 30 possible points (Table 3). Participants also peddled the under-desk elliptical an average of 21.57 times across the three-month intervention.

DISCUSSION

The current study explored how a 14-week physical and cognitive exercise intervention could affect cognitive outcomes and salivary biomarkers BDNF, IGF1, and cortisol. Our hypotheses were partially confirmed. BDNF, IGF1, and cortisol all had moderate positive correlations with at least one measure of executive functioning. However, moderate positive correlations were not revealed for all three measures of executive functioning for all three of these biomarkers. Yet, overall executive functioning as well as score on the Montreal Cognitive Assessment increased in the seven participants over the 14 week intervention, thereby confirming our hypothesis that cognition would increase after the three-month paradigm. Our hypothesis that negative mood scores would decrease on the Brunnel Mood Scale was not confirmed. Scores stayed the same for the seven participants across the intervention. Assessing mood in relation to the salivary biomarkers BDNF, IGF1, and cortisol along with the cognitive measures was an original idea that did not work out. The small sample size available for biomarker processing as well as our normative population did not allow for this idea to be pursued further.

The results of the current study both mirrored and contrasted similar literature. For instance, research has demonstrated that exergaming can improve cognition (Anderson-Hanley et al., 2012). Participants in the current study had increases in cognition across the intervention as well (Table 3). Additionally, the moderate positive correlations for IGF1 and digit span backwards for both the 6-week and 14-week time points paralleled research that has shown increases in executive functioning and IGF1 after an exercise intervention in healthy older adults (Bellar et al., 2011). For BDNF, the current study's results add to

previous research indicating that BDNF might be mediating the increases in executive functioning that occur after an exercise intervention (Leckie et al., 2014).

Our three measures of executive functioning, Color Trails, Stroop, and Digit Span Backward increased and decreased across the three-month intervention (Table 3). Both Color Trails and Digit Span Backward improved across the 14-week intervention while Stroop scores improved at six weeks but went back to scores similar to baseline at 14 weeks. This contrasts a recent review demonstrating that mental and physical exercise in tandem should have beneficial effects on cognition (Zhu et al., 2016). However, research has also noted that both participant age and whether or not the exercise was done in a group or private setting could moderate the effects of exercise on cognition (Zhu et al., 2016). Thus, the high average age (76.1) as well as the private setting that this study's intervention was conducted in may have affected the increases in executive functioning across the study.

This pilot research suggests that change in cognitive function over a period of exergaming is related to salivary biomarkers cortisol, BDNF, and IGF1. These data provide preliminary evidence that could bolster recommendations by clinicians who encourage older adults to partake in either exergames or both physical and cognitive exercises to prevent cognitive decline and promote healthy aging. Yet, it must be noted that the data between salivary biomarkers and measures of cognition are only correlational: we do not know if higher IGF1 and BDNF or lower cortisol are causing these increases in cognition. However, these neurotrophins and hormone levels could only be experimentally manipulated in animal research, which is difficult to generalize to a human population.

Additionally, the analysis of these biomarkers was problematic because of our small sample size. For instance, one outlier in a small sample size could result in a significant or

non-significant correlation between the biomarker and measure of executive functioning. Therefore, our small sample size could have made it both more or less likely that correlations between biomarkers and executive functioning would occur. Additionally, we did not exclude the current study to only healthy older adults. Thus, our sample could have had either diagnosed or undiagnosed older adults with MCI or dementia. These differences between participants could have affected our results with such a small sample.

Additionally, our results for cortisol may have been limited by the fact that cortisol was not taken at a consistent time of day. Participants were evaluated when they were available, which ranged from 9am to 4pm in the afternoon. Participants could not always meet at the same time for every evaluation, meaning some of these saliva samples were taken at different times of the day for the same participant. Thus, natural changes in cortisol that occur throughout the day could have affected the current results, because research has noted that higher cortisol is associated with better cognitive functioning in the morning and lower cognitive functioning in the evening (Geerlings et al., 2015). However, the majority of participant evaluations were in the afternoon, providing that participant levels of cortisol should have generally decreased, which would indicate better cognitive functioning across the intervention (Geerlings et al., 2015).

It is also possible that the levels of BDNF, IGF1 and cortisol in our saliva samples were too low for the assays to detect. Recent literature has proposed this problem with human saliva samples (Whitcomb & Schisterman, 2008). Whitcomb and Schisterman (2008) propose that some of these biomarkers might not have been detected because the limit of detection on the statistical programming used might have been too high. If the limit of detection were made lower, then it is possible that more results could have been obtained for

wells where no cortisol, BDNF, or IGF1 was found. This could have affected our change scores, since numbers that were reported as zero or close to zero might be higher if the assay had a higher sensitivity and lower level of detection. Unfortunately, the level of detection cannot be changed after the samples have been processed. However, future research can try using a lower level of detection when running human BDNF and IGF1 saliva samples. Yet, lowering the level of detection also runs the risk of the assay being unable to detect the trace amounts of hormone or neurotrophin present.

The amount of BDNF, IGF1, and cortisol found in the saliva samples in the current study were fairly low (Table 4). However, low concentrations of hormones and proteins can be common when processing saliva samples (Whitcomb & Schisterman, 2008). Additionally, the current study used kits that were able to process saliva, but were created for blood serum samples. Therefore, the standards that were used for the BDNF and IGF1 analyses may have skewed our results. This was not the case with our cortisol analyses, which were done on assays that were meant for saliva processing.

The assays used to process BDNF and IGF1 were made for blood serum samples because this is what the majority of researchers use when assessing these neurotrophins (Heaney et al., 2012; Walsh et al., 2016; Ziegenhorn et al., 2007). Thus, there is limited literature on levels of BDNF and IGF1 in saliva samples of older adults, making it difficult to know if the protein levels obtained in the current study were abnormally low or on target with what other research has found. However, one recent paper reported that control participants had an average of approximately 13 nmol/L of salivary cortisol at 8am and approximately 4 nmol/L of salivary cortisol at 10pm (Correa et al., 2015). The average age of these controls was 58.29 +/- 3.16 years old (Correa et al., 2015). These reported variations provide that the

cortisol assessed in the current study might not have significantly changed across the intervention because the samples were taken at different times of the day. Therefore, cortisol levels may have been decreasing across the intervention for our participants, but our results make it difficult to definitively know this because of the variation in the time that these samples were taken.

The iPACES pilot study had many strengths that should be repeated in future work. First off, the tablet and peddler were easily portable and could be placed in the homes of the co-residing pairs. This made it easier for the pair to exercise because they did not have to transport themselves to do so. However, on average, participants peddled less than recommended levels of at least 3 times a week for 14 weeks. Instead, participants were generally peddling around two times per week. Thus, future work should investigate different ways to motivate participants to exercise at recommended levels. It is possible that participants in the current study were not exercising at recommended levels because they did not want to play the Memory Lane™ game when they were exercising. Yet, the Memory Lane™ game that was programmed onto the tablet had the nature of a video game, which should have made the participants more interested in the study because it was different from conventional exercise. Additionally, the within subjects design was especially helpful for the pilot trial because only seventeen completed, allowing for better statistical analyses.

However, despite these strengths, the iPACES pilot study had a few limitations. First off, the drop out rate was roughly half of participants. There were a few reported reasons for this. For instance, for a few participants, the tablet and peddler were in a common area where they reported that it was too loud for them to focus on the memory game. Other participants realized that they could not commit to exercising 3-5 times a week after trying to do it the

first week or two of the study. Lastly, some older adults thought the tablet was too difficult to use, and therefore no longer wanted to be enrolled.

Despite these limitations, the pilot study's successes provide that work similar to this should still be done in the future. Future work should include larger cohorts and preferably have a game interface that is easier for an older adult to use. Additionally, future studies should focus on making the Memory Lane™ game an app that people could download on their smart phones or tablets so that they could use an interface or device that they are already comfortable using. Participants might also be more motivated during testing if the neuropsychological tests were given through the same tablet that had the game one it.

Future studies could also explore other biomarkers that may mediate the relationship between exergaming interventions and increases in cognitive functioning. For instance, recent research has explored how physical and mental training paradigms affect brain network configurations (Foster, 2015). There is also research on why exercise may lead to neural plasticity and neurogenesis, which is something important to maintain in an aging population where these two processes are slowing down (Kempermann et al., 2010).

Overall, the current study contributes to the small amount of literature there is in the field of exergaming, cognition, and biomarkers. It is the hope that future research will further clarify the roles of BDNF, IGF1 and cortisol in combined physical and cognitive exercise interventions. Hopefully these findings will allow physicians to provide clearer recommendations to their older adult patients to promote healthy aging as well as delay and prevention of cognitive decline.

REFERENCES

Aleman, A., & Torres-Alemán, I. (2009). Circulating insulin-like growth factor I and cognitive function: Neuromodulation throughout the lifespan. *Progress in Neurobiology*, *89*(3), 256–265. http://doi.org/10.1016/j.pneurobio.2009.07.008

Anderson-Hanley, C., Arciero, P., Brickman, A., Nimon, J., Okuma, N., Westen, S., . . . Zimmerman, E. (2012). Exergaming and Older Adult Cognition. *American Journal of Preventive Medicine,* 109-119.

Bamidis, P. D., Vivas, A. B., Styliadis, C., Frantzidis, C., Klados, M., Schlee, W., … Papageorgiou, S. G. (2014). A review of physical and cognitive interventions in aging. *Neuroscience and Biobehavioral Reviews*, *44*, 206–220. http://doi.org/10.1016/j.neubiorev.2014.03.019

Bekinschtein, P., Cammarota, M., Katche, C., Slipczuk, L., Rossato, J. I., Goldin, A., … Medina, J. H. (2008). BDNF is essential to promote persistence of long-term memory storage. *Proceedings of the National Academy of Sciences of the United States of America*, *105*(7), 2711–6. http://doi.org/10.1073/pnas.0711863105

Bekinschtein, P., Cammarota, M., & Medina, J. H. (2014). BDNF and memory processing. *Neuropharmacology*, *76*(PART C), 677–683. http://doi.org/10.1016/j.neuropharm.2013.04.024

Bellar, D., Glickman, E. L., Juvancic-Heltzel, J., & Gunstad, J. (2011). Serum insulin like growth factor-1 is associated with working memory, executive function and selective attention in a sample of healthy, fit older adults. *Neuroscience*, *178*, 133–137. http://doi.org/10.1016/j.neuroscience.2010.12.023

Brown, B. M., Peiffer, J. J., & Martins, R. N. (2013). Multiple effects of physical activity on molecular and cognitive signs of brain aging: can exercise slow neurodegeneration and delay Alzheimer's disease? *Molecular Psychiatry*, *18*(8), 864–74. http://doi.org/10.1038/mp.2012.162

Bunce, D., Batterham, P., Mackinnon, A., & Christensen, H. (2012). Depression, anxiety and cognition in community-dwelling adults aged 70 years and over. *Journal of Psychiatric Research, 46*(12), 1662-1666. doi:10.1016/j.jpsychires.2012.08.023

Burton, C., Campbell, P., Jordan, K., Strauss, V., & Mallen, C. (2012). The association of anxiety and depression with future dementia diagnosis: A case-control study in primary care. *Family Practice,* (30), 25-30. doi:10.1093/fampra/cms044

Chao, Y.-Y., Scherer, Y. K., & Montgomery, C. A. (2014). Effects of Using Nintendo Wii™ Exergames in Older Adults: A Review of the Literature. *Journal of Aging and Health*, *27*(3), 379–402. http://doi.org/10.1177/0898264314551171

Coelho, F. G. de M., Gobbi, S., Andreatto, C. A. A., Corazza, D. I., Pedroso, R. V., & Santos-Galduróz, R. F. (2013). Physical exercise modulates peripheral levels of brain-derived neurotrophic factor (BDNF): A systematic review of experimental studies in the elderly. *Archives of Gerontology and Geriatrics*, *56*(1), 10–15. http://doi.org/10.1016/j.archger.2012.06.003

Colcombe, S., & Kramer, A. F. (2003). Fitness effects on the cognitive function of older adults. *Psychological Science*, *14*, 125. http://doi.org/10.1111/1467-9280.t01-1-01430

Corbett, A., Owen, A., Hampshire, A., Grahn, J., Stenton, R., Dajani, S., Burns, A., Howard, R., Williams, N., Williams, G., Ballard, C. (2015). The Effect of an Online Cognitive Training Package in Healthy Older Adults: An Online Randomized Controlled Trial, *Journal of the American Medical Directors Association, 16, Issue 11*(1), 990-997.

Erickson, K. I., Miller, D. L., & Roecklein, K. a. (2012). The Aging Hippocampus: Interactions between Exercise, Depression, and BDNF. *The Neuroscientist*, *18*(1), 82–97. http://doi.org/10.1177/1073858410397054

Foster, P. P. (2015). Role of physical and mental training in brain network configuration. *Frontiers in Aging Neuroscience*, *7*(JUN), 1–13. http://doi.org/10.3389/fnagi.2015.00117

Gallacher, J., Bayer, A., Fish, M., Pickering, J., Pedro, S., Dunstan, F., . . . Ben-Shlomo, Y. (2009). Does Anxiety Affect Risk of Dementia? Findings From the Caerphilly Prospective Study. *Psychosomatic Medicine, 71*(6), 659-666. doi:10.1097/PSY.0b013e3181a6177c

Gallagher, D., Coen, R., Kilroy, D., Belinski, K., Bruce, I., Coakley, D., . . . Lawlor, B. (2011). Anxiety and behavioural disturbance as markers of prodromal Alzheimer's disease in patients with mild cognitive impairment. *Int. J. Geriat. Psychiatry International Journal of Geriatric Psychiatry, 26*(2), 166-172. doi:10.1002/gps.25

Hayes, L. D., Grace, F. M., Baker, J. S., & Sculthorpe, N. (2015). Exercise-Induced Responses in Salivary Testosterone, Cortisol, and Their Ratios in Men: A Meta-Analysis. *Sports Medicine*, *45*(5), 713–726. http://doi.org/10.1007/s40279-015-0306-y

Heaney, J. L. J., Carroll, D., & Phillips, A. C. (2013). DHEA, DHEA-S and cortisol responses to acute exercise in older adults in relation to exercise training status and sex. *Age*, *35*(2), 395–405. http://doi.org/10.1007/s11357-011-9345-y

Hek, K., Direk, N., Newson, R. S., Hofman, A., Hoogendijk, W. J. G., Mulder, C. L., & Tiemeier, H. (2013). Anxiety disorders and salivary cortisol levels in older adults: A population-based study. *Psychoneuroendocrinology*, *38*(2), 300–305. http://doi.org/10.1016/j.psyneuen.2012.06.006

Hötting, K., & Röder, B. (2013). Beneficial effects of physical exercise on neuroplasticity and cognition. *Neuroscience and Biobehavioral Reviews*, *37*(9), 2243–2257. http://doi.org/10.1016/j.neubiorev.2013.04.005

Kempermann, G., Fabel, K., Ehninger, D., Babu, H., Leal-Galicia, P., Garthe, A., & Wolf, S. A. (2010). Why and how physical activity promotes experience-induced brain plasticity. *Frontiers in Neuroscience*, *4*(DEC), 1–9. http://doi.org/10.3389/fnins.2010.00189

Leckie, R. L., Oberlin, L. E., Voss, M. W., Prakash, R. S., Szabo-Reed, A., Chaddock-Heyman, L., … Erickson, K. I. (2014). BDNF mediates improvements in executive function following a 1-year exercise intervention. *Frontiers in Human Neuroscience*, *8*(December), 1–12. http://doi.org/10.3389/fnhum.2014.00985

Lista, I., & Sorrentino, G. (2010). Biological mechanisms of physical activity in preventing cognitive decline. *Cellular and Molecular Neurobiology*, *30*(4), 493–503. http://doi.org/10.1007/s10571-009-9488-x

Lampit, A., Hallock, H., & Valenzuela, M. (2014). Computerized Cognitive Training in Cognitively Healthy Older Adults: A Systematic Review and Meta-Analysis of Effect Modifiers. *PLoS Medicine*, *11*(11). https://doi.org/10.1371/journal.pmed.1001756

Lara, V. P., Caramelli, P., Teixeira, A. L., Barbosa, M. T., Carmona, K. C., Carvalho, M. G., … Gomes, K. B. (2013). High cortisol levels are associated with cognitive impairment no-dementia (CIND) and dementia. *Clinica Chimica Acta*, *423*, 18–22. http://doi.org/10.1016/j.cca.2013.04.013

Lara, J., Cooper, R., Nissan, J., Ginty, A. T., Khaw, K.-T., Deary, I. J., … Mathers, J. C. (2015). A proposed panel of biomarkers of healthy ageing. *BMC Medicine*, *13*(1), 222. http://doi.org/10.1186/s12916-015-0470-9

Lupien, S. J., de Leon, M., de Santi, S., Convit, A., Tarshish, C., Nair, N. P., … Meaney, M. J. (1998). Cortisol levels during human aging predict hippocampal atrophy and memory deficits. *Nature Neuroscience*, *1*(1), 69–73. http://doi.org/10.1038/271

Maass, A., Düzel, S., Brigadski, T., Goerke, M., Becke, A., Sobieray, U., … Düzel, E. (2016). Relationships of peripheral IGF-1, VEGF and BDNF levels to exercise-related changes in memory, hippocampal perfusion and volumes in older adults. *NeuroImage*, *131*, 142–154. http://doi.org/10.1016/j.neuroimage.2015.10.084

Maillot, P., Perrot, A., & Hartley, A. (2012). Effects of interactive physical-activity video-game training on physical and cognitive function in older adults. *Psychology and Aging*, *27*(3), 589–600. http://doi.org/10.1037/a0026268

Middleton, L., Barnes, D., Lui, L., & Yaffe, K. (2010). Physical Activity Over the Life Course and Its Association with Cognitive Performance and Impairment in Old Age.

Journal of the American Geriatrics Society, 58(7), 1322-1326. doi:10.1111/j.1532-5415.2010.02903.x

Popp, J., Wolfsgruber, S., Heuser, I., Peters, O., Hüll, M., Schröder, J., … Jessen, F. (2015). Cerebrospinal fluid cortisol and clinical disease progression in MCI and dementia of Alzheimer's type. *Neurobiology of Aging, 36*(2), 601–607. http://doi.org/10.1016/j.neurobiolaging.2014.10.031

Prince, M., Guerchet, M., Prima, M. (2015). The epidemiology and impact of dementia, current state and future trends. Retrieved from http://www.who.int/mental_health/neurology/dementia/dementia_thematicbrief_epidemiology.pdf

Roig, M., Nordbrandt, S., Geertsen, S. S., & Nielsen, J. B. (2013). The effects of cardiovascular exercise on human memory: A review with meta-analysis. *Neuroscience and Biobehavioral Reviews*, *37*(8), 1645–1666. http://doi.org/10.1016/j.neubiorev.2013.06.012

Ruiz, J. R., Gil-Bea, F., Bustamante-Ara, N., Rodriguez-Rmo, G., Fiuzza-Lucces, C., Serra-Rexach, J. A., … Lucia, A. (2015). Resistance Training Does not have an E ff ect on Cognition or Related Serum Biomarkers in Nonagenarians : A Randomized Controlled Trial. *International Journal of Sports Medicine*, *36*, 54–60. http://doi.org/10.1055/s-0034-1375693

Segal, S., Cotman, C., & Cahill, L. (2012). NIH Public Access. *J Alzheimers Dis*, *32*(4), 1011–1018. http://doi.org/10.3233/JAD-2012-121078.Exercise-Induced

Suliman, S., Hemmings, S. M. J., & Seedat, S. (2013). Brain-Derived Neurotrophic Factor (BDNF) protein levels in anxiety disorders: systematic review and meta-regression analysis. *Frontiers in Integrative Neuroscience*, *7*(July), 55. http://doi.org/10.3389/fnint.2013.00055

Szuhany, K. L., Bugatti, M., & Otto, M. W. (2015). A meta-analytic review of the effects of exercise on brain-derived neurotrophic factor. *Journal of Psychiatric Research*, *60*, 56–64. http://doi.org/10.1016/j.jpsychires.2014.10.003

Trejo, J. L., LLorens-Martín, M. V., & Torres-Alemán, I. (2008). The effects of exercise on spatial learning and anxiety-like behavior are mediated by an IGF-I-dependent mechanism related to hippocampal neurogenesis. *Molecular and Cellular Neuroscience*, *37*(2), 402–411. http://doi.org/10.1016/j.mcn.2007.10.016

Tumati, S., Burger, H., Martens, S., van der Schouw, Y. T., & Aleman, A. (2016). Association between Cognition and Serum Insulin-Like Growth Factor-1 in Middle-Aged & Older Men: An 8 Year Follow-Up Study. *Plos One*, *11*(4), e0154450. http://doi.org/10.1371/journal.pone.0154450

"Types of Dementia." (2017). Retrived from http://www.alz.org/dementia/types-of-dementia.asp

van Uffelen, J., Chin, A., Paw, M., Hopman-Rock, M., & van Mechelen, W. (2008). The Effects of Exercise on Cognition in Older Adults With and Without Cognitive Decline: A Systematic Review. *Clinical Journal of Sport Medicine*, *18*(6), 486–500.

Vaughan, S., Wallis, M., Polit, D., Steele, M., Shum, D., & Morris, N. (2014). The effects of multimodal exercise on cognitive and physical functioning and brain-derived neurotrophic factor in older women: a randomised controlled trial. *Age and Ageing*, *43*(5), 623–629. http://doi.org/10.1093/ageing/afu010

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. *Frontiers in Aging Neuroscience*, *2*(AUG), 1–17. http://doi.org/10.3389/fnagi.2010.00032

Walsh, J. J., Scribbans, T. D., Bentley, R. F., Kellawan, J. M., Gurd, B., & Tschakovsky, M. E. (2016). Neurotrophic growth factor responses to lower body resistance training in older adults. *Applied Physiology Nutrition and Metabolism*, *41*(3), 315–323. https://doi.org/10.1139/apnm-2015-0410

Ziegenhorn, A. A., Schulte-Herbrüggen, O., Danker-Hopfe, H., Malbranc, M., Hartung, H. D., Anders, D., … Hellweg, R. (2007). Serum neurotrophins-A study on the time course and influencing factors in a large old age sample. *Neurobiology of Aging*, *28*(9), 1436–1445. https://doi.org/10.1016/j.neurobiolaging.2006.06.011

TABLES AND FIGURES

Table 1. Brunnel Mood Scale scores from N= 5 participants. (Two participants included in the biomarker analysis did not have data). Every participant had scores of zero except for one participant who had a score of 1 for all 3 time points.

	Average Depression Scores (N=5)	Average Tension Scores (N = 5)
Baseline	0	0.2
Week 2	0	0.2
Week 14	0	0.2

Table 2. Demographic Data. N = 7

	Average	Standard Deviation
Age	76.1	9.6
Years of Education	16.6	2.3

Table 3. Performance on Cognitive Measures. N=7. Data for digits backward for N=2 was unavailable for the 6-Week evaluation.

	Baseline Average	Baseline Standard Deviation	6-Week Average	6-Week Standard Deviation	14-Week Average	14-Week Standard Deviation
Stroop C (seconds)	76.1	54.8	94.1	116.4	67.2	55.7
Color Trails 2 (seconds)	112.3	59.9	103.8	66.5	115.9	82.4
Digit Span Backward (score)	7.6	2.3	7	2.5	6.1	2.4
MoCA	23.71	5.38	n/a	n/a	24.14	6.57

Table 4. Biomarker Concentrations from ELISA Assays.

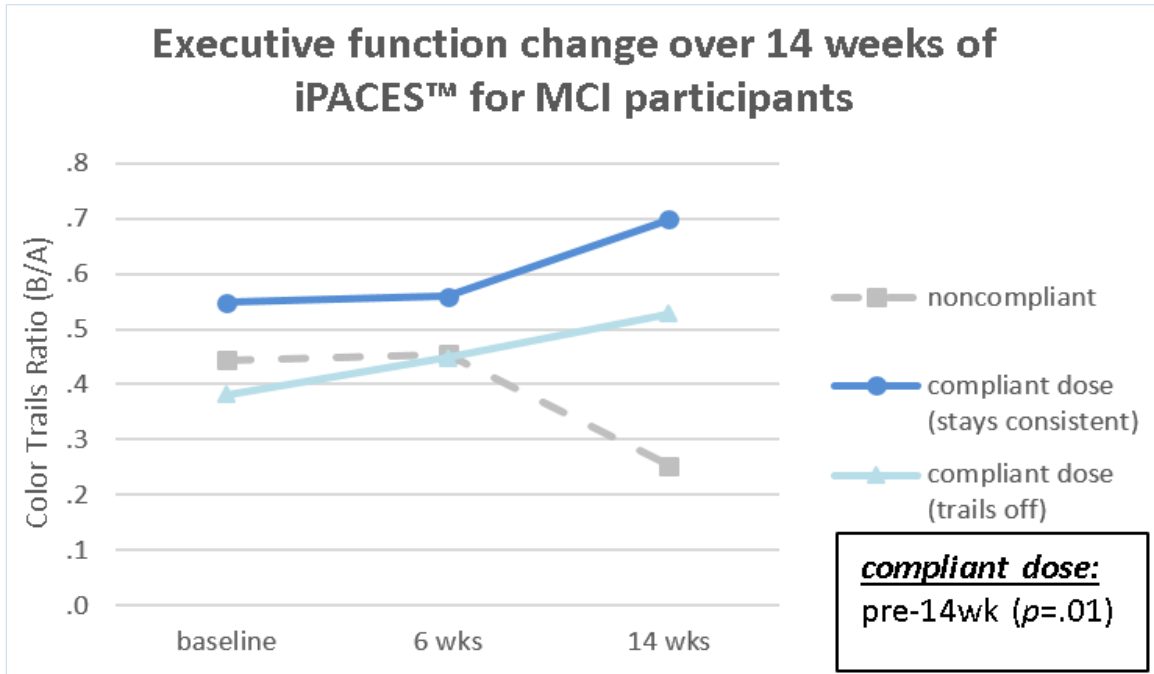|	Baseline Average	Baseline Standard Deviation	6-Week Average	6-Week Standard Deviation	14-Week Average	14-Week Standard Deviation
BDNF	0.09	0.03	1.22	0.02	0.08	0.04
IGF1	0.57	1.00	0.20	0.35	0.07	0.07
Cortisol	3.60	3.07	2.07	1.09	3.50	2.03

Figure 1. Executive function scores (Color Trails Ratio B/A) of three MCI participants across 14 weeks. Two were compliant with the exercise protocol and one was not.
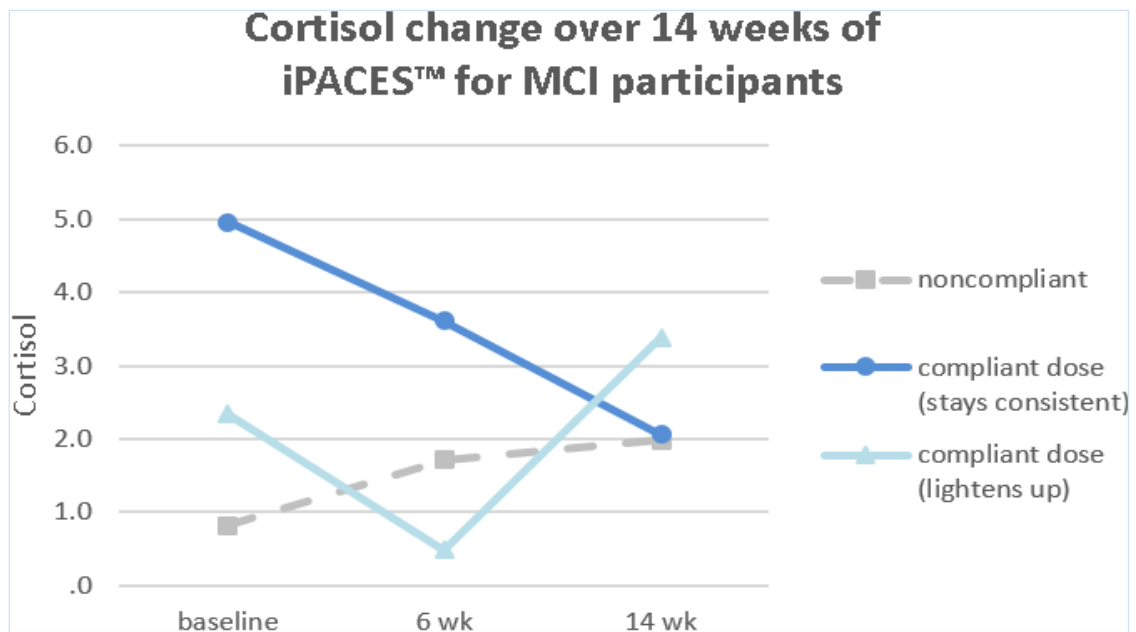
Figure 2. Cortisol levels (ng/mL) of three MCI participants across 14 weeks. Two were compliant with the exercise protocol and one was not.

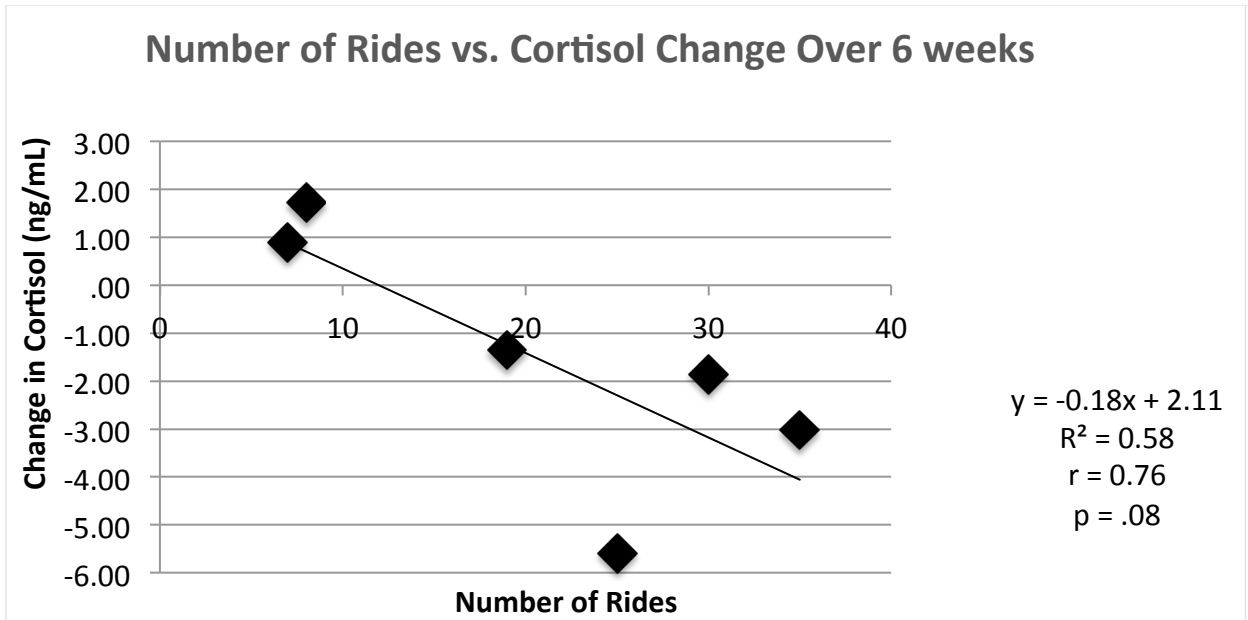**Figure 3.** Number of Rides (times the participant pedaled) a participant took across the intervention compared to the participant's change in cortisol (ng/mL) after six weeks.
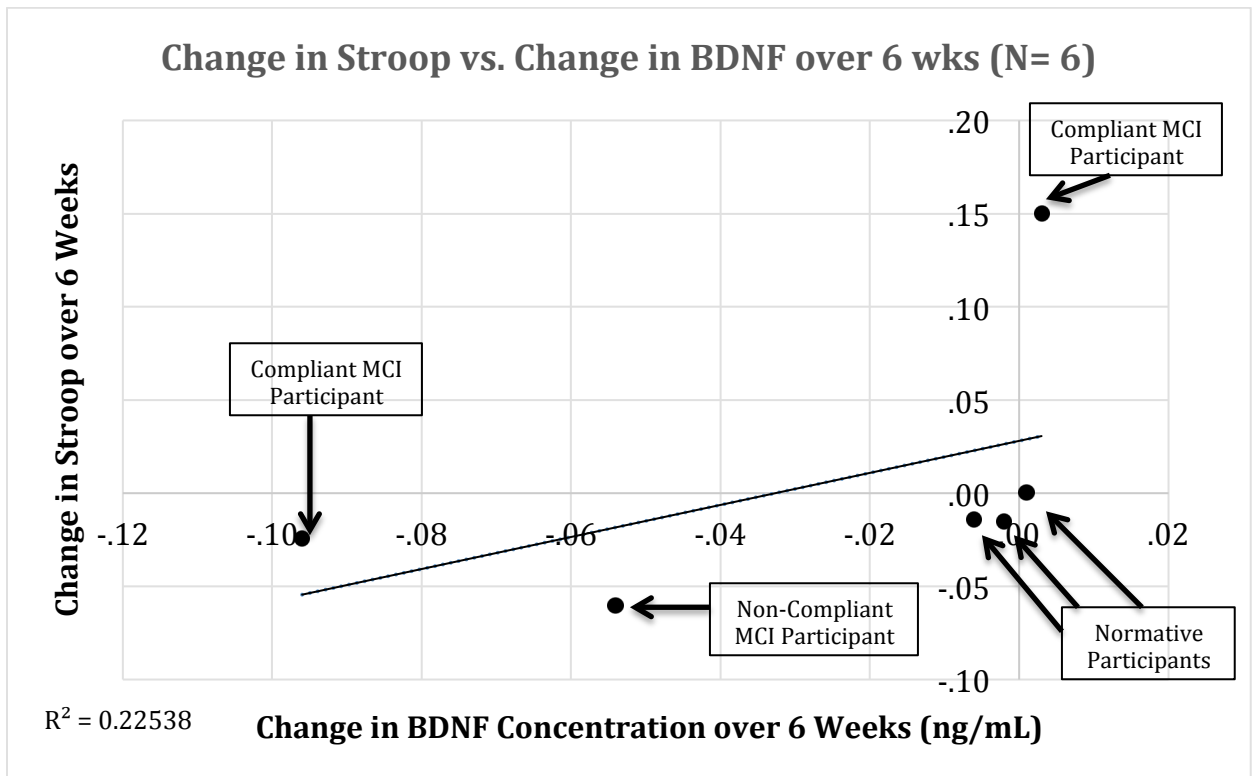
Figure 4. Change in Stroop Ratio score (A/C) after six weeks compared to change in Brain-Derived Neurotrophic Factor (BDNF) levels (ng/mL) after six weeks. Those who are labeled as compliant followed the suggested exercise protocol.

APPENDIX 1

Literature on Anxiety, Depression, and MCI/Dementia

In relating anxiety more generally to mild cognitive impairment and dementia, studies on anxiety and older adult cognition often come paired with depression. This is logical considering the high comorbidity of these two mental disorders. Numerous cross-sectional studies have shown a negative relationship between anxiety and/or stress with intellect, but that these two things also co-vary with one another across time. In comparison, effects of depressive symptoms seem to be more extreme over time (Bunce et al, 2012). In a recent study, 896 participants above age 70 reported their levels of depression and anxiety and were tested on their executive functioning. The subjects were assessed up to four times over a period of twelve years. Speed of information processing, verbal fluency tasks, episodic memory, and face and word recognition tasks were used for tests of executive functioning. Inferior mental health was found to have a negative effect on the initial levels of cognitive performance, but was not associated with any significant cognitive change over time. However, depression related cognitive deficits proved to be a prodromal symptom (an symptom indicating an onset of a disease) for dementia, while anxiety related cognitive problems presented a marker of normal aging (Bunce et al, 2012).

In the previously mentioned study, subjects were mostly well educated, cognitively intact, and had low levels of depression and anxiety as a group. In other research, participants with a diagnosis of depression and/or anxiety were assessed. In one study, patients were recruited and were split into dementia and non-dementia categories, with mean ages 80.87 and 81.4 respectively (Burton et al., 2013). An anxiety diagnosis was shown to be significantly associated with a future dementia diagnosis, even after adjusting for risk factors

such as smoking, obesity, heart disease, depression, etc. An interaction analysis demonstrated that a diagnosis of depression alone was significantly associated with dementia when compared to subjects without anxiety or depression. But, this association was weaker when compared to subjects with comorbid depression and anxiety, or anxiety alone (Burton et al, 2013). Thus, this study established the need to look at mental health in exploring prevention for MCI and dementia.

In a longitudinal study, only anxiety was looked at in its relation to dementia. Male participants were recruited whom had baseline anxiety and either already had a dementia diagnosis or was eligible for a dementia examination. 1160 men had follow up assessments for an average of 17 years. The results concluded that anxiety is a risk factor for Cognitive Impairment Not Dementia (CIND) and dementia. However, the researchers did not come to a conclusion on whether this association was independent of depression, further demonstrating the strong link between these two mental disorders (Gallacher et al, 2009).

Again looking at a non-normative population, MCI patients and their neuropsychiatric symptoms were inspected to see which symptoms became predictive of Alzheimer's disease (Gallagher et al, 2011). Patients with a mean age of 73.7 and a diagnosis of MCI were assessed. Patients were seen at intervals of 6-12 months. Seventy-six percent of patients had at least one neuropsychiatric symptom at baseline, 52% of which was anxiety. Of this 76%, 43% converted into Alzheimer's disease, although they had greater cognitive impairment at baseline. Consequently, anxiety and other neuropsychiatric symptoms may be signs of severity rather than predictors of disease progression (Gallagher et al, 2011). Thus, it is possible that anxiety is a prodromal symptom to MCI and dementia, but future work must explore this further.

APPENDIX 2

Initial Protocol Script

Participant ID# _____   Date _____   Time (am/pm): _____
Location: _____   Evaluator Initials: _____

The Interactive Physical and Cognitive Exercise Study (iPACES)
Initial Evaluation Protocol Script

_____ Pre-session checklist:
      _____ 2 copies of consent form, IDMC, doctor approval & demographic
questionnaires
      _____ 2 copies of neuropsych folder (protocol/response record forms for appropr
          eval: T1, T2, T3, T4, etc.)
      _____ Neuropsych kit (materials: Color Trails, Stroop stimuli, ADAS stimuli, etc.)
      _____ Clipboard, stopwatch, regular pencil, pen, notepad, colored pencils, sharpie
      _____ Physiological measures: portable scale, measuring tape, blood pressure
          machine
      _____ 4 saliva collection tubes, ice-cup and 2 pairs surgical gloves
      _____ Thank you gift
      _____ Create a quiet and confidential space (post sign, turn off cell/office phone
          ringer)

_____ Welcome participant to the study.
**I greatly appreciate you taking the time to meet with me today so that we might
learn more about the benefits of exercise. Please understand that most of what I
say to you will be read directly from this packet in order to ensure consistency
across evaluations. We want to make sure that the directions are explained to
each participant in the same way to prevent any confusion. This evaluation
process should take about two hours. Please let me know if you have any
questions at any time.**

_____ Give participant a copy of the Informed Consent Form.
**I'd like to start by going over some paperwork. Please read this Informed
Consent form carefully and sign at the bottom** (*review consent with participant*). **If
you have any questions, do not hesitate to ask.**

_____ **IDMC screening**
Go through the screening questions with the participant and sign off as the evaluator
if the participant appears to understand the questions

_____ **Doctor Permission Form**
Have participant fill out PCP contact information and sign for permission to contact

_____ Give participant a copy of the **saliva oral preparation sheet**
review with participant

_____ Saliva Collection Questionnaire
Go through the saliva questionnaire with the participants and mark whether or not
they adhered to the collection guidelines.

_____ Administer Demographic Questionnaire, PAR-Q, and Exercise History
Questionnaire

Please fill out these questionnaires to the best of your ability. Remember that all answers will remain confidential.

PRE-SINGLE BOUT

____ **Collect Saliva Sample**
Wear safety equipment i.e. a pair of gloves. For collection, you need to put the saliva sample in ice-cup immediately after collection. Process may take 15-20 minutes. **Please allow some saliva to collect and when you feel like you normally want to swallow, please lightly spit through the straw into the collection vial. Repeat until the vial is filled to the designated black line (2mL). Please don't forcefully spit into the container as this can contaminate the sample. If you are having trouble producing enough saliva, think of a favorite food. We have some lemon extract that you can <u>smell</u> (not taste), which often helps**.

_____ **Now, I have a variety of puzzle-like tasks for us to work on, such as repeating numbers and working with shapes. Hopefully, you will find most of the tasks very interesting. Some tasks you will probably feel are very easy while others will seem quite difficult. No one is expected to be able to do all the tasks given, but I do want you to do your very best on each task. Try not to get discouraged if you find something hard, it is normal to find some tasks more difficult since they are designed to test the limits of your abilities. Just do the best you can. Do you have any questions before we begin?**
- *Check to see if they need to use the restroom before beginning*
- *Ask to turn phone off/ringer to silent to minimize distractions*
- *Check to confirm wearing glasses/hearing aids if needed.*

_____ Administer Word List Memory (LIST 1)
Trial 1: **Now, I want to see how well you can learn a list of words. I am going to show you some words printed on these cards one at a time. Please read each word out loud and try to remember it, because later I will ask you to try to remember all of the words I have shown you. Ready? Read the word and try to remember it.** *Present each word card for approximately 1-2 seconds.*

Good, now tell me all the words you can remember. *Record responses (write first couple of ltrs if necessary to keep up with participant's rate of production).*

Trials 2 & 3: **Now I'm going to show you the same words again. Read each word out loud and try to remember it.** Do not warn the participant that they will be asked to later recall the words.

When complete, record time on clock: _____ + 5' = _____ time to do recall

_____ Administer Color Trails A (time to complete if less than 60 sec or stop participant at 60 sec and record # correct)

PRACTICE: Color Trails 1-A
In this box are different colored circles with numbers in them. When I say, "begin", I want you to take this <u>pen</u> and connect the circles by going from 1 *(point to the 1),* **2** *(point to the 2),* **3** *(point to the 3)***, and so on, until you reach the end. I want you to connect the circles in the correct order as quickly as you can, without lifting the pen from the paper. If you make a mistake, I will point it out. When I do, I want you to move the pen back to the last correct circle and continue from there. The line that you draw must go through the circles and must do so in the correct order. Do you have any questions?**

Okay, let's practice. Put your pen here where this hand tells you to start. When I say, "begin", connect the circles in order as quickly as you can until you reach the circle next to the hand telling you to stop. Ready? Begin.

TEST: Color Trails 1-A
Now I have a sheet with several more numbers and circles. Connect the circles in order like you did just a moment ago. Again, work as quickly as you can, and do not lift the pen from the paper as you go. Make sure that your lines touch the circles.

Be sure to be ready with the stopwatch, even a one second difference in recording time can be significant. Point to the first circle and say the following: **You will start here, where the hand tells you to start, and end where the hand tells you to stop. Ready? Begin.** *(Begin timing. Be sure to record the # and color of the dot completed at 60 seconds, as well as time to complete all).*

Record circle color and number at 60 seconds: Color =_____ Number = _____
Record time to complete (in seconds): _____sec

PRACTICE: Color Trails 2-A
In this box are different colored circles with numbers in them. This time I want you to take the pen and connect the circles in order by going from *this* color 1 *(point to the pink 1),* **to *this* color 2** *(point to the yellow 2),* **to *this* color 3** *(point to*

the pink 3), **and so on, until you reach the last number next to the hand telling you to stop.** *Take the pen and point to the example below the box as you say the following:* **Notice that the color changes each time you go to the next number. I want you to work as quickly as you can. Do not lift the pen from the paper once you have started. If you make a mistake, I will point it out. When I do, I want you to move the pen to the last correct circle and continue from there. As before, the line you draw must go through the circles in the correct order. Do you have any questions?**

Okay, let's practice. Put your pen here next to the hand telling you to start. When I say, "begin", connect the circles in order as quickly as you can, changing from one color to the next, until you reach the hand telling you to stop. Ready? Begin.

TEST: Color Trails 2-A
Now I have a sheet with several more numbers and colored circles. Connect the circles like you did just a moment ago. Again, work as quickly as you can. *Point to the first circle and say the following:* **You will start here, where the hand tells you to start, and end where the hand tells you to stop. Ready? Begin.** *(Begin timing)*

Record circle color and number at 60 seconds: Color =_____ Number = _____
Record time to complete (in seconds): _____sec

_____ Administer Word List Recall *(5' after last list recall - record time on clock:_____)*
Now I want you to try to remember the words that I showed you earlier on printed cards. Can you tell me any of those words? *Allow a maximum of two minutes for recall. Record responses (write first couple of ltrs if necessary to keep up with participant's rate of production).*

_____ Administer the Stroop Task (VERSION 1)

Before showing the examinee any of the cards, say:
COLOR BLOCKS:
I am going to show you a few different pages. On this first page, there are some colored blocks. Please tell me the names of the colors you see on this top, sample row *(point to the row).* *If necessary, clarify that the names to use are: red, blue, & green. If the examinee cannot distinguish the colors, perhaps due to color-blindness, move on to the next task.*

If the examinee completes the sample line successfully, say: **Good. Now I want you to tell me the names of each color block starting here and going as quickly as you can, without making mistakes, across the row and down to the next line and across, etc., until you finish all the rows** *(point to the end).* **Are you ready? Go.**

Be sure to start & stop the timer precisely. Mark all answers on your record sheet so that you can tally the number of errors later. Examinee can self-correct, but do not prompt for corrections.

BLACK WORDS:
Ok good, on the next page you will see that the task is similar, but slightly different. Here, read the words as quickly as you can. Please try the sample line *(point)*.

Fine. Now I want you to start here *(point)* **and read across as quickly as you can without making mistakes. Again, go across each row and then down until you finish all the rows** *(point to the end)*. **Are you ready? Go.** *Be sure to start & stop the timer precisely. Mark all answers on your record sheet so that you can tally the number of errors later. Examinee can self-correct, but do not prompt for correction.*

COLORED WORDS (incongruous/interference):
Good. On this last page, your task is to tell me the color of the ink and ignore the written word. *Feel free to empathize if the examinee laughs, gasps, etc. – e.g., say something like:* I realize this is getting more challenging, but do the best you can). Please try the sample line.

Fine. *If not, please explain again and repeat practice until clear understands, or abandon task.* **Start here** *(point)* **and read across and then down as quickly as you can without making mistakes until the end** *(point)*. **Are you ready? Go.** *Be sure to start & stop the timer precisely. Mark all answers on your record sheet so that you can tally the number of errors later. Examinee can self-correct, but do not prompt for corrections.*

_____ Administer Digit Span (digits forward – VERSION 1)
I am going to say some numbers. Then when I am through, I want you to repeat them right after me. For example, if I say 8-9 you will say 8-9. You'll just say exactly what I say. *Read numbers at rate of one second per number, with downward intonation at end. Be sure to record __all__ responses verbatim whether right or wrong. Discontinue after 2 failures of the same length of digits.*

_____ Administer Digit Span (digits backward – VERSION 1)
Now I am going to say some more numbers. But this time when I stop, I want you to say them backward. For example, if I say 7-9, what would you say? *Read numbers at rate of one second per number, with downward intonation at end. Be sure to record __all__ responses verbatim whether right or wrong. Discontinue after 2 failures of the same length of digits.*

_____ Administer MoCA.

_____ Physiological Measurements

Height = _____ (in / cm – *circle one*)   Weight = _____ (lb / kg – *circle one*)

Blood Pressure = _____/_____ mm/hg   Pulse = _____bpm

INTRODUCE TO CONDITION

INSTRUCTIONS FOR COGNITIVE TRAINING ONLY :
____   You will be given a cognitive task to complete in the form of a computer game. As you begin a list of words will appear and you will be asked to memorize this list.

As you move further along the trail, you will come to forks in the road where you will be asked to choose to turn either left or right depending on the place you'd like to go. We ask that you choose where to go based on the places you memorized earlier in the trail. For example, if "museum" was in your original list, then when you come to the fork in the road and are presented with the choice of turning left for "museum" or turning right for "doctor's," you should turn left for museum. Once you have completed this task all the way through, you will be asked to do the same task in reverse.

Once you successfully complete one list both forwards and backwards, you will receive another list of words of the same length. Once you complete this second task of the same length in its totality, you will be moved on to the next level where you will be asked to remember one more word than was in the previous sequence.

_____Commence single-bout of game play

Allow them to pedal/steer for 2-3 minutes, address questions. **Now, I would like you to play the game/exercise for 20 minutes.**

Note start time on clock: _____ When complete, record time on clock: _____

_____Have participant record ride summary data from screen in logbook.

POST SINGLE-BOUT

_____ Administer Flow & EIFI, Brunnel Mood scale
After completion of the 20-minute single bout, have the participant complete the
Flow and EIFI questionnaires.

____ **Collect Saliva Sample**
Wear safety equipment i.e. a pair of gloves. For collection, you need to put the saliva
sample in ice-cup immediately after collection. Process may take 15-20 minutes.
**Please allow some saliva to collect and when you feel like you normally want to
swallow, please lightly spit through the straw into the collection vial. Repeat
until the vial is filled to the designated black line (2mL). Please don't forcefully
spit into the container as this can contaminate the sample. If you are having
trouble producing enough saliva, think of a favorite food. We have some lemon
extract that you can** <u>smell</u> **(not taste), which often helps**.

_____ Repeat neuropsych tests as above using alternate forms
**You will now take the same neuropsychological tests you completed earlier.
After we are done with the evaluations, we will move on to the final part of the
study. Do you have any questions?**

_____ Administer Word List Memory (LIST 2)
**Now, I want to see how well you can learn a list of words. I am going to show
you some words printed on these cards one at a time. Please read each word out
loud and try to remember it, because later I will ask you to try to remember all
of the words I have shown you. Ready? Read the word and try to remember it.**
Present each word card for approximately 1-2 seconds. **Good, now tell me all the
words you can remember.** *Record responses (write first couple of ltrs if necessary to
keep up with participant's rate of production).*

**Now I'm going to show you the same words again. Read each word out loud and
try to remember it. Do not warn the participant that they will be asked to later
recall the words.**
Repeat the list 1 more time as above (so 3 total).

**When complete, record time on clock: _____ + 5' = _____ time to do
recall**

_____ Administer Color Trails B
<u>PRACTICE: Color Trails 1-B</u>
**In this box are different colored circles with numbers in them. When I say,
"begin", I want you to take this** <u>pen</u> **and connect the circles by going from 1**
(point to the 1), **2** *(point to the 2),* **3** *(point to the 3)***, and so on, until you reach the
end. I want you to connect the circles in the correct order as quickly as you can,**

without lifting the pen from the paper. If you make a mistake, I will point it out. When I do, I want you to move the pen back to the last correct circle and continue from there. The line that you draw must go through the circles and must do so in the correct order. Do you have any questions?

Okay, let's practice. Put your pen here where this hand tells you to start. When I say, "begin", connect the circles in order as quickly as you can until you reach the circle next to the hand telling you to stop. Ready? Begin.

TEST: Color Trails 1-B
Now I have a sheet with several more numbers and circles. Connect the circles in order like you did just a moment ago. Again, work as quickly as you can, and do not lift the pen from the paper as you go. Make sure that your lines touch the circles. *Point to the first circle and say the following:* **You will start here, where the hand tells you to start, and end where the hand tells you to stop. Ready? Begin.** *(Begin timing. Be sure to record the # of the dot just completed at 60 seconds, as well as time to complete all).*

Record circle color and number at 60 seconds: Color =_____ Number = _____
Record time to complete (in seconds): _____sec

PRACTICE: Color Trails 2-B
In this box are different colored circles with numbers in them. This time I want you to take the pen and connect the circles in order by going from *this* color 1 *(point to the pink 1)***, to *this* color 2** *(point to the yellow 2)***, to *this* color 3** *(point to the pink 3)***, and so on, until you reach the last number next to the hand telling you to stop.** *Take the pen and point to the example below the box as you say the following:* **Notice that the color changes each time you go to the next number. I want you to work as quickly as you can. Do not lift the pen from the paper once you have started. If you make a mistake, I will point it out. When I do, I want you to move the pen to the last correct circle and continue from there. As before, the line you draw must go through the circles in the correct order. Do you have any questions?**

Okay, let's practice. Put your pen here next to the hand telling you to start. When I say, "begin", connect the circles in order as quickly as you can, changing from one color to the next, until you reach the hand telling you to stop. Ready? Begin.

TEST: Color Trails 2-B
Now I have a sheet with several more numbers and colored circles. Connect the circles like you did just a moment ago. Again, work as quickly as you can. *Point to the first circle and say the following:* **You will start here, where the hand tells you to start, and end where the hand tells you to stop. Ready? Begin.** *(Begin timing)*

Record circle color and number at 60 seconds: Color =_____ Number = _____
Record time to complete (in seconds): _____sec

_____ Administer Word List Recall *(5' after last list recall - record time on clock: _____)*
Now I want you to try to remember the words that I showed you earlier on printed cards. Can you tell me any of those words? *Allow a maximum of two minutes for recall. Record responses (write first couple of ltrs if necessary to keep up with participant's rate of production).*

_____ Administer the Stroop Task (VERSION 2)
Before showing the examinee any of the cards, say:
COLOR BLOCKS:
I am going to show you a few different pages. On this first page, there are some colored blocks. Please tell me the names of the colors you see on this top, sample row *(point to the row). If necessary, clarify that the names to use are: red, blue, & green. If the examinee cannot distinguish the colors, perhaps due to color-blindness, move on to the next task.*

If the examinee completes the sample line successfully, say: **Good. Now I want you to tell me the names of each color block starting here and going as quickly as you can, without making mistakes, across the row and down to the next line and across, etc., until you finish all the rows** *(point to the end). **Are you ready? Go.*** *Be sure to start & stop the timer precisely. Mark all answers on your record sheet so that you can tally the number of errors later. Examinee can self-correct, but do not prompt for corrections.*

BLACK WORDS:
Ok good, on the next page you will see that the task is similar, but slightly different. Here, read the words as quickly as you can. Please try the sample line *(point).*

Fine. Now I want you to start here *(point)* **and read across as quickly as you can without making mistakes. Again, go across each row and then down until you finish all the rows** *(point to the end).* **Are you ready? Go.** *Be sure to start & stop the timer precisely. Mark all answers on your record sheet so that you can tally the number of errors later. Examinee can self-correct, but do not prompt for correction.*

COLORED WORDS (incongruous/interference):
Good. On this last page, your task is to tell me the color of the ink and ignore the written word. *Feel free to empathize if the examinee laughs, gasps, etc. – e.g., say something like:* I realize this is getting more challenging, but do the best you can). Please try the sample line.

Fine. *If not, please explain again and repeat practice until clear understands, or abandon task.* **Start here** *(point)* **and read across and then down as quickly as you can without making mistakes until the end** *(point).* **Are you ready? Go.** *Be sure to start & stop the timer precisely. Mark all answers on your record sheet so that you can tally the number of errors later. Examinee can self-correct, but do not prompt for corrections.*

_____ Administer Digit Span (digits forward – VERSION 2)
I am going to say some numbers. Then when I am through, I want you to repeat them right after me. For example, if I say 8-9 you will say 8-9. You'll just say exactly what I say. *Read numbers at rate of one second per number, with downward intonation at end. Be sure to record <u>all</u> responses verbatim whether right or wrong. Discontinue after 2 failures of the same length of digits.*

_____ Administer Digit Span (digits backward – VERSION 2)
Now I am going to say some more numbers. But this time when I stop, I want you to say them backward. For example, if I say 7-9, what would you say? *Read numbers at rate of one second per number, with downward intonation at end. Be sure to record <u>all</u> responses verbatim whether right or wrong. Discontinue after 2 failures of the same length of digits.*

_____ Thank the participant. **You did a fine job today! I want to <u>thank you</u> for taking the time and putting in the effort to go through these tasks to help us with this research project. Do you have any questions or concerns I can address now?** *If they ask questions that you feel you cannot adequately address, tell them you will get back to them. If they ask how they did, note that you thought they did fine, but that you can't answer specific Qs (e.g., how many did I get right?) since they may take the tests again. Note that their formal results cannot be made available to them since they are not considered "clinically valid" due to the fact that this was a research study only.*

_____ **Recall the goal is to play the game/exercise at least 3 times per week for 20-30 minutes each time. A member of the research team will monitor your progress by reviewing computer and paper log records. We will call you at the end of this first week to see if you have any questions or problems. If the weekly logs indicate you are having difficulty (such as no rides for a week, we will call you and check in).**

_____ **Remember, that if you have any questions, problems, or concerns, call us at 518-388-6430.**

APPENDIX 3

CONSENT TO PARTICIPATE IN HUMAN RESEARCH

Title of Research Study: *Interactive Physical and Cognitive Exercise Study (iPACES)*

Principal Investigator(s): *Cay Anderson-Hanley, PhD (Union College)*
Address: *Healthy Aging & Neuropsychology Lab, 807 Union Street, Schenectady, NY 12308*
Phone Number: *(518) 388-6430*

You are being asked to take part in a human research study entitled the "*Interactive Physical and Cognitive Exercise Study (iPACES).*" This study is intended to clarify the benefits to brain health and thinking processes that result from different forms of exercise. In particular, this study will investigate the possible benefits of physical exercise (such as pedaling an under-table stationary elliptical) or mental exercise (such as playing a videogame on a portable tablet), or combining these activities together (as in the iPACES exergame).

This consent form contains information about the study, including the risks and benefits of participating, so that you and or your co-residing study partner can make an informed decision about whether to participate. The person doing the research will also discuss the study and its risks and benefits with you.

Once you understand the study, you and or your co-residing study partner will be asked to sign this form if you agree to take part in the study. You and your co-residing study partner will be given a signed copy of the form to keep as a record.

By signing this document you and your co-residing study partner do not change your legal rights, but indicate that you understand the information, and that you give your consent to complete the periodic evaluations of your brain health and thinking processes over the course of the 14-week exercise intervention.

PURPOSE OF THE RESEARCH STUDY

This study has been designed for several reasons:
1. to clarify the benefits to brain health and thinking process of an exercise intervention
2. to clarify the best combination of mental and physical exercise
3. to replicate benefits found in prior research for older adults

DESCRIPTION OF THE RESEARCH STUDY

If you and your co-residing study partner agree to participate in this study, the following will occur:
1. A research team member will contact you and discuss the study with you. If you are interested in participating, your primary care physician and cardiologist (if applicable) will be asked to approve your participation in three months of exercise.
2. If you or you and your co-residing study partner agree to participate, an initial

meeting will be arranged.

3. During the initial meeting (which will last approximately 2.5 hours), you alone or you and your co-residing study partner will meet with a member of the research team at the location where you will exercise using the portable equipment provided by the research (e.g., typically at your home or a communal space). A researcher will conduct evaluations with you privately, in a room separate from your co-residing study partner. The following are the planned procedures:

   a. A member of the research team will review this informed consent form with you. You and your legally authorized representative (if applicable) will be asked to sign this form before beginning any study procedures. You will also be asked to sign a form asking for your doctor(s) to approve participation in physical exercise.

   b. Physiological measures will be taken (e.g., height, weight, blood pressure, heart rate). Saliva samples will be collected pre and post testing or gaming.

   c. A set of pencil and paper tests of thinking will be administered (e.g., puzzle-like tasks such as recalling a list of items or connecting dots in order).

   d. *A brief break will be taken*

   e. You will be shown how to use the Interactive Physical and Cognitive Exercise System– that is, how to play the game on a tablet provided during the study, and after 2 weeks also how to pedal on the elliptical and monitor your heart rate while exercising.

   f. Finally, a brief set of pencil and paper tests will be administered after 20 minutes of game-play.

4. After the initial meeting, you will begin game-play for at least 20 minutes, 3-5 times per week, for two weeks.

5. The research team will monitor your progress weekly (via your written log and the bike's computer data archive).

6. After two weeks of game-play, with approval from your primary physician and/or cardiologist to exercise, a research member will conduct a 2.5 hour evaluation (e.g., basic physiological measures, saliva collection and pencil and paper tests of thinking) with you and your co-residing study partner (separately) and will introduce the physical exercise equipment (e.g., under-table elliptical pedaler).

7. At week four and week six, a one-hour mid-point evaluation will be scheduled with you and your co-residing study partner (e.g., basic physiological measures, saliva collection and pencil and paper tests of thinking).

8. At week 14, a comprehensive evaluation (similar to the initial evaluation) will be scheduled with you and your co-residing study partner (conducted separately).

There is a possibility that we would re-contact you or your designee, to invite you to participate in a follow-up study. We will ask you to provide contact information so that we might stay in touch after the study (e.g., phone, email, address). We will also use this contact information to notify you and your co-residing study partner of the availability of study results.

You your co-residing study partner should continue to see your regular health care provider(s) while participating in the study. Sometimes, people need to be taken out of a

study even if they do not want to stop. This could happen if you do not follow instructions, the study is no longer safe for you, or the study is stopped. If this happens, you will be told and the reason will be explained to you.

POSSIBLE BENEFITS OF THE RESEARCH

You and your co-residing study partner's participation in this study may or may not result in any direct benefit to you. Most people find the procedures used in the study to be interesting. Also, you have the chance to exercise which may help your health. The knowledge gained from this study may help other individuals with memory difficulties.

POTENTIAL RISKS

For your safety, you must follow all instructions given to you by the study doctor and research staff while you are in this study. Tell your regular health care providers that you are in this study, and given them the name and phone number of the study doctor. Being in this study may involve some added risks or changes in your normal daily activities.

Risks/Side Effects of Exercise
There are some risks related to exercise.
- You may feel typical effects of starting a new exercise program (such as sweating or sore muscles). Exercise should be done only with the approval of your doctor. You should ease into your new exercise, increasing your exercise little by little, in order to minimize risk of muscle strain, joint pain, or other injury. You will be given a heart rate range to target while pedaling.
- The tablets contain a virtual reality screen. There is a risk of "cybersickness" which is similar motion sickness (e.g., dizziness, nausea, eyestrain) from following along with the virtual path. Symptoms are temporary and effects may vary from person to person.
- There is a rare chance of serious harm during any exercise (e.g., heart attack, stroke, or even death). Before starting this exercise, you must have note from your primary doctor (and your heart doctor if you have one). We will help with this paperwork.
- Because you will be exercising in the privacy of your home, we require a co-residing study partner, to limit the risks in case there an emergency arises. For your safety, we want you to coordinate sessions with your study partner using the "buddy system" during exercise. You might also choose to use a fall-detection/life-alert system while you are exercising.
- If you are a single participant exercising in a public/communal space (i.e. exercise room at your retirement community), please be aware of the following risks: Choosing to exercise in an unsupervised setting presents additional risk as there is no one to respond to any emergency that may arise as a result. For your safety, we encourage you to bring a buddy and/or use a fall detector/life alert system while you are exercising.

Risks/Side Effects of Questionnaires
This study also includes questions about your feelings and state of well-being, as well as tests

of thinking.
- While some questions are hard, most people usually find these tasks interesting.
- You may wish to talk to someone about some of the issues raised. We will be happy to recommend someone to you. Some of the personal questions may make you feel uncomfortable. You may refuse to answer such questions or withdraw from the study.

Other Risks/Side Effects
This research may involve other risks to you that are currently unforeseeable. You will be told if any new information is learned that might affect you or that might change how you feel about being in this study.

The information in this form is just for this study. The list given above does not include any risks or discomforts that may come from the care you receive outside this study. Please speak with your regular health care provider(s) if you have any questions about your usual care. For your safety, please tell the study doctor or research staff about any care you receive that is not part of this study.

ALTERNATE PROCEDURES OR TREATMENTS

The alternative to participating in this study is simply to decline; participating or declining will not affect your ongoing, current standard of care. As a potential participant in this study you and your co-residing study partner are urged to discuss all possible interventions (e.g., the exercise activities) and possible consequences with your doctor.

CONFIDENTIALITY

Your privacy and research records will be kept confidential by the research team, and your identity will be protected to the extent permitted by law. However, authorized research investigators and agents of the US Food and Drug Administration (FDA), and Union College Institutional Review Board (IRB), have the right to inspect the records involving you. Additionally, because you will be participating in coordination with a co-residing study partner, some information may become known to this partner.

Research records will be coded through the use of a study ID number and any information collected from you will only be identified with your study ID number. The code that links your name to your study ID number will be kept in a secured location and available only to the PI or selected members of the research team. Collected and coded data will be stored in a locked office in the PI's data entry center.

If you agree to be in this study, your name and your co-residing study partner's name will be added to a master list of all subjects who are in the study. The master list will be kept with the other records from the study. All records from this study will be kept indefinitely.

Results of the study may be published. If the results of this study are reported in medical journals or at meetings, the authors will not share personal details about you. You will not be identified by name, recognizable photo, or any other means unless you give them specific permission to do so.

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov,* as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of results. You can search this website at any time.

You should understand that we will in all cases, take the necessary action, including reporting to authorities, to prevent serious harm to yourself, children, or others (for example, in the case of elder abuse or neglect).

PAYMENT FOR PARTICIPATION

You or your co-residing study partner will not be paid for participation in this study, but you and your co-residing study partner will receive small "thank you" gifts after each of the five evaluations (e.g., water bottle, mug, etc.).

PAYING THE COST OF THE RESEARCH

There is no cost to you for participating in this study.

VOLUNTARY NATURE OF PARTICIPATION AND WITHDRAWAL

You or you and your co-residing study partner's decision to participate in this research must be completely voluntary. You are free to choose either to enter the research study or not to enter the study. There will be no penalty or loss of benefits to you if you decide not to participate. Before you make any decision, one of the persons in charge of the research will give you a chance to ask questions you may have about the research study. Do not sign this form unless you have had the chance to ask questions and have received satisfactory answers.

Even after agreeing to take part in this research study, you may withdraw from the study at any time. If you do decide to withdraw from the study, there will be no penalty or loss of benefits to you. After withdrawal, you will be offered all available care that suits your needs and medical condition.

Please tell the study doctor or a member of the research staff if you decide you want to stop. They will explain what you need to do to withdraw from the study. You may be asked to come in for a final study visit or return study supplies, if you have them. If you do decide to withdraw from the study, there will be no penalty or loss of benefits to you.

NEW INFORMATION ARISING DURING THE RESEARCH

During this research project, the investigators may know new information regarding risks and benefits of the study. If this occurs, they will tell you and your co-residing study partner about this new information. New information may show that you should no longer participate in the research. If this occurs, the persons supervising the research will stop your participation in it. In either case, you will be offered all available care that suits your needs and medical conditions.

INVESTIGATOR STATEMENT

This study has a non-commercial or "not for profit" research sponsor. The clinical investigator(s) involved in this study receives no personal money or payment from this sponsor. Payment is, however, made to the investigator's office in an amount that **only meets** the direct clinical and administrative costs of serving as investigators for this study.

PERSONS TO CONTACT

The person in charge of this research is the principal investigator listed on the first page of this form. Whenever you have questions about this research project or you think you have been injured as a result of the research, you may contact the research staff at **(518) 388-6430**. You may also contact the principal investigator, Dr. Cay Anderson-Hanley at (518) 388-6355. Always dial 911 first if it is a medical emergency.

NOTE FROM THE IRB

This protocol, its risks and benefits, and this informed consent were reviewed by the Institutional Review Board (IRB) also called the Human Subjects Review Committee (HSRC), as it is known at Union College. An IRB is a regularly convened committee whose mission is to review human subject research protocols to guarantee, among other things, that the research under review satisfies the qualities of respect for autonomy (your rights as a human subject), beneficence (the apparent benefits outweigh the apparent risks), and justice (the selection of study participants who also suffer from your disease and may share in the benefits of this study is fair) as outlined by the Belmont Report of 1979. The IRB finds that this research study satisfies these criteria. If you have questions about this protocol or your rights as a research subject, please contact the Union College IRB at (518) 388-6233.

CONSENT

By signing this form, you agree that:

1.   You have fully read or have had read and explained to you in your native language this informed consent form describing a research project.

2.   You have had the opportunity to question one of the persons in charge of this research and have received satisfactory answers.

3.   You have been given a signed copy of this informed consent form, which is yours to keep.

4.   You understand that you are being asked to participate in research and you are not participating in any other research project at this time or have informed the investigator. You have been told the risks and benefits involved in participating in this research, and you freely give your consent to participate in the research project outlined in this form, under the conditions indicated in it.

5.   You understand that you may refuse to participate in the research project or may withdraw at any time without penalty.

_____   _____

Signature of Participant   Date

_____   _____

Signature of Surrogate or Legal Representative (*if applicable*)   Date

STATEMENT OF PERSON ADMINISTERING THE INFORMED CONSENT

I have carefully explained to the subject the nature of the above research study. I hereby certify to the best of my knowledge the subject signing this consent form understands the nature, demands, risks, alternative treatments and benefits involved in participating in this study. A medical problem or language or education barrier has not precluded a clear understanding of the subject's involvement in the study.

_____   _____

Signature of Person who Obtained Consent   Date

ACKNOWLEDGEMENTS