Neuro-exergaming for older adults with mild cognitive impairment (MCI):
A single bout of interactive Physical and Cognitive Exercise (iPACES v2.5)

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ABSTRACT

PULEIO, ALEXA Neuro-exergaming for older adults with mild cognitive impairment (MCI): A single bout of interactive Physical and Cognitive Exercise (iPACES v2.5)

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Mild neurocognitive disorder, formerly known as Mild Cognitive Impairment (MCI), poses a serious risk to the older population. This disease may be a precursor to a more debilitating dementia, such as Alzheimer's Disease, and it affects the cognitive abilities as well as overall quality of life of those who suffer from it (Alzheimers Association, 2014). Finding preventative ways to combat these illnesses is imperative for our increasing older population at risk. Prior research has shown benefits to cognition of physical exercise (Colcombe & Kramer, 2003), but only a fraction of older adults actually achieve recommended levels (Chodzko-Zajko et al., 2009). Some researchers have explored the use of potentially more motivating exer-games and found benefits above and beyond physical exercise alone perhaps due to synergistic effects of physical and mental engagements (Anderson-Hanley et al., 2012A, Zhu et al., 2016). The current study attempts to replicate and extend prior research by examining the cognitive impact of a single bout of a neuro-exergame in which older adults engaged interactive Physical and Cognitive Exercise (iPACES v2.5). This involved pedaling an under-table elliptical while playing an iPad-based videogame, which simulated independent living everyday function of running errands and retracing one's path home. Eighteen older adults (mean age = 68.4 years old) were assessed pre- and post-exercise with neuropsychological tests of executive function (Stroop and Trails) as well as verbal memory (ADAS Word Recall). While no significant changes were observed in the sample taken as a whole, a repeated measures ANOVA (controlling for age) indicated a significantly greater benefit to verbal memory for MCI

participants in contrast with normative older adults ($p = .008$). Further research is needed to confirm this finding in a larger sample, but it is consistent with some prior research on single bouts of exercise benefiting cognition of MCI more than normative older adults (Anderson-Hanley et al., 2016, Cohen et al., 2014). The implications of this type of research suggest that neuro-exergaming is feasible, including for those with MCI, and may yield immediate benefits to cognition; follow-up trials are needed to examine long-term use, factors affecting outcomes, and underlying mechanisms.

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The current epidemic of increased rates of dementia around the world poses a serious

health risk to the older population. By 2050, due to a continual increase in population size, it is

estimated that around 9 million Americans will be diagnosed with Alzheimer's disease, AD

(Alzheimer's Association, 2014). This severe form of dementia, as well as Mild Cognitive

Impairment (MCI), also termed Mild Neurocognitive Disorder (mNCD) per the most recent

edition of the Diagnostic and Statistical Manual (DSM-5; American Psychiatric Association,

2013), greatly threaten the health of our growing and aging population. MCI in some cases

considered to be the prodromal stage of this type of dementia, and can be described as deficits in

memory as well as executive function, visuospatial skills, or language (Petersen & Negash,

2008). While there is a possibility that MCI may or may not progress to a major neurocognitive

disorder such as dementia due to Alzheimer's disease and related disorders (ADRDs), the

debilitating problems caused by both conditions can significantly affect one's quality of life

(Sachs-Ericsson & Blazer, 2014). The best way to deal with this rising epidemic is to intervene

before individuals are diagnosed with the disease (Korczyn & Vakhapova, 2007, Petersen &

Negash, 2008). Given the lack of any cure and the limited utility of medications in preventing

cognitive decline (Ahlskog et al., 2011), this thesis project explores the possibility of intervening

in the course of cognitive decline using a behavioral intervention focused on physical and mental

exercise (Colcombe & Kramer, 2003, Cui et al., 2018).

Neurobiological Mechanisms Linking Physical Exercise to Cognitive Benefits

The benefits of exercise, specifically cardiovascular forms, have been explored and

research has shown that the decline of both major and mild neurocognitive disorders can

sometimes be slowed down, in part due to neurobiological mechanisms such as increased blood

perfusion to the brain, improved neuroplasticity, and reduced neuropathology found in dementia (Ahlskog et al., 2011). Exercise is involved with increasing biomarkers that improve cognitive functioning ((Kirk-Sanchez, & McGough, 2013). One neurobiological marker that has been implicated in the cascade of aerobic and muscle activity is brain-derived neurotrophic factor (BDNF) which is involved in improving blood flow and promoting neuronal growth and survival (Rasmussen et al., 2009). Individuals with Alzheimer's disease have been reported to have lower levels of this neurotrophin than healthy adults and even those with vascular dementia (Yasutake et al., 2006).

A risk factor for developing AD is the presence of the apolipoprotein E ε4 gene (ApoE-ε4; Petersen et al., 2009). This allele is also related to developing MCI (Boyle et al., 2009), which suggests that the disease may be a precursor for the more debilitating dementia, AD (Petersen & Negash, 2008). Previous research examining the effect of exercise for those at risk for developing MCI or AD was conducted on individuals who possessed this genetic trait. A study by Smith and colleagues (2011) had results that displayed that adults who reported to engage in high levels of physical activity, and especially those who had one or two ApoE-ε4 alleles, displayed greater semantic memory processing than those who were less physically active. A similar study by Etnier and colleagues (2007) assessed the effect of an exercise test performed at maximal physical effort and performance on verbal memory and executive function measures. Results found a significant improvement in verbal memory scores for women with both alleles for the ApoE-ε4 allele. In both studies, individuals at risk for AD and MCI benefitted the most from physical exercise.

Benefits of Long-Term Physical Exercise

Consistent exercise routines also benefit those with various risk factors such as glucose

intolerance (Anderson-Hanley et al., 2012B) and illnesses such as hypertension, metabolic syndrome, and diabetes, which are associated with greater BMI's, high blood pressure, and inflammation (Kirk-Sanchez & McGough, 2013). Healthy older adults reap cognitive advantages to physical activity as well. A meta-analysis by Rathore & Lom (2017) displayed a small positive effect in improved working memory when healthy participants engaged in sustained physical activity. Older adults who engage in long-term exercise have displayed improved executive function and memory, along with other cognitive scores (Ahslkog et al., 2011, Colcombe & Kramer, 2003).

In a specific study by Lautenschlager and colleagues (2008), participants over 50 years old with memory issues were recruited to engage in an 18-month intervention to assess the efficacy of physical exercise on improving cognition. Participants in the exercise group wore a pedometer to measure the amount of activity they performed, as well as number of steps completed per day. The Alzheimer's Disease Assessment Scale (ADAS-Cog) was used to measure cognitive function. At the end of the intervention, participants assigned to the exercise condition displayed significantly greater ADAS-Cog results and better delayed recall than those in the no-exercise condition.

Benefits of Short-Term/Single-Bout Physical Exercise

Even a single bout of exercise has shown positive effects on cognition. A meta-analysis by Chang and colleagues (2012) displayed a significant effect of a single bout of exercise on cognitive performance during and after the activity, as well as a delay following the end of the activity, with higher intensity of exercise influencing better quality of performance after about a minute of completion. This meta-analysis observed that a minimum of 20 min of exercising was necessary to see a positive effect. In a study by Nanda, Balde & Manjunatha, (2013) adults who

engaged in 30 min of pedaling a stationary bicycle at moderate intensity, improved at cognitive assessments aimed to measure planning, memory, and reasoning. Further research by Hillman and colleagues (2009) assessed effects of a young children engaging in a 20 min moderately intense exercise (walking on a treadmill). These singular sessions displayed improvement in academic performance and attention. The effects of a single bout prove to be beneficial to one's mental abilities across various age groups, and the impact of short-term exercise seems particularly potent for certain subgroups at risk for developing MCI (Anderson-Hanley et al., 2016, Cohen et al., 2014).

Benefits of Combined Physical and Mental Exercise

The current literature reveals the diverse improvements in health that result from engaging in physical exercise; however, fewer older adults participate in these activities as they age (Chodzko-Zajko et al., 2009). With such promising results from physical activity, finding ways to encourage more elderly to participate in exercise may help ameliorate the current epidemic of neurocognitive dementia. A combination of stimulating mental games while exercising has been a feasible method to engage individuals in exercise to not only improve physical but also mental health. This combination can be done in three different ways, including interactively (two activities performed at the same time in which they both affect each other), sequentially (one activity is performed before the other), and simultaneously (both activities are conducted at the same time except are individual and do not influence one-another; Anderson-Hanley et al., 2018). The research on combined interventions has been growing such that there are now several reviews and meta-analyses suggesting some interesting differential and synergistic effects worthy of continued exploration (Ballesteros et al., 2018, Bruderer-Hofstetter, 2018, Joubert & Chainay, 2018, Zhu et al., 2016,). The combined physical and cognitive activity

had displayed greater effects than either alone (Gheysen et al., 2018) as well as significant improvement in visuo-spatial abilities and executive function (Mura et al., 2017).

Prior research in our lab has also displayed significant results using the combined interaction of mental and physical exercise on cognitive abilities. In the Cybercycle Study by Anderson-Hanley and colleagues (2012), participants pedaled a bike while playing a virtual reality game, simulating a bike path, designed to engage and thus motivate the player. Over a three-month time period, findings discovered that those who played the interactive game significantly improved in executive function tests, including Color Trails and Stroop Task C, than those who simply exercised. Also, participants that used the cybercycle displayed a 23% decreased risk of developing MCI as well as an increase in BDNF than those who engaged in standard exercise. These improvements were not due to increased motivation to exercise at full capacity, but instead due to the interaction of physical and mental activity.

The Aerobic and Cognitive Exercise (ACES) study by Anderson-Hanley and colleagues (2018A), further delved into the question of interactive benefits to cognition. The study used three different conditions: exer-tour which was designed to simulate riding along a bike path using low mental effort while pedaling a bike, exer-score which simulated a video game and required high mental effort while exercising with the bike, and game-only where the participants simply played the video game and did not exercise. This long-term intervention was conducted for six months, with results that displayed an improvement in the Stroop Task results for both exer-tour and exer-score conditions.

A neuro-exergame developed by our lab, the interactive Physical and Cognitive Exercise System (iPACES; Anderson-Hanley et al., 2017) has been used in multiple studies to further discern the effects of a combined physical and exercise program. In a long-term iPACES study

(Anderson-Hanley et al., 2018B) the neuro-exergaming dose was assigned to participants over a long-term period for three months. The cognitive performance of participants was compared from the baseline to the middle and end of the intervention. An increase in executive function scores were found significant from the baseline to end of intervention. The most recent iPACES study (Wall et al., 2018) included an updated Memory Lane game where executive function was also measured during baseline and at points throughout and at the end of the intervention. The results displayed a significant increase in executive function scores once again, further building upon prior research of the effectiveness of the interaction of pedaling while playing the memory game.

The first Interactive Physical and Cognitive Exercise System (iPACES) pilot study (Anderson-Hanley, Maloney, Barcelos, Striegnitz, & Kramer, 2017) examined and compared the effect on cognition of three different, randomly assigned, experimental groups, with single bouts of exercise using iPACES on a tablet. In the neuro-exergaming condition, participants pedaled while playing the memory games. For the exergaming group, participants exercised while playing a more traditional video game, riding a cybercycle which simulates a bike ride without the memory challenge posed in iPACES. For the neuro-gaming group, participants completed the game without exercising. The results of this pilot study displayed the greatest pre- to post-improvement in executive function measures with neuro-exergaming. Neuro-gaming only also displayed a significant improvement, but exergaming displayed a decline in performance.

The current study attempts to replicate and extend prior findings from iPACES research in order to further understand the effect of a single bout of exercise pedaling an under-table stationary pedaler while playing the memory game.

It was hypothesized that:

1. similar to prior findings using the neuro-exergame, it is expected that the effect of a single bout of exercise while playing iPACES v2.5 will significantly improve executive functioning scores from the pre-test to the post-test in participants.

    a. Controlling for relevant variables, such as age and education, the effects will be greater for participants who achieved an adequate dose, by completing the full 20 minutes of exercise.

2. any improvement in performance will exceed that typically due to practice effects (assessed via comparison with archived control sample/normative data for test-retest change in the absence of intervention).

3. participants within the MCI range via MoCA score (Carson et al., 2018) will improve significantly greater on neuropsychological tests than participants within the normal range.

<div align="center">METHODS</div>

Participants

Older adults, ages 50+, were recruited for the current study at two separate sites in the northeast USA, to voluntarily engage in a single bout of exercise while playing the iPACES Memory Lane v2.5 game. Nine participants were enrolled from a physical therapy center associated with an academic training program as part of a liberal arts college. Another nine were recruited through another liberal arts college and a nearby senior living apartments. Various recruitment methods were used, including: posted fliers, outreach emails to wellness program lists, and demonstrations of the game at the senior apartment community. Exclusion criteria included any physical or mental impairment that would affect a participant's ability to complete or understand the cognitive tasks, pedaling, or playing the interactive memory game.

Participants provided informed consent; the protocol was approved by the Institutional Review Board (IRB) at Union College. In anticipation of recruiting potentially vulnerable population, participants were screened using the Impaired Decision-Making Capacity, which is a structured interview to ensure appropriate consent could be obtained and included ensuring the ability to remember and understand the study.

Those enrolled in the study consisted of 12 females and six males. All were Caucasian. The mean age of all the participants was 68.4 (SD = 9.1), education (in years) was 15.7 (SD = 2.08) and the mean body mass index was 26.1 (SD = 2.7). As seen in Figure 1 (CONSORT diagram), 15 of the 18 participants enrolled in the study, completed the 20-min single bout of exercise using the pedaler and game. Reasons for discontinuing early included: fatigue or pain in the knee while exercising. Sixteen of the participants did not report any neurodegenerative diseases; two of the participants were on medication for parkinsonism, so tremor did not interfere with the neuropsychological evaluation or exercise.

Procedures

The participants were first screened for the study by phone to determine whether they met inclusion criteria, including use of the Impaired Decision-Making Capacity interview. A time was scheduled for the evaluation where they then reviewed and signed the informed consent form. Given the above noted literature on biomarker correlates linking exercise to cognition, saliva samples were collected via passive drool to be archived for separate analyses (to follow these cognitive analyses). Participants completed a demographic form, including age, height, weight, marital status, computer use, and exercise history. Neuropsychological tests were administered to assess the participant's cognitive performance before and after the SB. The primary focus was on the cognitive domain of executive function and a verbal memory task was

also included given some promising prior findings in both realms (Colcombe & Kramer, 2003).

The protocol was designed with a nested additional hypothesis to examine the comparability of

electronic vs paper forms of tests of cognition (Fuller et al., 2016) and are reported elsewhere

(Johnson, 2019). For that purpose, test order was randomly assigned for each participant, with

either paper-first or electronic-first for the Stroop Task.

Participants were informed to pedal to reach their target heart rate during the single bout

of exercise. Information regarding their total score, minutes pedaled, and average heart rate on

the memory game was recorded. An updated version (v2) of the iPACES Memory Lane neuro-

exergame[1] (Wall et al., 2018) was played on an iPad. Participants used the iPad to steer the

direction of their bike path by tilting the device left or right. Participants were first given

instructions in the game play on how to steer down the simulation of riding a bike down a road.

They were instructed to remember words presented to them at the beginning of the path in order

and to choose their destination between a fork in the road based on the list of locations presented

with at the beginning. Once the participants correctly followed the order of locations, their bike

path turned them around in a circle and they were asked to follow the bike path in the reverse

order of the list of locations. Coins on the street were used as an engaging feature of the game, as

well as boost the players score. The faster the participant pedaled the stationary elliptical, the

faster they traveled down the bike path. On the screen also displayed the total time, how far they

were on the path, and their heart rate. The combination of the iPACES Memory Lane game and

stationary pedaling enabled the interactive physical and cognitive exercise effect during the

single bout.

Post-exercise, a saliva sample was collected as above, and questionnaires regarding

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[1] the iPACES neuro-exergame designed by our lab and refined in collaboration with software gaming company: 1st Playable in Troy, NY (via collaborative NIA STTR grant).

experiences during and after the exercise were provided. Alternate forms of the same neuropsychological assessments (e.g, Stroop and Trails) were then conducted. Participants received a thank you gift of choice, including either a mug, bag, or pen/pad of paper.

Measures

Neuropsychological Tests

Paper Stroop Test (Van der Elst et al., 2006). The 40-item task involves measuring executive function and has strong reliability and validity. Participants were provided three separate pieces of paper, one with colored blocks, one with black ink words of the three colors, and one with incongruent words of the three different colors, red, green, and blue (ex. "blue" written in red ink). For each piece of paper, the participants were asked to complete a practice row by verbally reading either the color block, the word, or the incongruent word. They were then timed and asked to complete a trial of 40 blocks or words, naming them as quickly and accurately as possible. The Stroop A/C metric (Lansbergen, Kenemans, & van Engeland, 2007) was used to assess performance on this task.

Color Trails (D'Elia et al., 1996). Forms C and D were another test used with high reliability and validity. This assessment measures both processing speed by connecting dots as quickly as possible and executive function by alternating colors. For each form, participants were asked to complete a practice trial before the timed trials. In the first task of one form, participants to connect numbered circles in order from 1 to 25, whereas the second task had participants connect the numbered circles in order, except alternating colors between yellow to pink. The Color Trails 1:2 ratio (Strauss, Sherman, & Spreen, 2006) was computed and used to assess performance.

Electronic Stroop Congruent Correct-Incongruent Incorrect Metric (CCII; Lesh et al.,

2013). This metric was used to assess the electronic Stroop Task on the Brain Baseline app which involved subtracting the percentage of incorrect incongruent responses from the percent of correct congruent responses. Incorrect incongruent responses display when the participant inaccurately chooses a word that does not match the color, and correct congruent responses display when the participant accurately responds to a word that matches its color, with an overall score of the metric reflecting the participants mental processing ability. The reliability and validity of brain baseline is unclear as of current. Each session lasted about 5 min with a mix of congruent/incongruent stimuli presented at a rapid rate. Outcomes provided were the time and accuracy completed for each stimulus.

Alzheimer's Disease Assessment Scale (ADAS) Word Recall Task (Mohs et al., 1997). This assessment was used to determine verbal memory and has a high reliability and validity. Participants verbally read a stream of 10 words displayed to them on cards, and then they were required to recall the words immediately after. This was then repeated two more times. After five min of completion of another neuropsychological task, the participants were asked to recall the list of words again, for delay recall. Different word lists were used for the pre- and post-single bout. To score this assessment, the total number of words recalled was added up for the ADAS total score. The total number of words recalled during the delay were used to for the ADAS delay score, which differs from typical

The Montreal Cognitive Assessment (MoCA) was used to assess overall cognitive function of the participants. This test taps multiple cognitive domains via: delayed word recall, clock drawing task, repetition of digits, trails, naming, and so forth. This test has high reliability and validity and is commonly used as a brief cognitive screen in research as well as in clinical settings (Nasreddine et al., 2005). The scores can be used to categorize participants in various

dementia to normative ranges, where scores above 23 represent normative and less than or equal to 23 indicate MCI range, which is a lower cutoff score than the typical value of 26, for enhanced diagnostic accuracy (Carson et al., 2018). The current study excluded participants with scores less than or equal to 17 to guard against including participants who more impaired, perhaps indicating early dementia (who were also noted to have difficulty completing tasks and misremembering instructions).

Materials

The latest iPACES Memory Lane game (v2.0 Wall et al., 2018) was developed by our lab and refined with the help of a professional software company that specializes in educational game development. This game was played on an iPad 2 Air. An under-table stationary elliptical (the Stamina 55-110 InMotion E1000 Elliptical Trainer). To connect the game to the pedaler, wireless Bluetooth devices were used, including a Polar cadence sensor to track pedaling and a Life Well heart rate monitor ring. Participants were told to maintain their heartrate at an ideal range in order to receive an effective dose.

<div align="center">RESULTS</div>

Participants with MoCA scores within the normative and MCI range (greater than 17; Carson et al., 2018) were included within analyses, thus two cases below the range were excluded. Paired samples t-tests were conducted for the entire sample that completed the single bout of exercise on each neuropsychological test between the pre- and post-single bout of exercise. The paired samples t-test for Stroop AC ratio pre- and post- was $t(12) = -.99$, $p = .34$, for CCII^2 was $t(11) = -1.26$, $p = .23$, and for Trails 1:2 ratio was $t(12) = -.65$, $p = .52$. The paired

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[2] Analyzing the effect of the pre- to post-CCII score for participants who completed the intervention using a one-tailed paired samples t-test would be significant, p = 0.045.

samples t-test for ADAS Word Recall Total was $t(8) = -1.23$, $p = 0.25$ and ADAS delay was $t(8) = -0.71$, $p = 0.50$. No significant change was found for any neuropsychological measure, therefore there was no need to test the second hypothesis with comparison measures to rule out practice effects.

To test the third hypothesis, the sample was divided into subgroups, those who had MoCA scores in the normative range (greater than 23) and those who had scores in the MCI range (less than or equal to 23; Carson et al., 2018). As seen in Figure 2, the overall change in pre- to post-scores was compared between the two groups. Paired samples t-tests were also conducted between the pre- to post-scores of the neuropsychological tests for each subgroup. The MCI group appeared to have greatly improved in the CCII task more than the normative group, and have declined in performance for the Stroop task, although none of these executive tests were significant for this subgroup. However, a trend toward significance was found for the normative group in the Stroop A/C Ratio, $p = 0.056$. No other significance was found for the other executive function measures.

As seen in Figure 3, the ADAS Word Recall Total Score improved more-so for the MCI group than the Normative group. A repeated measures ANOVA was conducted on the MCI and Normative groups, with a covariate for age, on the ADAS Word Recall Total Score before and after the single bout of exercise. A significant interaction was found, $F(6,1) = 15.4$ $p = 0.008$, suggesting the MCI group improved from the pre- to post-single bout in score more-so than the normative group.

<div align="center">DISCUSSION</div>

The current study examines the possible benefits of short term exercise on cognitive function, specifically executive function and verbal memory skills. A total of 16 analyses were

conducted out of 18 participants enrolled in the study, with no significance found in the overall group; however, a significant effect was found comparing subgroups. A neuro-exergame has shown promising results in both long-term and short term neuropsychological abilities (Anderson-Hanley et al., 2018, Bruderer-Hofstetter, 2018, Wall, et al., 2018). In contrast with our first hypothesis, the change in cognitive measures from pre- to post-single bout in the entire group showed no significant effect, suggesting that the single 20-min bout of exercise was not sufficient to yield change in cognitive abilities of the sample overall, which included a range of participants from normative to MCI. Thus, following prior research which found differential effects among normative and MCI subgroups, a significant interaction was found, wherein MCI exercisers improved significantly on verbal memory, while normative exercisers did not. However, this significance was found on an independent test, with no comparison of the different between group effects.

With the current study's data set, participants who were considered to be more at risk for developing these illnesses (falling within the MCI group) significantly improved at the verbal memory task, performing almost identically to the normative group post-exercise. This finding suggests that the neuro-exergame may have short term benefits to the verbal memory of those with cognitive deficits, however no effect was seen in executive function measures. These results are similar to a finding in the study by Etnier and colleagues (2007) that also assessed both cognitive domains, with the greater risk of developing dementia being linked to the ApoE-ε4 allele. An improvement in verbal memory was also seen in the study by Lautenschlager and colleagues (2008). This improvement suggests that iPACES may provide immediate verbal memory benefits to those at risk for developing dementia, which could be due to increased blood perfusion in the brain (Joubert & Chainay, 2018) or other mechanisms (Kramer & Colcombe,

2018) yet to be explored in further research to analyze biomarkers from this sample and others.

It is interesting to note that prior studies evaluating the single bout of exergaming for MCI versus normative groups also found significant improvement in executive functioning (Anderson-Hanley et al., 2016, Cohen et al., 2014). While there was not significant interaction for executive functioning when comparing MCI vs normative subsamples, it is anecdotally observed that the large change appears to have been for the MCI group (on the Stroop CCII); however, this did not reach significance, likely due to the very small sample. Change in the normative subgroup nearly reached significance (p = .056). More research is needed to clarify whether both verbal memory and executive function can be reliable improved in MCI with a single bout of exercise and what variables might be affecting detection of change (for example, this sample was considerably younger and less impaired, with an average age of 67 years old, than one study above where average age was 85 and MCI cutoff was MoCA <21; Cohen et al., 2014).

Limitations

The present study has many limitations, especially due to the small sample size from complications of recruiting sufficient numbers of older adults. Some of the equipment provided faulty data as well, with iPad glitches preventing completion of the electronic Stroop Task for a participant. The single bout of 20 min of exercise may also not provide ample influence on cognition due to the short period of time, especially if participants did not reach their ideal heart rate goal, which was unable to be measured due to faulty heartrate monitors. Difficulties using the heart rate rings caused loss of information on average heart rate achieved while playing the game. This resulted in inability to determine whether all of the participants reached a level where they achieved an effective dose of exercise.

The Brain Baseline App has had some difficulties in the current as well as prior within our lab. Many older adults noted struggling with understanding the instructions posed by the neuropsychological test in the app, which therefore could have affected their scores, and thus the data would not accurately affect performance.

The MoCA assessment is meant to be a screening instrument and while widely used for research purposes, it does not reliably diagnose a participant with MCI, and simply works as a general estimate for assuming one's cognitive abilities. As discussed in the paper by Petersen and colleagues (2009), MCI cannot be determined simply by a screening test due to its extensive diagnostic criteria including neuropathology, and a wide range of cognitive deficits.

The current study sample group's average age was 67.1 years old, which is typically younger than past studies. A large subset of the participants was sought through a community gym, suggesting that this group may have better physical fitness because of access to exercise equipment for cognition, therefore they may have also higher baseline cognitive abilities due to age and fitness factors (Ahlskog et al., 2011).

Future Research

The current iPACES provides a feasible intervention for adults at risk for developing MCI and ADRD's. In order to fully test the benefits of the exergame in the MCI population, more definitive evaluations determining participant's cognitive status are necessary (Petersen et al., 2009) which would involve a more extensive neuropsychological assessment (Petersen & Negash, 2008). Possible testing for the ApoE-ε4 allele in participants would also provide more definitive biological evidence for testing to determine the risk of cognitive impairment of the participants, and thus the effectiveness of iPACES in ameliorating deficits in cognitive domains (Etnier, 2007) Measuring neurotrophic levels before and after the neuro-exergame while

assessing the risk for developing MCI and AD would strengthen research on this neuro-exergame to determine its ability to improve neuropathology involved in dementia (Yasutake, 2006).

In conclusion, neuro-exergaming as a single-bout for older adults may benefit the cognition of those with MCI, specifically in verbal memory skill. While this may not provide a cure, clinicians could potentially use the neuro-exergame as an intervention for patients to prevent progression of further cognitive decline. Further research replicating the current study along with measuring biomarkers to assess underlying mechanisms and improving equipment and materials is needed to understand the full effect of iPACES.

ACKNOWLEDGEMENTS

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┌─────────────────────────────────────┐
│   Assessed for eligibility (n = 27)  │
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                 │
                 │        ┌──────────────────────────────────────────────┐
                 │───────▶│ Excluded (n = 10)                            │
                 │        │  ♦ Not meeting inclusion criteria (n = 4)     │
                 │        │  ♦ Declined to participate (n = 6)            │
                 │        │    (did not respond to outreach, did not      │
                 │        │    show up)                                   │
                 ▼        └──────────────────────────────────────────────┘
        ┌─────────────────┐
        │   Enrollment    │
        └─────────────────┘   ┌──────────────────────────────────────────┐
                 │            │ Enrolled in single bout (n = 18)          │
                 ▼            └──────────────────────────────────────────┘
        ┌─────────────────┐
        │  Single Bout    │
        └─────────────────┘   ┌──────────────────────────────────────────┐
                 │            │ Adequate dose (n = 15)                    │
                 │            │ Inadequate dose (discontinued due to      │
                 │            │ discomfort during exercise; n = 3)        │
                 ▼            └──────────────────────────────────────────┘
        ┌─────────────────┐
        │    Analysis     │
        └─────────────────┘   ┌──────────────────────────────────────────┐
                              │ Analysed (n = 13)                         │
                              │  ♦ Excluded from analysis (MoCA <= 17,    │
                              │  dementia range; n = 2)                   │
                              └──────────────────────────────────────────┘
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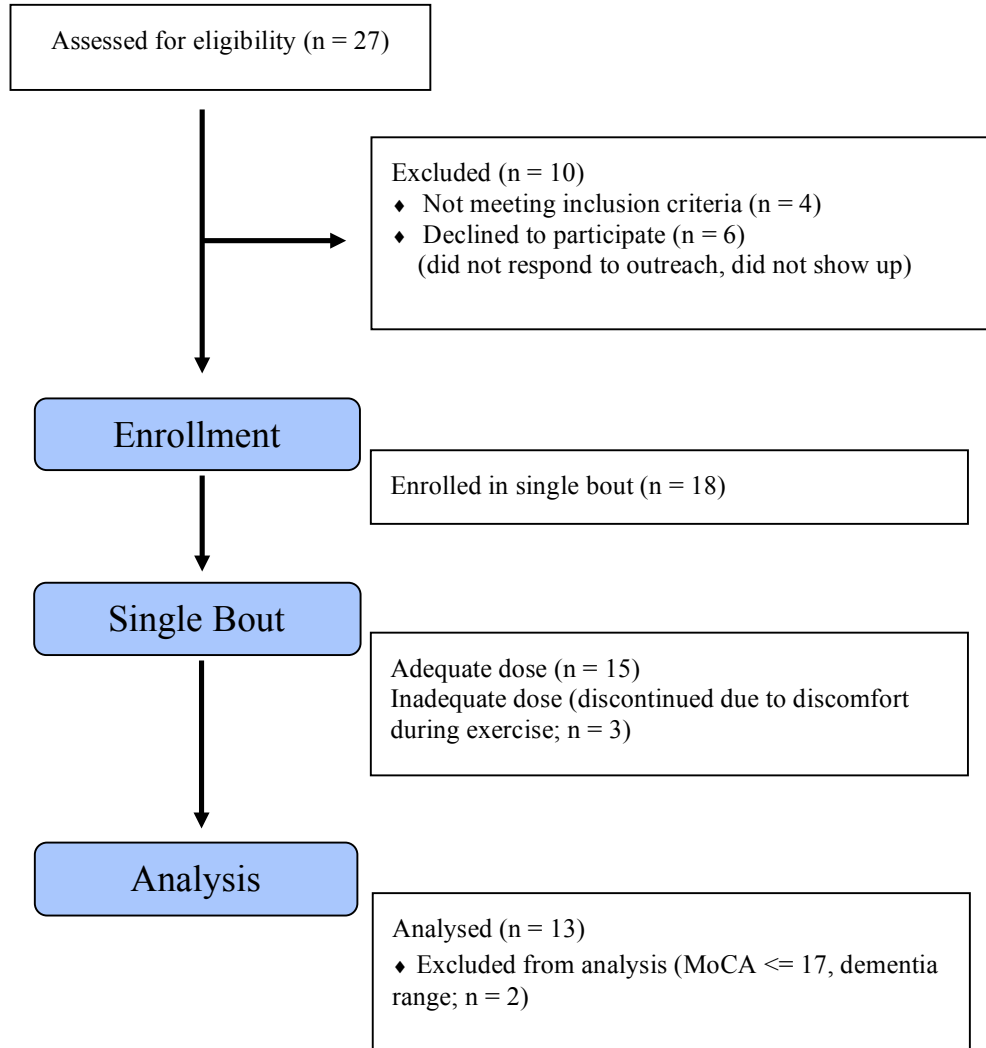
Figure 1. CONSORT Flow Diagram displaying the process of participant enrollment, study evaluation with the neuro-exergame & analysis of results.

Table 1. Demographics of subsets of participants, excluding dementia (MoCA <=17).

Demographics	Normative Complete			MCI Complete			Total (excluding dementia)		
	ave	SD	n	ave	SD	n	ave	SD	n
age	68.67	7.35	9	60.20	5.97	5	67.1	8.42	16
education (yrs)	15.33	1.66	9	16	3.16	5	15.6	2.13	16
sex (% female)	67%		9	80%		5	69%		16
cog fn (MoCA)	26.44	2.4	9	22.83	0.75	5			16
retired	89%		9	40%		5	75%		16
BMI	25.38	1.95	9	26.44	4.02	5	25.8	2.62	16
experience bike	2.56	0.88	9	2.8	1.3	5	2.75	1	16
experience computers	3.11	0.93	9	2.8	0.84	5	2.88	0.89	16
experience videogames	1.56	1.01	9	1.6	0.89	5	1.44	0.96	16
motivated	2.38	0.52	9	2.6	0.89	5	2.43	0.65	16

Table 2. Results of the neuropsychological tests from pre- and post- SB, excluding dementia. (MoCA <= 17)

| Neuropsychological Tests	Normative Complete				MCI Complete				Total (excluding dementia)			
Pre-Single Bout	ave	SD	n	p	ave	SD	n	p	ave	SD	n	p
ADAS Word Recall Total	21.80	4.55	5		19.2	2.49	5		20.22	3.83	9	
ADAS Word Delay Total	6.80	2.77	5		6.2	1.92	5		6.33	2.35	9	
Color Trails 1/2	0.43	0.12	9		0.399	0.081	6		0.423	0.106	14	
CCII	0.95	0.054	9		0.882	0.15	6		0.92	0.107	14	
Stroop A/C	0.45	0.098	9		0.483	0.1	6		0.471	10.76	14	
Post-Single Bout												
ADAS Word Recall Total	21.20	2.77	5	0.529	21.4	2.61	5	0.161	21.33	2.69	9	0.254
ADAS Word Delay Total	6.60	1.82	5	0.854	7	1.22	5	0.242	6.78	1.41	9	0.498
Color Trails 1/2	0.48	0.15	9	0.44	0.436	0.173	6	0.618	0.451	0.153	14	0.555
CCII	0.95	0.05	9	0.989	0.974	0.037	5	0.263	0.961	0.046	13	0.229
Stroop A/C	0.53	0.134	9	0.056	0.449	0.091	6	0.19	0.501	0.123	14	0.268
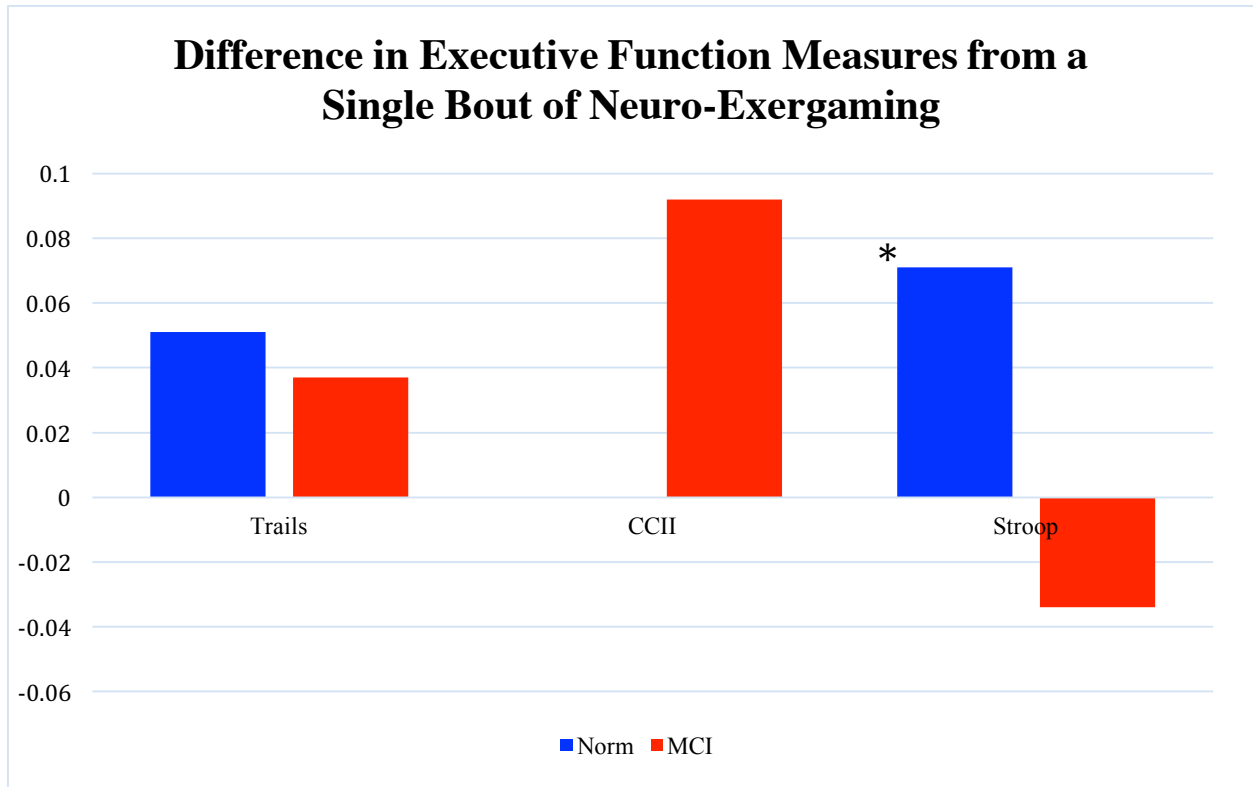
Figure 2. The difference in scores from pre- to post-single bout between the normative and MCI subgroups, excluding incomplete group of the SB and dementia cases. There was a similar change for both subgroups in the Trails Task. There was no difference from pre- to post-single bout for the normative group and an increase in accuracy for the MCI group for CCII, with no significant effect. There was an increase in the Stroop A/C ratio for the normative group and a decrease for the MCI group. *There was a 0.07 increase from pre- to post-single bout in the Stroop task for the normative group, suggesting significant improvement ($p = 0.056$).
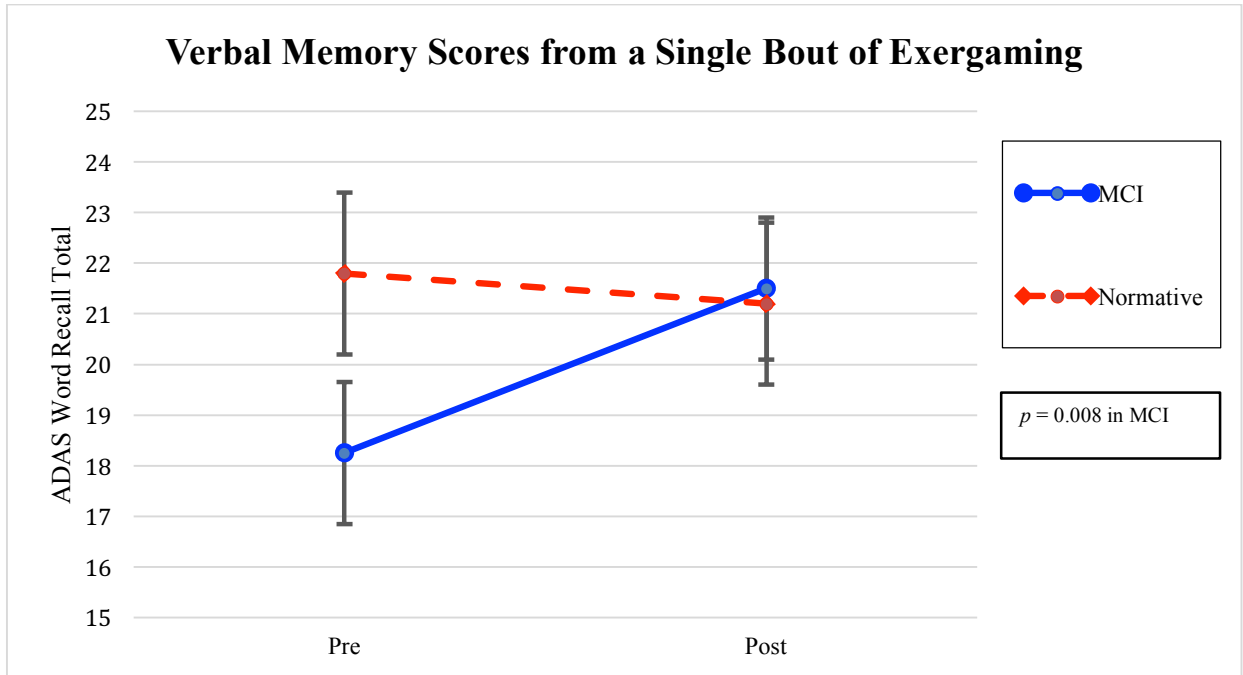
Figure 3. Graph displaying the change in ADAS Word Recall Total scores from pre- to post-single bout, comparing MCI (MoCA <= 23) vs. Normative group (MoCA > 23). A significant effect is seen in the MCI group, suggesting the short-term bout of the neuro-exergame improved verbal memory scores for this subgroup.

Appendix A

CONSENT TO PARTICIPATE IN HUMAN RESEARCH

Title of Research Study: *Interactive Physical and Cognitive Exercise Study (iPACES™ v2.5)*

Principal Investigator(s): *Cay Anderson-Hanley, PhD and Alexa Puleio (Union College)*

HANLab: *Healthy Aging & Neuropsychology Lab, 807 Union Street, Schenectady, NY 12308*
CBMW: *Gordon's Center for Balance, Mobility & Wellness, 26 Hull St., Wenham, MA 01984*
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™ v2.5)*." 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 investigates the possible benefits of physical exercise (such as pedaling an under-table stationary elliptical) and mental exercise (such as playing a videogame on a portable iPad), especially when combining these activities together interactively (as in the iPACES™ exergame).

This consent form contains information about the study, including the risks and benefits of participating, so that you 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 will be asked to sign this form if you agree to take part in the study. You will be given a signed copy of the form to keep as a record.

By signing this document you do not change your legal rights, but indicate that you understand the information, and that you give your consent to complete the evaluation of your brain health and thinking processes during the single bout study.

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 agree to participate in this study, the following will occur:
1. A research team member will contact you and discuss the study with you.
2. If you agree to participate, an initial meeting will be arranged (e.g., at the Union College Healthy Aging & Neuropsychology Lab: HANLab or Gordon's Center for Balance, Mobility & Wellness: CMBW).
3. During the meeting (which will last approximately 2 hours), you will meet with a member of the research team at the location where you will be evaluated and briefly exercise (HANLab or CBMW) using the exercise equipment provided by the research. A

    researcher will conduct evaluations with you privately. 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.

    b. Physiological measures will be taken (e.g., height, weight, heart rate and background questionnaires completed (e.g., medical and exercise history).

    c. Saliva samples will be gathered (passive drool/spit into vial).

    d. Tests of thinking will be administered (e.g., puzzle-like tasks such as connecting dots in order or recalling a list of words). Some tests will be paper and pencil tasks and some will be computerized, on an iPad.

4. A researcher will demonstrate how to play an exergame using an iPad while pedaling and steering to control your progress (iPACES™ v2.5). You will then pedal and play the exergame for a 20-minute session.

5. Following the exercise session you will complete a few more puzzle-like tests of thinking and fill out questionnaires regarding your experience with the exergame.

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.

POSSIBLE BENEFITS OF THE RESEARCH

Your 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 research staff while you are in this study. Tell your regular health care providers that you are in this study, and give them the name and phone number of the research lab. Being in this study may involve some added risks or changes in your normal daily experiences.

Risks/Side Effects of Exercise
There are some risks related to exercise.

- You may feel typical effects of exercise (such as sweating). You should ease into the exercise session in order to minimize risk of muscle strain, joint pain, or other injury. You will be given an ideal heart rate range to target while pedaling and should not exceed. There is a rare chance of serious harm during any exercise (e.g., heart attack, stroke, or even death).
- The iPads contain a virtual reality screen. There is a risk of "cyber-sickness" 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.

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 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 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 study as part of a larger clinical trial report may become 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).

PAYING THE COST OF THE RESEARCH

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

VOLUNTARY NATURE OF PARTICIPATION AND WITHDRAWAL

Your decision to participate in this research should be 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 research staff if you decide you want to stop. They will explain what you need to do to withdraw from the study. 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 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 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 research 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

Appendix B

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

The Interactive Physical and Cognitive Exercise Study (iPACES v2.5)
Initial Evaluation Protocol Script (<mark>paper-1st</mark>)

_____ Pre-session checklist:
       _____ 1 copies of consent form, IDMC, and demographic questionnaires
       _____ 1 copies of neuropsych folder protocol
       _____ Neuropsych kit (materials: 2 Color Trails, 2 Stroop stimuli, 2 ADAS stimuli)
       _____ Clipboard, pen, notepad, sharpie
       _____ iPad
       _____ Saliva collection materials (1 tube, 1 straw, 1 towelette)
       _____ 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.**

_____ Give participant a copy of the **saliva oral preparation sheet** (*review with participant first visit*)

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

____ **Collect Saliva Sample**
Wear safety equipment i.e. a pair of gloves. For collection, you need to put the saliva sample on ice immediately after collection - therefore you will need to bring a container with ice. Instruct the participant to allow some saliva to collect under their tongue...when they feel like they would normally want to swallow, they should drool/lightly spit through a straw into the collection vial. They will repeat until the vial is to the designated line (3 mL). Let the participant know that it often takes some time (we don't want the participant to forcefully spit into the container as this can contaminate the sample). If the participant is having trouble producing enough saliva, they can think of a favorite food. Also, we have some lemon extract that they can <u>smell</u> (not taste), which often helps. Process may take 15-20 minutes.
Label tube with ID number, date, & PRE for pre single bout.

_____ Administer Demographic Questionnaire, 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

_____ **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 3/pre)

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 the Stroop Task (paper 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 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 Brain Baseline Tests: Stroop

This next task is going to be on this iPad tablet. The task has been programmed onto the tablet for you. All you have to do is follow the directions on the screen. If you have any questions at any time, please let me know. When you are ready, you may press Begin. When you have completed the task, please let me know.

When the participant has completed the task, put the iPad to the side.

_____ Administer MoCA.

_____ Set up iPad for iPACES

Make sure that database is cleared so that you can enter new ppt information
Connect to Bluetooth for heart rate monitor & cadence

PASSWORDS:
   Bluetooth: aceslive01
   Heart Rate Monitor: BLE
   Cadence password: 1. E7432F1
                     2. BD9F4D14

INTRODUCE TO CONDITION

INSTRUCTIONS:
Encourage them to take a drink of water.
You will be pedaling to control your progress along a virtual bike path
Try pedaling a few times *(position the pedaler so comfortable, etc. and have them do a few "rotations").*

On this iPad screen you will be able to see your HR and should little by little bring it up to the target heart rate. Let's check your resting HR now and compute your target HR:

      Resting HR (Heart Rate at Rest: HRR) = _____ (measured on screen)

      Calculate Target Heart Rate:

      $[([(220- \underline{\hspace{1cm}} age) - \underline{\hspace{1cm}} HRR]*.60) + \underline{\hspace{1cm}} HRR] = \underline{\hspace{1cm}}$

      Target HR = [(Heart Rate max – Heart Rate Rest) *.60) + Heart Rate Rest]

      You should aim for this target heart rate.

      $[([(220- \underline{\hspace{1cm}} age) - \underline{\hspace{1cm}} HRR]*.80) + \underline{\hspace{1cm}} HRR] = \underline{\hspace{1cm}}$

      Max HR = [(Heart Rate max – Heart Rate Rest) *.60) + Heart Rate Rest]

      You should slow down if you get up to this maximum heart rate.

Point out the warning label on the screen of the iPad – say:
If you feel faint, dizzy, have sharp pain, or other discomfort, stop exercising.

    _____ 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 (follow instructions on screen)
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: _____

_____ Record ride summary data from screen in logbook.

POST SINGLE-BOUT
_____ Administer EIFI & Flow
    After completion of the 20-minute single bout, have the participant complete the Flow and EIFI questionnaires.

_____ Administer Word List Memory (LIST 2/post)

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

_____ Collect Saliva Sample
Wear safety equipment i.e. a pair of gloves. For collection, you need to put the saliva sample on ice immediately after collection - therefore you will need to bring a container with ice. Instruct the participant to allow some saliva to collect under their tongue...when they feel like they would normally want to swallow, they should drool/lightly spit through a straw into the collection vial. They will repeat until the vial is to the designated line (3 mL). Let the participant know that it often takes some time (we don't want the participant to forcefully spit into the container as this can contaminate the sample). If the participant is having trouble producing enough saliva, they can think of a favorite food. Also, we have some lemon extract that they can <u>smell</u> (not taste), which often helps. Process may take 15-20 minutes.
Label tube with ID number, date, & POST for post single bout.

_____ 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 the Stroop Task (VERSION 2)
Before showing the examinee any of the cards, say:
<u>COLOR BLOCKS:</u>
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.*

<u>BLACK WORDS</u>:
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 Color Trails B
PRACTICE: Color Trails 1-B
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 Brain Baseline Tests: Stroop

This next task is going to be on this iPad tablet. The task has been programmed onto the tablet for you. All you have to do is follow the directions on the screen. If you have any questions at any time, please let me know. When you are ready, you may press Begin. When you have completed the task, please let me know.

When the participant has completed the task, put the iPad to the side.

_____ Thank the participant. **You did a fine job today! I want to thank you 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.*

Would you like to receive the results of the study once complete? (most likely next spring?)

email address: _____

(if not email, then snail mail address: _____)

Is it ok if we contact you in the future in case we do a follow-up study? (possibly at CBMW or maybe even the portable iPACES delivered to your home?)

yes or no (circle one)

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