DANCE, DANCE REVOLUTION: CHANGE IN EXECUTIVE FUNCTION FOLLOWING A VIDEO DANCE INTERVENTION IN POSTMENOPAUSAL WOMEN

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ABSTRACT

There is substantial evidence supporting aerobic exercise as an efficable opponent of the growing problem of cognitive decline (CD). Most exercise interventions have examined their relationship to brain health using simple aerobic exercises and achieved favorable results. There is potential to improve cognitive outcomes by using a complex aerobic exercise such as video dance. In this study, we compared brain activation from the digit symbol substitution task in 39 postmenopausal women (mean age = 55.2 years, SD = 10.2 years, mean weight = 175.8 lbs., SD 24.0) who completed baseline and follow-up fMRI scans. These women were divided into three groups; video dance, walk and delayed entry controls. Activation maps were created for the change between baseline and follow-up time points for each group: video dance, walk and delayed entry controls. The activation maps were qualitatively examined for differences between the three groups. Results indicate that the video dance group showed significant, positive activation in areas of the brain associated with executive function potentially due to the complexity of the exercise intervention. The public health significance of these finds are that video dance is an inexpensive, safe, and easy to implement intervention which may impede the progression of cognitive decline and decrease the expression of CD and Alzheimer's disease (AD) symptoms, and could lead to the decrease of disease in the population. Any reduction in

the incidence of CD also reduces stress on the healthcare system, individuals, and reduces the overall prevalence of disease in the population.

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PREFACE

I would like to thank my husband, George Haff, for putting up with me during my time in graduate school. My family for understanding my absence in their lives, and realizing that it was temporary. My friend Kathryn L. Edelman who was a big help throughout the entire process. Dr. Destiny Babjack and Phil Greer for guidance and feedback. My adviser, Dr. Nancy Glynn for her patience and prodding. My essay committee Dr. Howard Aizenstein, Dr. Kirk Erickson, and Dr. Nancy Glynn for the useful feedback. Dr. Stephanie Studenski and Dr. Caterina Rosano for allowing me to examine these data from their study.

1.0 INTRODUCTION

1.1.1 Aging Population and Cognitive Decline

As the population of the United States ages and people are living longer, the public health community must prepare to deal with the impact on the healthcare system. Over the next several years, the number of elders will significantly increase. The number of Americans 65 years old or older are expected to increase by more than double, bringing the count to nearly 89 million US citizens by the year 2050.[1] Not only will the healthcare system need to accommodate an increase in the number of elders, there are other considerations that come with growth of the aging population. Of these, cognitive health and impairment are arguably the most pressing public health concerns.

Cognitive decline (CD), or cognitive impairment (CI), is damage to the cognitive processes, e.g., memory and attention, that negatively impact the things an individual can do in everyday life.[2] Cognitive function generally transitions from optimal function in our youth to more disadvantageous function later in life. This is usually a gradual transition that sometimes accompanies the normal aging process, but can evolve into CD, or Alzheimer's disease (AD), which is accompanied by steeper and more severe cognitive impairments. Cognitive changes manifest distinctly in each person's life, slowly eroding independence; the ability to care for oneself, the ability to manage finances and medications, and to prepare meals.[2] Ultimately, CD can lead to negative mental health outcomes, disability, and an increased risk of mortality for those affected by any type of CD be it a precursor to AD, or not. [3-5]

1.1.2 Public Health Significance

CD and AD will change the face of the healthcare system because the impacts of these incurable conditions are far reaching. CD and AD care are expensive -- the price tag for Medicare, Medicaid, and individual out-of-pocket is high. In any of its forms, dementia is costly; direct and indirect cost of care have been estimated between $159 billion to $215 billion in 2010 alone.[2] The monetary strain on the healthcare system will only increase as the aging population of the US grows. By the year 2050, the cost of care for elders living with Alzheimer's disease will reach $1.08 trillion per year, a fivefold escalation.[6] The US healthcare system and taxpayers will not be able to shoulder the economic burden under the current system. Care for those suffering from CD and AD will need to be rethought in order to avoid a healthcare and economic crisis.

The price for CD and AD care are not limited to the healthcare system tallies. The costs of CD and AD extend beyond the medical costs for the diseased and ailing to their loved ones. "Family care partners of individuals with dementia are at greater risk for anxiety, depression, and poorer quality of life than care partners of individuals with other conditions. Between 28% and 55% have depression, compared with 15% in the non-caregiving older adult population."[2] Caregiver and family members devote their time and attention to preserve the health of their loved ones while risking their own health and well-being, which in turn further depletes resources from the healthcare system and decreases the overall health of the nation.

There are many benefits in avoiding the costs of CD and AD care. Most notably, elders would live longer, healthier, and more independent lives if the number of healthy years can be extended by avoiding any CD. From a public health perspective, finding tangible avenues of prevention or early treatment for CD and AD could reduce current financial burdens on the healthcare system, reduce individual financial burden and stress, and decrease the overall incidence and prevalence of disease in the population. Although some drug treatments are available and under development, "there are no disease-modifying therapies, studies have shown consistently that active management can significantly improve quality of life through all stages of the disease for individuals with dementia and their care partners."[2] The lack of feasible drug treatments only adds urgency to the need to find an affordable, efficable treatment to slow, halt, or reverse the onset and progression of CD and AD.

Accumulating evidence suggests that a host of modifiable behaviors can impact the trajectory and onset of CD and AD. These include activities like brain training,[7-9] vitamin supplements,[10,11] various diet modifications, [10,12,13] yoga and meditation, [14-16] and both anaerobic and aerobic exercise.[17-24] Of these options, cardiorespiratory exercise not only has the potential to preserve cognitive functioning, it also has the potential to decrease risk factors and other comorbidities that frequently accompany aging, e.g., diabetes, cardiovascular disease, balance and mobility issues.[18,25]

1.1.3 Exercise and Executive Function

Animal models have shown promise in revealing the molecular mechanisms by which cardiovascular exercise promotes brain health. There is evidence that Brain-derived neurotropic factor (BDNF) and nerve growth factor (NGF) along with other neurotransmitters promote neurogenesis, and that exercise facilitates an increase in these chemicals.[26] BDNF and NGF are neurotrophins that impede brain senescence in animal models; brain health is promoted by exercise induced neurotrophins increase.[27,28] Exercise has also been shown to increase BDNF and NGF in the hippocampus, contributing to neuron growth and propagation, thus protecting and enhancing cognitive function in rodents.[27-29] Behaviorally, these mechanisms translate into an increase in spatial memory; the rats that exercise learn the maze cues faster.[30,31] These animal models create a foundation from which human studies can be planned and implemented.

The epidemiological literature supports the fact that better physical health is correlated with prolonged healthy cognitive function.[17,32] In a Canadian population of men and women 65 years and older over a five year period, walking was found to reduce the risk of developing CI by 58%, AD by 50% and any type of dementia by 63%.[33] One of the first multicenter randomized clinical trials called the Lifestyle Interventions and Independence for Elders Pilot study found that there are both physical and mental benefits produced from aerobic exercise.[5] These studies highlight the importance of exercise in maintaining healthy cognitive function and support the correlation between increased physical activity and improved cognitive performance.

The relationship between physical activity and cognitive health goes beyond increased healthy brain function. There is also evidence exercise interventions prevent the negative changes that occur in the brain as it ages. A study done in 2006 found that over an approximate six year period, people 65 years and older that exercised three or more times a week were less likely to develop dementia.[34] Yaffe and colleagues, established that for community dwelling women 65 year old over a 6-8 years or older period, exercise can decreases the risk of CD from 66-74%.[35] This research points to an important relationship between physical fitness and brain health. However, the underlying physical mechanisms the animal models have proposed are unable to be connect to the behavioral effects seen in the epidemiological studies.

As technology becomes more sophisticated, so do the types of experiments and interventions that are able to be studied. Scientists have used magnetic resonance imaging (MRI) to assess the anatomy of the brain in conjunction with functional magnetic resonance imaging (fMRI) to ascertain how brain processes work. Imaging studies have attempted to establish how physical fitness affects brain health. This begins with understanding some of the circumstances which are sub-optimal for brain function. Typically, the presence of white matter hyperintensities (WMH) has been associated with decreases in task accuracy.[36] However, the same study has also shown the ability of brains with a higher instances of WMH to alter activation patterns; they recruit additional areas of the parietal lobe to maintain accuracy during task performance. This additional brain activity is likely to be a result of the brain's ability to adapt by using other available resources to maintain similar performance despite underlying structural damage.[36]

This adaptive capacity is enhanced by physical activity. The physical changes induced by increasing cardiorespiratory fitness include an influx of resources to the brain to stimulate new cell and blood vessel growth, which lead to decreased brain atrophy and greater brain volume.[3,37,38] In this scenario, the areas of the brain that receive blood supply from multiple sources would be most reflective of these types of changes.[3,37,38] These areas include those specific to executive function, e.g., the frontal cortices, and there is evidence of increased signal in the parietal region after sustained physical activity.[36,38] This increased signal is thought to compensate for mechanisms of structural deficiencies, but is also evidence of cortical plasticity.

Cortical plasticity is not a new idea, but it has not been the norm in discussions about aging. Historically, the brain has been regarded as having an expiration date, and while this is in part true, it does not necessarily mean that there is no hope to fight cognitive decay commonly associated with age.[3,39] Exercise positively affects cognitive function by increasing brain mass; it is also important in influencing neural connectivity networks.[36,37,40] A person's level of aerobic fitness in part determines what resources are available while preforming cognitive function. If an elder exhibits neural atrophy and WHMs, then the brain must compensate to perform at a level comparable to someone else without physiological deficits. One way to facilitate this compensation it to increase the supply lines to the brain via aerobic stimulation of blood vessel and new cell growth. In brain areas where there is damage, the connections can't be direct and these resources propagate through different pathways, similar to a plant growing in a sidewalk crack. This detour facilitates connections which allow recruitment of axillary brain areas to maintain performance levels on fMRI tasks by incorporating the temporal and parietal lobes to the "usual" processing loop.

This processing loop includes a collection of brain areas that are associated with executive function. Executive function incorporates several cognitive domains. Among them are: working memory, attention, task switching, and coordination of multiple tasks.[40] Simple aerobic exercise can enrich control of executive and attentional networks behaviorally manifesting as gains in processing speed and accuracy in tasks measuring executive function.[3,38,40] A measure of executive function used both in epidemiological and imaging studies is the digit symbol substitution task (DSST). The DSST has been characterized as a reliable measure of working memory and processing speed.[5,38,41,42] Declines in DSST scores can be operationalized as indicators of CD, and are also indicative of increased mortality risk, cognitive decline and other changes associated with aging.[36,38,42-45] In order to address current gaps in the knowledge, the impact of a complex cardiorespiratory fitness regimen has on cognitive function is examined in the context of brain imaging. This study uses the change in DSST activation patterns to characterize the relationship between a complex aerobic task and healthy cognitive function.

Randomized control trials illustrating the relationship between aerobic exercise and healthy cognition are in short supply.[46,47] In the video game Dance Dance Revolution, this executive function component is comprised of coordinating body movements in synchronization with the rhythm of a song. Each level increases in difficultly, demanding increased physical activity and mental coordination. Research that explores the relationship between physically active video games which are aerobically demanding and stimulate higher cognitive processes, and the yield to cognitive function is still in its infancy.[48] Thus, my hypothesis is that the DSST activation patterns of the exercise group will significantly differ from those of the brisk walk group and delayed entry control group. I suspect brain activation patterns will include areas typically activated by the DSST (frontal cortex and parietal regions). Also, due to the complex nature of the DDR task, I expect to see DSST activation in areas that have been altered as a result of exercise, specifically areas of the fronto-parietal network. These areas include inferior parietal cortices, supplementary motor cortex, frontal eye fields, visual cortex, inferior frontal cortex, and parts of the temporo-parietal junction.[49] These areas have been shown to be susceptible to recruitment for[36,38,49] and the fronto-parietal network is associated with top down processing of attention (both spatial and distributive), working memory, encoding, and response mappings.[41,49]

2.0 METHODS

2.1.1 fMRI and Physical Activity Intervention

The data for this study is from the Adherence and Health Effects of Video Dance Exercise and Brisk Walking in Postmenopausal Women: A Randomized Control Trial[50] conducted at the University of Pittsburgh, NIH NCT01443455. The main study examined adherence to a video dance exercise (DDR) program in comparison to brisk walking (Walk) and delayed entry controls (Wait) over a six month time period. Detailed information about the intervention can be found elsewhere.[41,50] Briefly, participants were screened for safety considerations relevant to an exercise intervention (physical health factors, risk of fracture, and serious comorbid conditions), and cognitive impairment.[41] Exclusion criteria included a history of osteoporosis, osteoporotic fractures, active cardiovascular disease, uncontrolled hypertension, exercise limiting weight bearing pain, seizure disorder, or any medication that would limit the safety of the study.[50] Participants were randomly assigned to one of the three arms of the intervention: DDR, Walk, and Wait.

Each group in the intervention was invited to participate in an fMRI ancillary study. If interested, they were additionally screened for safety concerns relevant to an MRI procedure, then scheduled for their fMRI baseline and follow-up. Follow-up fMRI scans took place about three months into the intervention. For the fMRI ancillary study, each participant signed an approved IRB consent specific to the fMRI procedure. Participants were alloted practice time outside of the scanner to learn the task and each scan was completed in under two hours.

2.1.2 Participants

Participants in the main trial were sedentary, post-menopausal women between the ages of 50 – 65 years with a BMI over 25.[41] A total of 39 women (mean age = 55.2 years, SD = 10.2 years, mean weight = 175.8 lbs., SD 24.0) participated in the ancillary study by completing baseline and follow-up fMRI scans. Of the 39 women, nineteen women were in the DDR group (mean age = 55.4 years, SD = 4.6, mean weight = 182.4 lbs., SD 25.2), fifteen women were in the walk group (mean age = 52.1 years, SD = 15.9 years, mean weight = 165.6 lbs., SD 21.7), and five women were in the wait group (mean age = 55.4 years, SD = 3.9 years, mean weight =179.4 lbs., SD 20.8).

2.1.3 Digit Symbol Substitution Task

The digit symbol substitution task (DSST) is a metric of executive function.[5,38,41-43] To

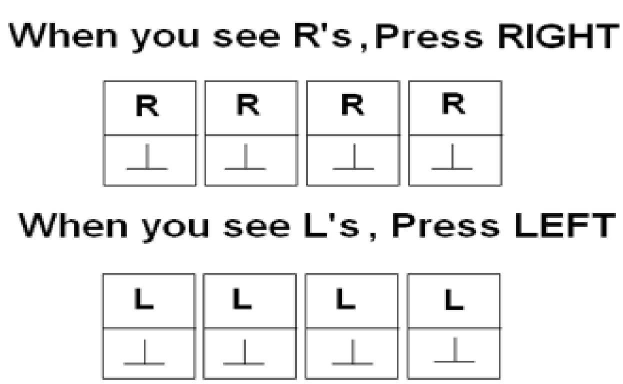

Figure 1. Sample Control Trial from the sDSST Task

perform the DSST successfully, a participant must employ several cognitive modalities such as perceptual organization, aspects of memory, visuomotor coordination, and selective attentional filtering.[42,44] This task has been adapted and validated for use during an fMRI scan.[36,44] The electronic version of the DSST is a block design that consists of presentation of a control block and then an experimental block.

During the experiment, a fixation appeared followed by a cue number and symbol pair. The participant must respond to the control trials, which assessed the participant's basic processing speed and response time for a finger press. The participant must respond to the control trial, which confirms the participant can distinguish left and right, with the correct button response. The correct button response is dictated by the letter the display shows (left or right), see Figure 1.[36] The structure of the experimental trial is the same. This time, the participant determined whether the cue symbol was correctly substituted within a string of number/trial pairs. Once the determination is made, a button press is used to indicate the perceived accuracy (right = correct/matching, left = incorrect/unmatching), see Figure 2.[36] Notably, the DSST has been used in a number of earlier studies to characterize the effects of aging on cognitive function.[36,38,42,44,45,51]

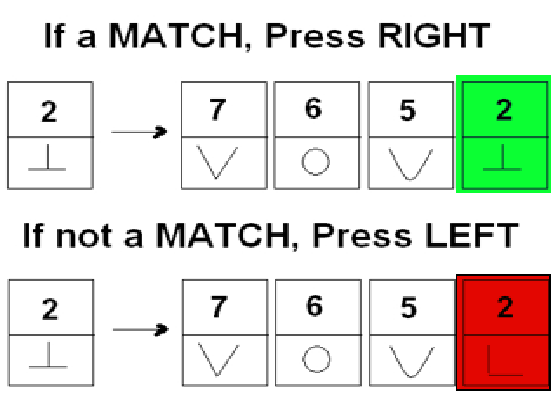

Figure 2. Sample Experiment Trial from the sDSST Task

2.1.4 fMRI protocol

All data acquisition occurred at the Neuroscience Imaging Center (NIC) on a 3 Tesla Siemens MAGNETOM Allegra scanner using a 12-channel head coil. Both baseline and follow-up scan protocols were identical. Collection of diffusion weighted imaging, high resolution anatomical images, and resting state scans were obtained. Prior to the fast echo-planar imaging (EPI) data collection, a 3 plane localizer and sagittal scan were collected. An EPI sequence (TR = 2, TE= 25, 34 slices) was used to collect the blood oxygen level dependent contrast (BOLD) data for the DSST task mentioned previously.

2.1.5 Preprocessing and Analysis of fMRI Data

All fMRI data were analyzed using Statistical Parametric Mapping (SPM8) v4667 and MatLab 7.9.0.529 R2009b. Each participant's imaging data was motion corrected by realigning all images in the session to the first image of that individual's same scan session. The images were then smoothed using an 8mm Gaussian kernel and normalized to a template image in Montreal Neurological Institute (MNI) space. Then a general linear model using restricted maximum likelihood estimation was employed to calculate the F statistic and create contrast maps for the Experimental > Control and Control > Experimental conditions. During this process further motion correction was performed to further eliminate effects caused by head motion. After level one contrasts were created, further comparison (level two analysis) were calculated to determine the within-group main effect. For each group, DDR, Walk and Wait, differences in activation between baseline (T1) and follow-up (T2) scans were calculated using a two sample paired t-test. The T-maps were then examined in XjView to determine the MNI coordinates of the active brain regions, and a qualitative comparison of the data were performed.

3.0 RESULTS

Within the DDR group, brain activation was significantly different for the DSST experimental condition at T2 compared to T1. The activation for the DSST T2 > DSST T1 contrast increased in several regions in the brain. The largest cluster of activation was situated around the area of the right supramarginal gyrus, right superior temporal gyrus, and Broadman area 39 (T = 3.61, cluster size 5, p = 0.001), see Figure3.**Figure 3.** DDR Activation T2 > T1 There was a smaller cluster of activation around the left amygdala, left parahippocampal gyrus and Broadman area 40 (T = 3.61, cluster size 5, p = 0.001).

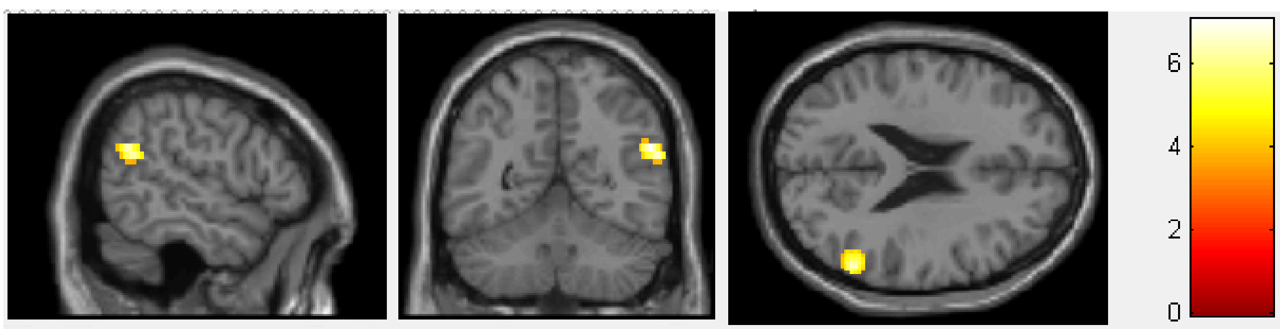

Figure 3. DDR Activation T2 > T1: Comparison of activation between baseline and follow-up times for the DDR group experimental condition

The Walk and Wait groups both had areas of significantly less cortical activation when the DSST baseline activity was compared to follow-up activity. The Walk group had significant negative activation for the T2 > T1 contrasts. This decrease in cortical activation was concentrated around the right anterior cingulate, right medial frontal gyrus, and right Broadman areas six and 32 (T = 3.85, cluster size 5, p = 0.001), see Figure 4. **Figure 4.** Walk Activation The Wait group had one major area of significant negative activation for the DSST T2 > T1 contrasts.

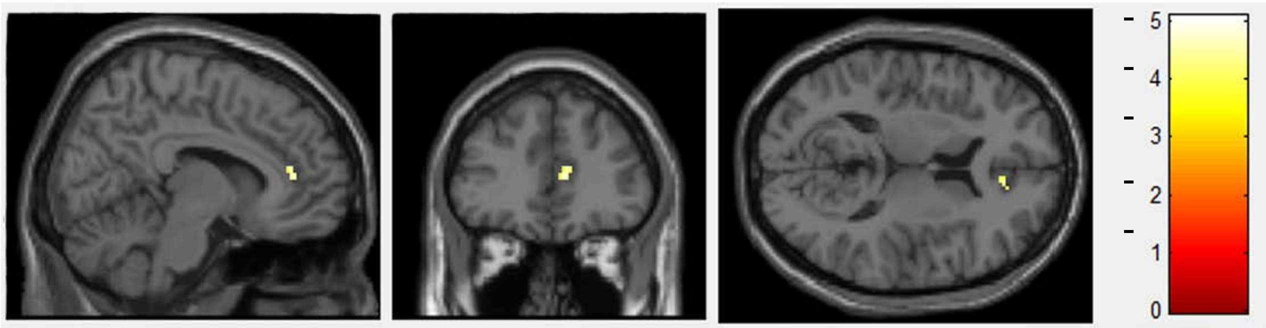

Figure 4. Walk Activation T2 > T1: Comparison of activation between baseline and follow-up times for Walk group

The reduction in cortical activity is located in the area of the inferior frontal gyrus (T = 7.17, cluster size 5, p = 0.001), see Figure 5.

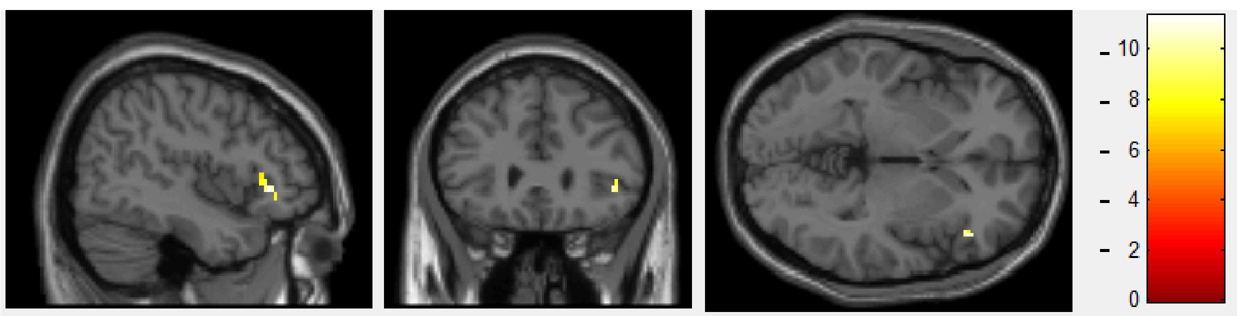

Figure 5. Wait Activation T2 > T1: Comparison of activation between baseline and follow-up times for Wait group

A qualitative comparison of the data between the baseline scan and the follow-up scan yielded different significantly active brain regions between the DDR, Walk, and Wait groups. The DDR group showed positive significant activation in the right temporal and parietal regions of the brain (cluster size 5, p = 0.001), while the Walk and Wait groups showed significant negative activation in the frontal regions of the brain (cluster size 5, p = 0.001).

Brain activation is summarized in Table 1, which also includes the central MNI xyz coordinates. The DDR group showed activation in brain areas associated brain networks involved in visuospatial working memory, fronto-parietal network, decision making areas and the fronto-executive network. These areas are characteristic of executive function, emotion, directed attention, and working memory.[38,49,52] The Walk group showed decreased cortical activation in memory[53] and executive function[38] areas while the Wait group had decreased cortical activation in the inferior temporal gyrus associated with executive function.[38]

Table 1. Active Brain Areas by Group

Group (N)	Brain Area	x	y	z	Network
DDR (19)	Right Supramarginal Gyrus, Right Brodmann Area 39, and Left Brodmann Area 40	50.00	-50.70	27.27	Visuospatial Working Memory[52]
	Right Superior Temporal Gyrus	56.15	-57.26	24.00	Fronto-parietal Network[49]
	Left Amygdala and Left Parahippocampal Gyrus	-18.00	-3.82	-14.17	Decision Making[54] and Fronto-executive Network[49]
Walk (15)	Right Medial Frontal Gyrus, Right Brodmann Area 6	14.11	-15.49	58.11	Memory Network[53]
	Right Anterior Cingulate, Right Brodmann Area 32	9.27	39.79	12.00	Executive Control Function[38]
Wait (5)	Inferior Frontal Gyrus	46.22	28.43	-1.57	Executive Control Function[38]

4.0 DISCUSSION

The DDR group showed significant, positive activation in the right supramarginal gyrus, right Brodmann area 39, and left Brodmann area 40, areas associated with visuospatial working memory.[52] In neuroimaging literature the supramarginal gyrus has been associated with information storage in working memory, and the right supramarginal gyrus specifically has been associated with visuospatial tasks.[52] Due to the nature of the DSST, it is expected to find activation in the region. This is also an area of executive function that has been shown to be affected by aerobic exercise.[36,37,40] The fact that the activation is the difference at T2, suggests the change is due to the intervention.

The DDR group's activation is did show an active cluster of voxels in the right superior temporal gyrus which is a part of the fronto-parietal network.[49] This network has been shown to associated with attention and working memory, especially when the task complexity exhausts typical working memory networks.[49] The DSST has not been shown to be particularity cognitively taxing,[41] especially to a well-practiced group of participants. Therefore, it is possible this activation is due to the strengthening of the networks because of the complex aerobic component of the intervention. There is however, much less involvement of the fronto-parietal network than hypothesized. It is possible this is due to the DSST not being complex enough to tax executive function to the point it needs to recruit the entire network.

The last active areas in the DDR group were the left amygdala and left parahippocampal gyrus. The amygdala and parahippocampal gyrus are both components of the limbic system.[55] This system has been noted to play a role in judgment, decision making and emotion in conjunction with rational decision making.[54,56,57] Activation in this areas is intutive because the DSST requires a choice. The positive activation at T2 could indicate that this area has also been effected by the video dance intervention.

Historically, the association between fitness and working memory has not been clear.[3,47] This could be due to the lack of complexity in the type of aerobic exercise traditionally undertaken in interventions. Video dance, as opposed to aerobic walking or stationary cycling, requires motor coordination, attention and motor coordination. This movement is often built on and repeated during the same song making each song a mini short-term memory work out. Consider the DDR activation areas, the positive activation maps indicate that complex exercise has altered the functional areas responsible for working memory, attention and decision making. These changes could be due the "complexity" component propagating the physiological alterations in the brain that support neural network integration, improving cognition in ways not seen in simple aerobic exercise interventions. In addition, these changes were seen over a three month period of time, which is relatively short period compared to other interventions.[37,46,47]

The Walk group had significant, decreased cortical activation in the right anterior cingulate, right Brodmann Area 32. The anterior cingulate cortex has been associated with the "presence of behavioral conflict and need to adapt attentional control processes."[58] Since the participants have performed this task prior and are provided with adequate practice time, their arousal is not increased enough to recruit these brain areas. The Walk group also showed a significant decrease in cortical activation right medial frontal gyrus, right Brodmann area 6, which has been associated with executive function.[38] This finding also points to the existence of a practice effect because the Walk participants were familiar with the DSST, they did not need to recruit higher functional areas to perform well on this test. It is also possible that the additional areas were not recruited because the Walk group was not subject to the “complex” component of the exercise intervention. This component feeds the underlying anatomy, providing the resources to initiate recruitment of these functional areas.

The Wait group presented decreased cortical activation in one area, the inferior frontal gyrus. The inferior frontal gyrus is a part of the fronto-parietal network which is associated with top-down attentional processing, cue recognition, and working memory.[49] Decreased cortical activation in this area could again be due to practice effects.

Between the T1 and T2 scans for each group the change in the DDR BOLD signal during the DSST task differed dramatically. Though the nature of this analysis is qualitative, it points to many areas for further quantitative analysis. Other factors that could help explain the relationship between complex cognitive function and brain health should considered when further exploration is undertaken. These factors include considering the effects of short or long term hormone replacement therapy (HRT), consideration of protective lifestyle factors (diet, meditation, vitamins, genetic background), inclusion of a fitness quantifier, metabolic factors (cortisol and insulin levels) and the presence of comorbid conditions.

This study is an important step in examining complex exercise as a means to preserving brain health. These results are significant to the field of public health because video dance is an inexpensive, safe, and easy to implement intervention that may be able to impede the progression of cognitive decline and decrease the expression of CD and AD symptoms. In the next ten years, if the onset of CD can be delayed for an individual for as little as five years, this would decrease incidence of CD/AD by about 50%.[5] Any reduction in the incidence of CD also reduces stress on the healthcare system, individuals, and reduces the overall prevalence of disease in the population. Due to the complexity of the exercise, video dance has the potential to stimulate more brain areas, and networks that would not be recruited during the performance of simple exercises.

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