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Cognitive training refines connectivity of the aging human brain to improve performance

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COGNITIVE TRAINING REFINES CONNECTIVITY OF THE AGING HUMAN
BRAIN TO IMPROVE PERFORMANCE

by

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BIOMEDICAL ENGINEERING

ABSTRACT

Cognitive deficits that occur as a function of age are highly variable within a sample of older adults of similar age. Training paradigms are available that can reverse cognitive declines that occur with age and improve behavioral performance. However, the benefits of training are also highly variable. The goal of this study was to use functional connectivity analyses on functional MRI data to help identify the source of this variability and to determine if cognitive training could alter network structure in the aging human brain. Resting-state functional connectivity data was acquired to investigate several neural networks in forty-one older adults. Standard functional connectivity and graph theory metrics were used to analyze the structure of networks in the brain. We found that training-related decreases in connectivity were correlated with improvement in behavioral performance on the CRT. This means that training refined network structure to ameliorate behavioral deficits. We also examined baseline connectivity differences between participants who were at high-risk for cognitive decline and those who were at low-risk. Previous studies examining age-related cognitive changes found that older adults' brains were dedifferentiated and suffered from altered connection strengths relative to younger adults. Therefore, we expected to see greater signs of dedifferentiation in our high-risk group. Although there were no significant differences, there were patterns in mean connectivity and mean clustering coefficient that indicated participants who were at high-risk for cognitive decline had stronger functional connectivity compared to partic-

ipants who were at low-risk for cognitive decline. This would be consistent with dedifferentiation and the results observed with training. Training may be differentiating the system by refining functional connectivity to improve behavioral performance. Further research needs to be done with a larger sample to better investigate differences in connectivity between high-risk and low-risk older adults.

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LIST OF ABBREVIATIONS

ANOVA   analysis of variance

BA   Brodmann Area

BOLD   blood oxygen level-dependent

C_i clustering coefficient

CRT   Complex Reaction Time

CRUNCH   compensation-related utilization of neural circuits hypothesis

fMRI   functional magnetic resonance imaging

HAROLD   hemispheric asymmetry reduction in older adults

Hz   Hertz

MNI   Montreal Neurological Institute

MRI   magnetic resonance imaging

mPFC   medial prefrontal cortex

MPRAGE   magnetization prepared rapid gradient echo

mm   millimeters

ms   milliseconds

PASA   posterior-anterior shift in aging

SPM   Statistical Parametric Mapping

T   Tesla

TE   echo time

TR   repetition time

UFOV   Useful Field of View ®

CHAPTER 1

INTRODUCTION

Magnetic resonance imaging (MRI) is a commonly used technique that allows for the examination of soft tissues in the body. MRI uses a strong magnetic field to align the spins of nuclei along a longitudinal plane. A radiofrequency pulse can be applied to the nuclei to flip them into a high-energy state. As the spins relax, or precess, they release energy at a specific frequency that can be detected by a nearby radiofrequency coil. The tissues surrounding the nuclei can affect the rate of precession and allow for the identification of different tissues.

Functional MRI (fMRI) is used to identify areas of activation in the brain by detecting changes in blood flow. When there is activity in part of the brain, there is an increase in blood flow to that region which results in an increase in the amount of oxygenated blood present. Deoxygenated blood is paramagnetic and affects precession of the surrounding nuclei to decrease the fMRI signal. Therefore, when more oxygenated blood is present in an activated region, there is an increase in the fMRI signal from that region. This is called the blood oxygen level-dependent, or BOLD signal. Therefore, fMRI measures brain activity indirectly by measuring changes in blood oxygenation. The changes in blood oxygenation take a few seconds to occur, which limits the temporal resolution of fMRI. Even with limited temporal resolution, fMRI has allowed great advancements to be made in the study of cognitive processes over the past two decades.

Functional MRI data is sensitive to various types of noise; therefore, it is important that several preprocessing steps are used to correct any problems with the data before it is analyzed. The first step is slice-timing correction. Typically, a volume of the brain is taken over a few seconds in a series of slices, so there are disparities between the times when the first and last slices are acquired. Slice timing correction resolves these disparities by interpolating between time points. The next step is realignment. This step seeks to reduce the effects of motion by correcting for any movements that were made during image acquisition. The next step is normalization, which transforms each individual's brain to fit onto a standard template. At this point, an additional step may be taken to eliminate the effects of movement on the data. This step is very important for functional connectivity analyses because motion can change connectivity results (Power et al., 2011; Van Dijk et al., 2011). This step includes: identification of volumes in which motion was present, interpolation of these volumes, application of a temporal filter to include frequencies of interest, and then removal of the bad volumes. This procedure has been shown to best resolve the problems of motion in functional connectivity data (Power et al., 2011). A final step that is used is spatial smoothing. This step maximizes the functional signal to noise ratio and improves the validity of statistical tests, although it slightly reduces spatial resolution (Huettel et al., 2009). These steps prepare functional MRI data for analysis.

One increasingly popular way to analyze fMRI data is with functional connectivity, which examines the correlation of low frequency fluctuations (<0.1 Hertz (Hz)) (Biswal et al., 1995). Functional connectivity is based on the principle that brain regions have spontaneous, low frequency fluctuations in the BOLD signal. The magnitude of a

functional connection is calculated by correlating the low frequency fluctuations of two brain regions. This correlation value has been interpreted as connectivity because previous work has shown that correlated activity is indicative of shared connections between brain regions (Biswal et al., 1995; Cordes et al., 2001). Therefore, remote brain regions that are working together will exhibit highly correlated patterns of fluctuations. Many networks in the brain, including the default mode network (Fox et al., 2005; Greicius et al., 2003; Raichle et al., 2001), frontoparietal control network (Dosenbach et al., 2006; Vincent et al., 2008), attention networks (Fox et al., 2005, 2006), and sensory networks (Biswal et al., 1995; Cordes et al., 2000; Damoiseaux et al., 2006) have been identified and studied with functional connectivity. Therefore, functional connectivity provides useful information about cognitive processes and neural networks.

There are several different approaches that can be used to analyze connectivity data. These include a seed-based approach, independent component analysis, or graph theory analysis (Joel et al., 2011). An increasing number of fMRI research studies are including graph theoretic measures of functional connectivity in their analyses (see Bullmore & Sporns, 2009 for a review). Graph theory aids in the interpretation of connectivity data because it provides a way to illustrate network structure and aids with the exploration of large-scale functional networks (Sepulcre et al., 2012). Therefore, functional connectivity metrics, in conjunction with graph theoretical analyses, provide valuable information about the structure of neural networks.

Functional connectivity analyses may be especially useful when examining the brain in altered states. The integrity of the connections identified can be affected by both age and disease. For example, connection strengths within the default mode network are

markedly reduced with aging (Andrews-Hanna et al., 2007). Altered functional connectivity has also been demonstrated in many neurological disorders such as schizophrenia, attention deficit hyperactivity disorder, and age-related cognitive impairment (Andrews-Hanna et al., 2007; Broyd et al., 2009; Damoiseaux et al., 2008; Whitfield-Gabrieli & Ford, 2012). Functional connectivity metrics are especially intriguing because they have been found to correlate with behavior (Hampson et al., 2006, 2011; He et al., 2007). Decreased connectivity in the elderly has been correlated with decreased behavioral performance on measures such as the Stroop test and digit span (Geerligs et al., 2012). Therefore, there is a clear connection between functional connectivity metrics and performance in everyday life. Functional connectivity provides a useful tool for furthering the understanding of age-related cognitive changes.

As people age, they experience many cognitive changes that result in impaired performance on everyday activities. However, the magnitude of these changes and the rate at which they affect an individual are highly variable. Declining speed of processing is one of the fundamental contributors to age-related cognitive impairment (Luszcz & Bryan, 1999). Speed of processing is defined as the ability to accurately perceive and process complex visual information. One way to measure visual processing speed is the Useful Field of View (UFOV®) test (Ball et al., 1993). Performance on the UFOV is predictive of driving performance, performance on everyday activities, and fall risk (Ball et al., 1993, 2006; Edwards et al., 2005; Owsley et al., 1998, 2001; Vance et al., 2006). The UFOV is able to classify people as either high-risk or low-risk for future cognitive decline based on their performance. This classification is not related to risk for mild cognitive impairment or Alzheimer's disease. These age-related cognitive declines can be very

detrimental to the lives of older adults; therefore, it is important that they can be prevented or reversed. Many cognitive training paradigms have been developed in an effort to improve the cognitive function of older adults.

Cognitive training paradigms have the potential to have long-lasting and beneficial effects on the behavior of older adults. Speed of processing training is a standardized, computer-based training paradigm that affects the way visual stimuli are processed. This computer-based training is useful and interesting because it not only improves processing speed, but also transfers to everyday functions (Edwards et al., 2002, 2005), prevents mobility declines (Edwards et al., 2009), protects against declines in health-related quality of life (Wolinsky et al., 2006), protects against depression (Wolinsky et al., 2009), and improves self-rated health in older adults (Wolinsky et al., 2011). These effects are especially beneficial to older adults because they have been shown to last up to five years after training (Wolinsky et al., 2006, 2009, 2011). A schematic of training is shown in Figure 1.

Previous studies have shown that speed of processing training can be extremely beneficial for older adults. However, just as cognitive declines are variable, the improvements gained from training are also variable in older adults. It is possible that the variability in training gains could be due to underlying changes in connectivity. Cognitive training paradigms that improve behavioral performance have been shown to modulate the underlying connectivity in the frontoparietal, fronto-executive, and default mode networks (Pieramico et al., 2012; Voss et al., 2011). However, many studies to date have used cognitive training paradigms that have not been well validated. It is important that future work examines the variability in cognitive declines in older adults and the mecha-

nisms by which training may be able to prevent or reverse declines that occur in the aging brain.

In the present study, the effects of speed of processing training on functional connectivity were examined using standard analyses along with graph theory metrics. Change in behavior was correlated with change in connectivity to determine if speed of processing training could improve behavioral performance via altered functional connections in several different networks. The relationship between baseline behavioral performance and functional connectivity was also examined. Connectivity in was compared between high-risk and low-risk older adults to determine if signs of dedifferentiation were present in functional connectivity data. This research is an important step in understanding the mechanisms by which training may exert its effects as well as understanding the neural correlates of behavioral variability in older adults. This research may assist with the development of future training paradigms so that they may specifically target functional connections that can be modified.

CHAPTER 2

COGNITIVE TRAINING REFINES CONNECTIVITY OF THE AGING HUMAN
BRAIN TO IMPROVE PERFORMANCE

by

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SUMMARY

Cognitive training paradigms can have numerous behavioral benefits for older adults; however, the neural correlates underlying training are not well known. Several studies examining training-related neural changes have found altered stimulus-based responses, but little has been done to examine how training alters the brain at rest via functional connectivity. Here we examine changes in resting-state functional connectivity within a sample of older adults and find that training-related improvement in behavioral performance is correlated with weakened network connectivity. This shows that speed of processing training can alter network structure in older adults by refining functional connections. This is consistent with an observed difference that participants at high-risk for cognitive decline have increased resting-state functional connectivity strengths relative to low-risk participants, although a larger sample size is needed to determine if this difference is significant. These results show that training may ameliorate behavioral deficits in part by refining network connectivity.

INTRODUCTION

It has been well established that older adults experience declines in various cognitive domains that can impact their performance on everyday activities and, therefore, affect their independence. Declining speed of processing is one of the fundamental contributors to age-related cognitive impairment (Luszcz & Bryan, 1999). Speed of processing can be accurately measured with the Useful Field of View (UFOV [®]) test. UFOV performance is a predictor of future cognitive decline and is linked to outside measures such as driving ability, risk for falls, and performance on everyday activities (Ball et al., 1993, 2006; Edwards et al., 2005; Owsley et al., 1998, 2001; Vance et al., 2006). The UFOV

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categorizes individuals as either high-risk or low-risk for future cognitive decline. This classification is independent from risk for mild cognitive impairment and Alzheimer's disease. Many studies have demonstrated that declines in processing speed can be reversed with a standardized, computer-based protocol called speed of processing training. A few of the benefits from speed of processing training are protection against mobility declines (Edwards et al., 2009), protection against declines in health-related quality of life (Wolinsky et al., 2006), and decreased risk of depression (Wolinsky et al., 2009). Speed of processing training has the potential to ameliorate some of the behavioral impairments that affect older adults, however, the improvements gained from training are highly variable. It is possible that variability in the brain may underlie the variability in training-based benefits. One way to examine variability in the brain is to look at how brain regions communicate with each other.

Brain regions must work together properly in order to carry out everyday activities efficiently. Functional connectivity analyses provide a way to assess this efficiency through the temporal correlation of low frequency fluctuations (<0.1 Hz) in fMRI data as a manifestation of system integrity (Biswal et al., 1995; Cordes et al., 2001). Previous studies have examined the effects of cognitive training on resting-state functional connectivity and found that in younger adults, functional connectivity increased between the left perisylvian region and regions around the lingual gyrus following training (Takeuchi et al., 2011). Therefore, training may alter functional connections to improve behavioral performance. It is essential to understand how metrics of functional connectivity can be altered to further our understanding of cognitive interventions and aging.

Several studies have correlated behavioral performance on psychometric measures with connectivity strength. These studies provide insight into changes that may be expected from training. Decreased connectivity has been related to poorer cognitive function, possibly because there is less efficient communication between brain regions (Geerligs et al., 2012; Goh, 2011). For example, it has been shown that as reaction time increases, task-based functional connectivity between the inferior frontal gyrus and other brain regions decreases (Chen et al., 2010). Another study has demonstrated that resting-state activity in the default mode network was negatively correlated with performance on the Trail Making Test-Part B (Damoiseaux et al., 2008). In contrast to these studies, a different study has shown that increased functional connectivity is detrimental to older adults. Resting-state connectivity between left and right BA 44/45 (Broca's area) was significantly negatively correlated with behavioral performance (Antonenko et al., 2012). Therefore, the relationship between connectivity and behavior and the mechanism by which training may exert its effects are unclear.

Other research has examined training-based changes in stimulus-driven effects. One hypothesis that has been suggested in a number of these studies –the dedifferentia-tion hypothesis— suggests that there is a loss of specificity in processing with advanced age. This means that during tasks, older adults show patterns of increased activation compared to younger adults (for a review see Goh, 2011). Several models have been developed to describe the increased patterns of activation that are present in the aging brain. These include the posterior-anterior shift in aging (PASA) model (Cabeza et al., 2004; Davis et al., 2008; Grady et al., 1994), the hemispheric asymmetry reduction in older adults (HAROLD) model (for a review see Cabeza, 2002), and the compensation-related

utilization of neural circuits hypothesis (CRUNCH) (Reuter-Lorenz & Cappell, 2008). Thus, there are many task-related neural changes that occur in the aging brain. These changes indicate a loss of specificity in processing with advanced age and therefore demonstrate dedifferentiation.

The dedifferentiation hypothesis suggests that as information flows through the system, it flows excessively to irrelevant, but connected regions in declining systems. This hypothesis is based on analyses describing how the system responds to stimuli, but it transfers to a prediction about how neural activity at rest may be altered by aging. On one hand, reduced distinctiveness and variability in behavioral performance has been related to dedifferentiation (Goh, 2011). On the other hand, changes in the connectivity of various neural networks have been related to altered behavioral performance (Geerligs et al., 2012; Hampson et al., 2006, 2011; He et al., 2007). Therefore, as suggested by Goh (2011), it is possible that dedifferentiation may have a direct relationship with altered neural connections. Specifically, the dedifferentiation hypothesis suggests that in individuals who are at high risk for cognitive decline, information may freely flow between all parts of a network and between networks in an inefficient manner. This unconstrained communication between brain regions is likely to occur during rest, and therefore may be observed through measurements of resting-state functional connectivity. Resting-state data is sensitive to neural changes and abnormalities. For example, neuroimaging data has shown that activity during resting-state can be altered with age and disease (Andrews-Hanna et al., 2007; Damoiseaux et al., 2008). Therefore, it may be possible that training can reverse signs of dedifferentiation and that we may observe this reversal in resting-state data.

In order to better understand the relationship between cognitive training and functional connectivity and to gain insight into the relationship between connectivity and behavior, training data needed to be examined within a cohort of older adults. We used two different techniques to assess the resting-state functional connectivity of the attention, default mode, frontal, and visual networks within a sample of older adults. We also assessed the connectivity among all the nodes in all of the networks to evaluate inter-network dynamics. We sought to examine the effects of training on the structure of these networks as revealed through functional connectivity analyses. We posited that a possible mechanism behind training-related improvements in behavioral performance could be through modifications in connectivity, and more specifically, through a refinement in connectivity indicating reversal of dedifferentiation. We also hypothesized that if training can alter connectivity to improve behavior, then we may observe differences in connectivity between high-risk and low-risk individuals at baseline, prior to training.

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

Whole Brain Analysis

To check the integrity of the networks of interest, a whole brain analysis was performed for each network using one region of interest from each as a seed. Seed regions were denoted by asterisks in Table S1. For each subject, the mean time course for each seed region was extracted and then the correlation coefficient was computed between the seed and every other voxel. The correlation coefficients were then transformed using the Fisher r-to-Z transformation to normalize the distribution. A T-contrast was created and the results for each network were plotted on a standard brain template (Figure 1). Results identified the expected networks and verified their integrity in this population.

Training-Related Performance Improvements Correlated With Weakened Network Connectivity

To examine the effects of speed of processing training on functional connectivity, we correlated the change behavioral performance with change in mean network connectivity in each of the networks, as well as with change in mean connectivity between all of the networks listed in Table S1. We hypothesized that training alleviates behavioral deficits in part by refining functional connectivity and thus differentiating the networks. For the speed of processing training group, change in performance on the Complex Reaction Time task (CRT) was positively correlated with change in mean Fisher Z connectivity (Figure 2). This meant that as participants improved on the task (i.e. took less time), they had lower connectivity values. This correlation was significant in the attention, frontal, and visual networks, as well as in the all-networks-combined condition. For the no-contact control and social contact control groups, change in CRT score and change in mean Fisher Z connectivity were not correlated.

Multiple linear regression analyses were used to determine whether the interaction between change in mean Fisher Z connectivity and group assignment significantly predicted change in behavior on the CRT. When comparing the training group to the contact control group, the interaction between group and change in connectivity significantly predicted change in CRT scores (p<0.03) in the attention, frontal and visual networks, as well as in the all-networks-combined condition. There was also a trend towards this finding in the default mode network (p=0.051). When comparing the training group to the no-contact control group, there was a trend showing that the interaction between group and change in connectivity predicted change in CRT scores in the networks also. These re-

sults indicated that training modifies functional connectivity to improve behavioral performance. The statistics from the multiple regressions were listed in Table S2.

Training-Related Performance Improvements Correlated With Refined Network Structure

To examine if training impacted network structure, we used the graph theoretical measure of clustering coefficient (C_i) to specifically examine efficiency of information transfer (Latora & Marchiori, 2001). C_i provided a measure of how connected a node's neighbors were to one another (Figure 3D). In the speed of processing training group, change in behavioral performance on the CRT was positively correlated with change in mean C_i in each of the networks examined (Figure 3). For the two control groups, there were no significant correlations between change in behavioral performance and change in C_i.

Multiple linear regression analyses were used to determine if the interaction between change in mean C_i and group assignment significantly predicted change in behavioral performance on the CRT. When comparing the training group to the contact control group, the interaction between group and change in C_i significantly predicted change in CRT scores ($p<0.05$) in the attention, default mode, frontal, and visual networks, and in the all-networks-combined condition. When comparing the training group to the no-contact control group, the interaction between group and change in C_i showed a trend towards predicting change in CRT performance. Together, these results showed that training could restructure networks to increase efficiency, which led to improved behavioral performance. The statistics for these regressions were listed in Table S2.

Comparing Connectivity Between High-Risk and Low-Risk Individuals

To determine if the observed effects of training were reflecting a behavioral pattern that existed at baseline in our subjects, we examined the connectivity in our participants at high-risk for cognitive decline compared to those at low-risk. Based on previous research, we hypothesized that networks in high-risk individuals would be dedifferentiated, therefore activity in one part of the system would automatically propagate throughout a larger proportion of the system. This would be consistent with the finding that training reduced connectivity to improve behavioral performance. To test this hypothesis, we examined functional connectivity strengths within and across the described networks at baseline during resting-state in high-risk and low-risk individuals. To separate our sample into two groups, we chose to use the risk classification provided by a measure of speed of processing called the Useful Field of View (UFOV®) test because UFOV performance has not only been linked to risk for future cognitive decline, but it has also been related to outside measures such as driving ability, risk for falls, and performance on everyday activities (Ball et al., 1993, 2006; Edwards et al., 2005; Owsley et al., 1998, 2001; Vance et al., 2006). For each subject, functional connectivity was calculated within each of our desired networks. Details of these calculations were described in the Experimental Procedures. The mean Z values were averaged for the high-risk individuals separately from the low-risk individuals. Although there were no significant differences in connectivity between the two groups in any of the networks examined, results were numerically in the expected direction, showing that high-risk individuals had stronger functional connectivity than low-risk individuals (Figure 4). These differences were consistent with the dedifferentiation hypothesis.

To further examine differences between high-risk and low-risk participants, we compared mean clustering coefficient between the two groups. We hypothesized that high-risk individuals would have more connected network structure than low-risk individuals, which would indicate decreased efficiency and would be consistent with the de-differentiation hypothesis. For each subject, a threshold was applied to the Fisher Z transformed r-values to create binary matrices for each network (see Experimental Procedures for more detail). Then, the mean C_i was calculated for each network. Although there were no significant differences in C_i between the two groups, results were numerically in the expected direction. That is, high-risk individuals had greater C_i in the networks examined compared to low-risk individuals (Figure 5). These results were in a direction that indicated there was a difference in network structure between low- and high-risk individuals. More specifically, high-risk individuals demonstrated signs dedifferentiation across all networks and had less efficient network structure.

DISCUSSION

The present analyses sought to further the understanding of the relationship between cognitive training and functional connectivity. We have shown that speed of processing training can refine connectivity within and across networks to improve behavioral performance in older adults. Importantly, the control groups did not experience these same changes, indicating that this effect was a result of training. This training-related refinement may be related to the refinement in connectivity that occurs during development in the human brain (Huttenlocher et al., 1982). This relationship existed within each of the examined networks, as well as across all of the networks. These results are consistent with the dedifferentiation hypothesis, which describes a loss of specificity in stim-

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ulus-driven processing, because age-related dedifferentiation may be observed as increased connectivity during rest within and across networks. Therefore, training may decrease the connectivity to *differentiate* the system. Interestingly, the training-related changes correlated with improvement in performance on the CRT, which is a task that was not directly trained. This shows that training-related connectivity changes transfer to other domains.

Previous studies have examined the effects of cognitive training on connectivity and shown that some training strategies may increase within-network connectivity *while the task is being performed* (Voss et al., 2011). This result is consistent with our data, as it is consistent with the idea that training results in coordinated processing of relevant stimulus information. Other studies have examined resting-state connectivity following training of younger (Takeuchi et al., 2011) and older (Pieramico et al., 2012) adults. Interestingly, Pieramico and colleagues showed that training changed connectivity within the default mode such that some regions showed stronger relationships to the default mode regions (posterior cingulate), while other regions (angular gyrus, precuneus) showed weaker relationships to the default mode following training, although these results were not corrected for multiple comparisons. While this study used a different training paradigm and a very different analysis strategy (independent components analysis), it is interesting that their results suggest, as ours do, that connectivity is modified with training (Pieramico et al., 2012). Additionally, Takeuchi and colleagues showed that training increased resting-state functional connectivity between the left perisylvian area and a region including the bilateral calcarine cortices and the bilateral lingual gyrus. This study also used a different training paradigm and examined different neural networks in

young adult participants, but it is interesting that they too find that connectivity is modified with training. The training paradigms used for each of these studies differ. Speed of processing training is the only paradigm that has been well validated and shown to transfer to other cognitive domains (Ball et al., 2007; Edwards et al., 2005; Wolinsky et al., 2006, 2009), thus the data presented here can draw on a long history showing that the precise training strategy employed in these participants has effects which transfer to tests of activities of daily living.

In order to further our understanding of how training affects network structure, we also used graph theory, which can be helpful for understanding how the structures of networks are different. In order to examine changes in the efficiency of the network, we used the graph theoretical metric C_i which is a measure of the local efficiency of information transfer (Achard & Bullmore, 2007). We found that trained individuals who improved their behavioral performance also experienced changed network structure in terms of C_i. Decreased mean C_i within and across networks was correlated with improved behavioral performance. These findings were also consistent with the dedifferentiation hypothesis and showed that individuals who improve at the task experience alterations in network structure to have more differentiated systems. These results, taken together, indicated that speed of processing training altered network structure to refine connectivity within and across networks.

To examine if the observed effect of training was related to a baseline difference between participants, we also compared connectivity before training between high-risk and low-risk participants. Although there were no significant differences between the two groups in any of the examined networks, the pattern that we saw was in the direction that

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we expected based on Figures 2 and 3. If training refined connectivity to improve per-

formance, then we expected that participants who are at high-risk for cognitive decline

and were lower performing would have increased connectivity relative to low-risk partic-

ipants. This finding was consistent with the finding that lower performance on an artifi-

cial grammar learning task is linked to stronger inter-hemispheric connectivity between

left and right BA 44/45 (Antonenko et al., 2012).

To further compare network connectivity between high-risk and low-risk partici-

pants, we used graph theory. The clustering coefficient within and across networks was in

the same direction as the mean connectivity data and indicated that better-performing

networks were less clustered and that signal propagation was more selective between and

within the networks of the brains of low-risk participants. Together, the connectivity and

graph theory measures pointed towards the possibility that there were differences in net-

work structure among older adults such that individuals at high-risk for cognitive decline

had stronger connectivity values within and across several important neural networks.

This indicated that there was less efficient communication in the networks of high-risk

systems. However, there was not sufficient power in the sample for the between-subjects

comparison, so future research needs to be done with a larger sample size to delve further

into this issue.

These results extended upon previous work on older adults' brain activity sug-

gesting a 'dedifferentiation hypothesis.' The dedifferentiation hypothesis proposed that

in high-risk individuals, information might freely flow between all parts of a network and

between networks in an inefficient manner. Previous studies have examined this effect

while participants perform cognitive tasks. This unconstrained communication between

brain regions was likely to occur during rest, and therefore might have been observed through measurements of resting-state functional connectivity. Using functional connectivity and graph theory metrics, we demonstrated that training can alter the connectivity of high-risk individuals to be more like that of low-risk individuals by differentiating the network and making it more efficient.

Methodological considerations

There were some methodological issues that needed to be addressed regarding the reported observations. The regions of interest that were used for the present study were based on coordinates obtained using resting-state data from younger adults. This caused concern because the anatomy of the brain differs between older adults and younger adults (Ge et al., 2002). To address this concern, we overlapped the results from the whole brain analysis, which used just one seed region, and the regions of interest created. The whole-brain analysis identified the expected networks and areas of activation overlap with the regions of interest created, so the regions of interest were presumed to correspond to the anticipated networks.

Another potential concern that needed to be addressed in this study, which used functional connectivity to compare two populations, was the effect of motion on connectivity data. It has been shown that motion increases short distance connectivity values while decreasing long-range values (Power et al., 2011; Van Dijk et al., 2011). It was possible that the high-risk individuals may have had more motion during imaging, leading to the numerical difference in values that we saw between our two groups. To control for this possibility, we took two tactics, over and above the strict motion scrubbing algorithm we used to omit raw data that might include motion artifacts (see methods). First,

we examined the mean amount of movement for each subject to determine if there were differences between the two groups. For this analysis, we averaged the absolute values of the contents of the movement file that is produced during realignment. This gave us six movement parameters for each subject. To identify movement differences between the groups, we performed an ANOVA with factors group by movement parameter. The main effect of group was not significant, $F(1,5) = 0.3$, $p > 0.05$.

To control for the remote possibility that some subtle, second order effect of movement influenced our results, we also examined correlations between two sets of regions: one long-range and one short-range set. Both sets of regions were within the 'default mode' network and were thought to have similar connectivity properties. The network pairs were a short-range connection between the angular gyrus and the precuneus, and a long-range connection between the precuneus and the medial prefrontal cortex (mPFC). If the observed difference in connectivity were due to motion in the high-risk group, we would have expected this group to have weaker long-range and higher short-range connectivity values than the low-risk group. However, the high-risk individuals had higher short- and long-range connections, which argued against the possibility that differences in motion accounted for the observed results.

CONCLUSIONS

In this study, we examined the effect of speed of processing training on functional connectivity and network structure and how this correlated with behavioral performance. We found that training refined connectivity to improve behavioral performance. These findings provided evidence that training may differentiate network structure and lead to increased network efficiency to improve performance. This finding was consistent with

the patterns observed in baseline connectivity values in high-risk and low-risk partici-

pants. These results suggested one mechanism by which cognitive training paradigms ex-

ert their effects. Future work should be done with a larger sample size to explore connec-

tivity differences between high-risk and low-risk individuals.

EXPERIMENTAL PROCEDURES

Participants

Study participants included 41 older adults (18 female, 9 African-American, mean

age 71.1±4.6 years) recruited from the University of Alabama at Birmingham and sur-

rounding community. Exclusion criteria were left-handedness, history of stroke or other

neurological problems, claustrophobia, steel implants, pacemaker, weight greater than

300 pounds, girth greater than sixty inches, corrected vision worse than 20/40, and inabil-

ity to achieve at least sixty-five percent accuracy on a UFOV-like task. Three individuals

were excluded from baseline data analysis due to excessive movement during fMRI

scans, and an additional 10 were excluded from training analyses due to excessive

movement or missing data. Procedures were completed in accordance with the guidelines

of the University of Alabama at Birmingham Institutional Review Board. Participants

gave written informed consent prior to enrolling in the study and were compensated for

their participation.

Experimental Overview

Over the course of this experiment, subjects were involved in several different

sessions. All participants had one brief screening session, a baseline session to acquire

behavioral measures, and a baseline fMRI session. At the screening visit, vision, mental

status, UFOV performance, and performance on a UFOV-like task were assessed. Partic-

ipants were classified as either low-risk or high-risk based on their performance on the first three subtests of the UFOV. A risk score of 1 to 2 was classified as low-risk and a score of 3 or higher was classified as high-risk. The baseline behavioral visit entailed an extensive battery of cognitive measures. Next, participants were randomized to one of three groups: a speed of processing training group (n=11), a contact control group (n=10), or a no-contact control group (n=7). There were equivalent numbers of high-risk and low-risk participants assigned to each group. Following training or a five-week period, participants returned for a post-test behavioral session and a post-test fMRI session.

Behavioral Training Sessions

Participants in the speed of processing training group attended 5 two-hour sessions completed within 5 weeks. The speed of processing training entailed computerized practice exercises that were guided by a trainer. The training was designed to improve the amount of visual information that an individual could process over brief periods of time. Training tasks included target awareness, identification, localization, and comparison. Difficulty level was tailored to the participant's ability and feedback was provided at the end of each block of 16 trials. The specific protocol has been described in detail previously (Ball et al., 2007; Edwards et al., 2005).

Participants assigned to the contact control group also completed 5 two-hour sessions within a 5-week period. During the sessions, participants completed a series of cognitively stimulating activities (e.g. word games, math problems, crossword puzzles) that were administered by a trainer.

Image Acquisition

All images were acquired using a 3T head-only Siemens Allegra scanner. A high-resolution structural T1-weighted MPRAGE image was collected for each participant (TR = 2.25s, TE = 2.6ms). Resting-state scans were acquired in two runs that were each six minutes long with a T2*-weighted echo planar imaging sequence (TR = 2s, TE = 30ms). Participants viewed a gray screen during image acquisition and were instructed to keep their eyes open and stay awake (Van Dijk 2010). One participant viewed a black screen due to technical difficulties.

Data Processing

Functional data first underwent standard preprocessing in SPM8 (Friston, 1995). These steps included slice timing correction, realignment, and normalization to MNI space. If a run had greater than 16 total volumes or 9 consecutive volumes with excessive movement, it was removed from further analyses. A custom denoising method was developed that has been shown to be the best method to remove the effects of motion (Power et al., 2011). The steps included: (1) Nuisance regression using the motion parameters from the realignment (2) Identification and interpolation of time points with bad motion (3) Temporal filtering with a band-pass filter ($0.01Hz<f<0.08Hz$) (4) Removal of bad volumes (5) Removal of signal from the white matter and cerebrospinal fluid (6) Spatial smoothing using Gaussian kernel of 6 mm full-width at half-maximum.

Data Analysis

Regions of interest were created as 5 mm spheres around the coordinates provided by Allen and colleagues (2011). A list of these coordinates can be found in Table S1. The resting-state BOLD time series was extracted for each region within a network for each subject. Next, we created a square correlation matrix for each network and all of the net-

works together. The Fisher Z transformation was applied to all of the Pearson's r correlation coefficients. For each of the matrices, the mean Fisher Z transformed r-value was calculated for each subject using only the upper triangular part of the matrix. To calculate the connectivity for all networks, every region of interest was correlated with every other region of interest to form a 27 x 27 matrix. The mean Fisher Z for all networks was calculated using the upper triangular part of this matrix.

Graph Theoretic Analysis

The present study used graph theory metrics along with standard functional connectivity analyses to organize the networks into describable configurations and provide information about the structure of the network. For the graph theoretical analysis, a threshold of 1.0852 was applied to the Fisher Z matrices to create binary matrices. This threshold was chosen because it was the mean plus one standard deviation value for all of the Fisher Z transformed r-values across all networks. Several different thresholds were tested, and each gave a trend towards the same result. Each region of interest became a node for the graph theoretical analysis and if the correlation value between two nodes reached threshold, they were defined as connected. A clustering coefficient (C_i), which is a ratio of how connected a node's neighbors are to one another compared to the maximum possible number of connections, was calculated for each network using the binary matrices. Mean C_i was calculated for each subject within each network by averaging the C_i of each node.

Behavioral Measures

Change in network connectivity was correlated with change in behavioral performance on the CRT. The CRT was a measure of reaction time and was scored as the

amount of time it took for a participant to recognize that one object had changed relative to the others and react to that target. There were either two or five distractors present. We examined the difference (posttest-baseline) of the average of these two times. A negative change score (posttest-baseline) indicated improvement on the task.

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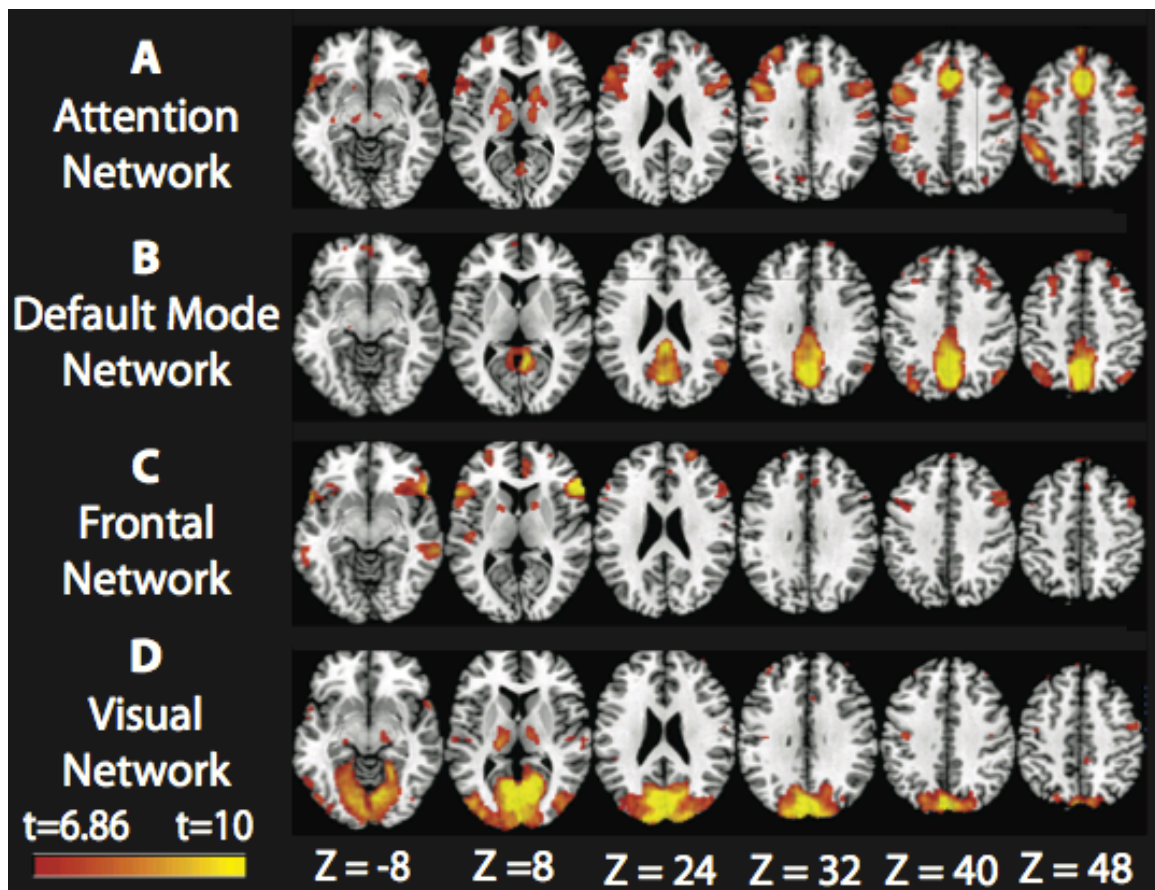
Figure 1 | Whole Brain T-Contrast Maps Demonstrated Integrity of the Networks of Interest. Whole-brain analyses of functional correlations between a seed region and each voxel across the entire brain. Seed regions were the (A) bilateral cingulate gyrus, (B) bilateral precuneus, (C) right inferior frontal gyrus, and (D) bilateral calcarine gyrus. Coordinates for the seed regions were listed in Table S1. For each network, a connectivity map was created for each subject. A T-contrast image was created from all of the individual subject's maps for each network (T>6.86, p<1e-06, FDR corrected at p=0.05).
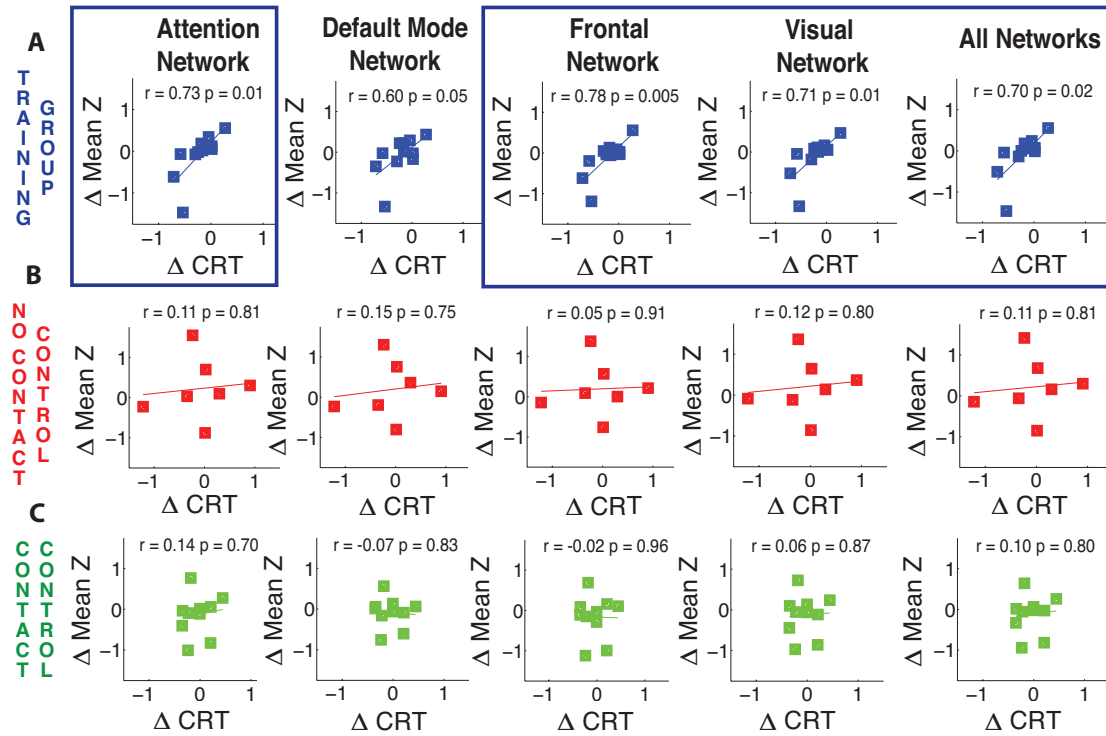
Figure 2 | Behavioral Improvement was Significantly Correlated with Weakened Network Connectivity in the Trained Group. The change in mean Fisher Z transformed r values were calculated for each network and are plotted against change in behavioral performance on the CRT for the (A) speed of processing training group, (B) no-contact control group, and (C) contact control group. The change in CRT score was significantly correlated with the change in the mean Fisher Z transformed r value in the attention, frontal, and visual networks, and all-networks-combined condition (p<0.05) for the training group only. Boxed plots denote significant correlations (p<0.05).
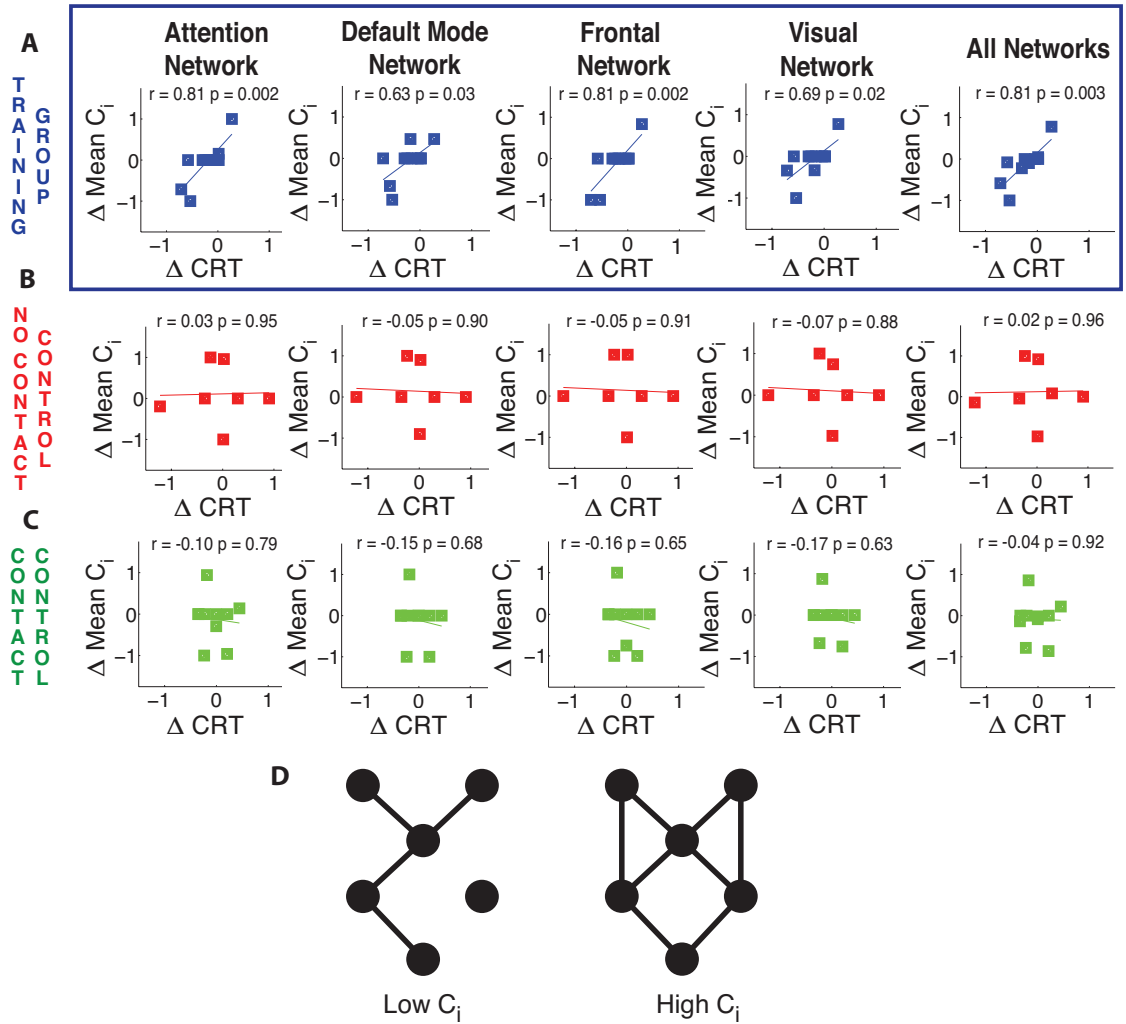
Figure 3 | Training Differentiated Network Structure. The change in the graph theoretical measure clustering coefficient (Ci) was calculated for each network and plotted against change in behavioral performance on the CRT for the (A) speed of processing training group (blue), (B) no-contact control group (red), and (C) contact control group (green). Boxed plots denote significant correlations ($p < 0.05$). (D) Example networks demonstrating clustering coefficient, which was defined as the connectedness of a node's neighbors.
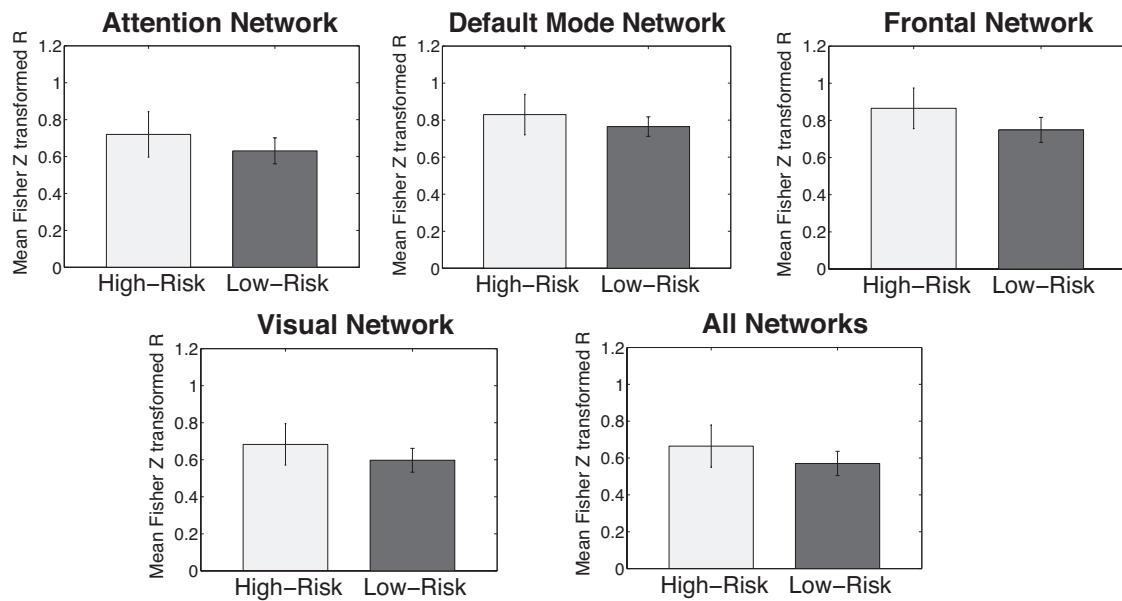
Figure 4 | Comparison of Connectivity Between High-Risk and Low-Risk Participants. Each bar depicts the mean Fisher Z transformed R correlation value for high-risk participants compared to low-risk participants in the attention, default mode, frontal, and visual networks, and for the all-networks-combined condition. Error bars represent standard error of the mean. Although there were no significant differences, the pattern of higher connectivity in high-risk participants compared to low-risk participants was expected based on the dedifferentiation hypothesis.
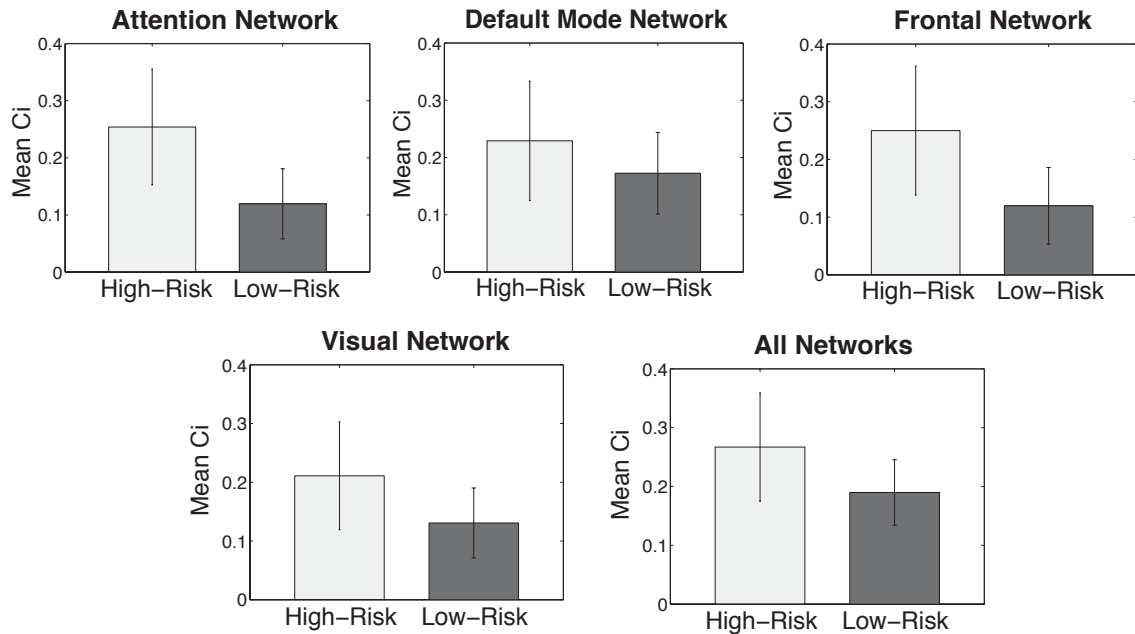
Figure 5 | Comparison of Clustering Coefficient Between High-Risk and Low-Risk Participants. Connectivity at baseline during resting-state was quantified for each network in terms of the graph theoretical measure clustering coefficient (C_i). Bars represent the mean clustering coefficient for each group across all networks. Error bars depict the standard error of the mean. Although there were no significant differences, the pattern of higher clustering in high-risk participants compared to low-risk participants was expected based on the dedifferentiation hypothesis.

| Network	Region	X	Y	Z
Attention	Bilateral Cingulate Gyrus *	0	22	45
	Left Inferior Frontal Gyrus	-43	24	21
	Left Inferior Parietal Lobule	-47	-57	39
	Left Insula	-46	15	-5
	Left Middle Frontal Gyrus	-32	53	21
	Left Superior Frontal Gyrus	-32	38	39
	Left Superior Temporal Gyrus	-56	-48	18
	Right Inferior Parietal Lobule	49	-54	39
	Right Insula	45	18	-6
	Right Middle Frontal Gyrus	34	24	44
	Right Superior Parietal Lobule	27	-65	44
	Right Superior Temporal Gyrus	57	-44	11
Auditory	Left Superior Temporal Gyrus	-51	-18	7
	Right Middle Cingulate Gyrus	52	-15	5
	Right Superior Temporal Gyrus	2	-4	49
Default Mode	Bilateral Medial Frontal Gyrus	-1	45	-9
	Bilateral Posterior Cingulate	0	-52	22
	Bilateral Precuneus *	1	-64	43
	Left Angular Gyrus	-43	-69	33
	Right Angular Gyrus	47	-66	32
Frontal	Left Inferior Frontal Gyrus	-55	22	7
	Left Middle Frontal Gyrus	-48	17	29
	Right Inferior Frontal Gyrus *	56	26	4
	Right Middle Frontal Gyrus	49	22	25
Sensorimotor	Bilateral Supplementary Motor Area	1	-3	61
	Left Precentral Gyrus	-52	-9	31
	Right Precentral Gyrus	52	-7	29
Visual	Bilateral Calcarine Gyrus *	1	-71	13
	Bilateral Cuneus	2	-84	28
	Bilateral Lingual Gyrus	1	-87	-2
	Bilateral Middle Cingulate Cortex	1	-45	32
	Left Inferior Parietal Lobule	-49	-55	42
	Left Inferior Temporal Gyrus	-47	-63	-14
	Left Lingual Gyrus	-29	-76	-7
	Right Inferior Parietal Lobule	42	-39	50
	Right Inferior Temporal Gyrus	48	-63	-8
	Right Lingual Gyrus	29	-76	-8

Figure S1: Coordinates of Regions of Interest, Related to Figure 1. Talairach coordinates of the regions of interest used in each network are listed. These are based off of networks described in Allen et al. (2011). Asterisks denote seed regions used in the whole brain analyses.

A

Network	F	df	p	R^2	Std beta	p
Attention	7.121	1,19	0.015	0.273	0.522	0.015
Default Mode	4.345	1,19	0.051	0.186	0.431	0.051
Frontal	8.262	1,19	0.01	0.303	0.551	0.01
Visual	6.626	1,19	0.019	0.259	0.508	0.019
All Networks	6.321	1,19	0.021	0.250	0.5	0.021

B

Network	F	df	p	R^2	Std beta	p
Attention	2.186	1,16	0.113	0.15	0.387	0.113
Default Mode	1.8	1,16	0.198	0.101	0.318	0.198
Frontal	3.241	1,16	0.091	0.168	0.41	0.091
Visual	2.653	1,16	0.123	0.142	0.377	0.123
All Networks	2.521	1,16	0.132	0.136	0.369	0.132

C

Network	F	df	p	R^2	Std beta	p
Attention	9.147	1,19	0.007	0.325	0.57	0.007
Default Mode	4.829	1,19	0.041	0.203	0.45	0.041
Frontal	9.249	1,19	0.007	0.327	0.572	0.007
Visual	6.461	1,19	0.02	0.254	0.504	0.02
All Networks	10.166	1,19	0.005	0.349	0.59	0.005

D

Network	F	df	p	R^2	Std beta	p
Attention	3.351	1,16	0.086	0.173	0.416	0.086
Default Mode	2.014	1,16	0.175	0.112	0.334	0.175
Frontal	3.483	1,16	0.08	0.179	0.423	0.08
Visual	2.384	1,16	0.142	0.13	0.36	0.142
All Networks	3.445	1,16	0.082	0.177	0.421	0.082

Table S2. Results of the Multiple Regressions. Results of the multiple regressions performed to compare the change in mean Fisher Z connectivity in the (A) training group to the contact control group and the (B) training group to the no-contact control group. Results are also listed for the multiple regressions performed to compare the change in clustering coefficient in the (C) training group to the contact control group and the (D) training group to the no-contact control group. The statistics reported are for the interaction between group and change in connectivity. The results show that this interaction significantly predicts change in behavior on the CRT.

CHAPTER 3

CONCLUSIONS

Functional MRI, and more specifically functional connectivity analyses of fMRI data, allows the structure and efficiency of neural networks to be studied. It is important to study neural networks in an older adult population to better understand age-related cognitive declines. There is great variability in the behavior of older adults; however, the neural correlates of this variability were previously unknown. In this work, we have shown that speed of processing training can refine connectivity of the aging human brain to improve behavioral performance. This was shown in terms of mean network connectivity and clustering coefficient. We also looked for differences in connectivity between high-risk and low-risk systems to help with the understanding of the training-related changes. Although there were no significant differences in the current sample, the patterns of connectivity for the two groups were in a direction that indicated that high-risk systems are dedifferentiated, meaning that information can more freely flow to irrelevant brain regions. Therefore, training may be differentiating networks to make them process information more efficiently.

The results of this study further the knowledge about the neural mechanisms behind speed of processing training. This work may also help in the development of future cognitive training paradigms so that they only include exercises that alter network connectivity. Future research should use a larger sample size to try to identify connectivity differences between high-risk and low-risk individuals. It should also aim to expand these

analyses to examine neural structure without using *a priori* assumptions about the size,

shape, and location of regions of interest within each network.

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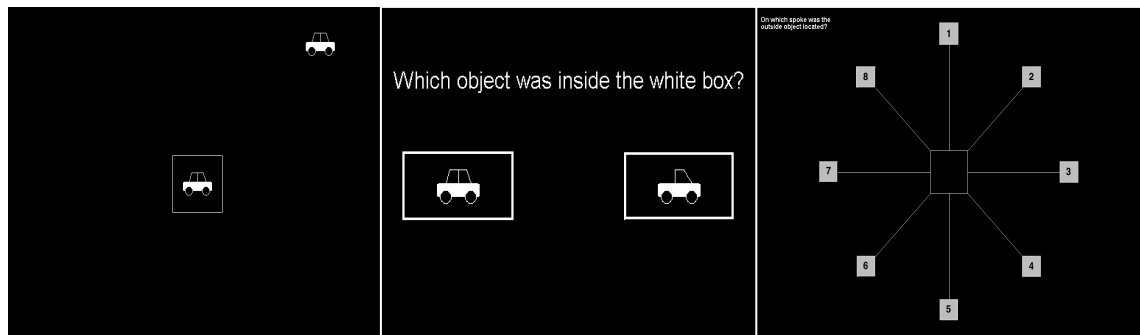
Figure 1 I Schematic of Speed of Processing Training. Left panel shows a panel of the participant viewing the central target, which can be either a car or a truck, and the peripheral target. The following two panels show response options, indicating the identity of the central object and the location of the peripheral target. Increasing the speed of stimulus presentation and including distractors can modify task difficulty.

APPENDIX A

IRB APPROVAL FORMS

Protection of Human Subjects
Assurance Identification/IRB Certification/Declaration of Exemption
(Common Rule)

Policy: Research activities involving human subjects may not be conducted or supported by the Departments and Agencies adopting the Common Rule (56 FR 28003, June 18, 1991) unless the activities are exempt from or approved in accordance with the Common Rule. See section 101(b) of the Common Rule for exemptions. Institutions submitting applications or proposals for support must submit certification of appropriate Institutional Review Board (IRB) review and approval to the Department or Agency in accordance with the Common Rule.

Institutions must have an assurance of compliance that applies to the research to be conducted and should submit certification of IRB review and approval with each application or proposal unless otherwise advised by the Department or Agency.

1. Request Type	2. Type of Mechanism	3. Name of Federal Department or Agency and, if known, Application or Proposal Identification No.
[X] ORIGINAL [] CONTINUATION [] EXEMPTION	[X] GRANT [] CONTRACT [] FELLOWSHIP [] COOPERATIVE AGREEMENT [] OTHER:_____	

4. Title of Application or Activity VINES: Visual Integrity and Neural Plasticity in the Elderly (Why is Processing Speed Training Effective? Translating Neural Mechanisms into Community-Based Products)	5. Name of Principal Investigator, Program Director, Fellow, or Other ROSS, LESLEY

6. Assurance Status of this Project *(Respond to one of the following)*

[X] This Assurance, on file with Department of Health and Human Services, covers this activity:
Assurance Identification No. FWA00005960 , the expiration date 08/29/2016 IRB Registration No. IRB00000196

[ ] This Assurance, on file with *(agency/dept)*_____, covers this activity.
Assurance No._____, the expiration date_____ IRB Registration/Identification No._____ *(if applicable)*

[ ] No assurance has been filed for this institution. This institution declares that it will provide an Assurance and Certification of IRB review and approval upon request.

[ ] Exemption Status: Human subjects are involved, but this activity qualifies for exemption under Section 101(b), paragraph_____.

7. Certification of IRB Review (Respond to one of the following IF you have an Assurance on file)

[X] This activity has been reviewed and approved by the IRB in accordance with the Common Rule and any other governing regulations.
by: [X] Full IRB Review on (date of IRB meeting) 11/2/2011 or [ ] Expedited Review on (date) _____
[ ] If less than one year approval, provide expiration date _____

[ ] This activity contains multiple projects, some of which have not been reviewed. The IRB has granted approval on condition that all projects covered by the Common Rule will be reviewed and approved before they are initiated and that appropriate further certification will be submitted.

8. Comments Protocol subject to Annual continuing review.	Title F110816006 VINES: Visual Integrity and Neural Plasticity in the Elderly (Why is Processing Speed Training Effective? Translating Neural Mechanisms into Community-Based Products)

IRB Approval Issued: 12|16|11

9. The official signing below certifies that the information provided above is correct and that, as required, future reviews will be performed until study closure and certification will be provided.	10. Name and Address of Institution University of Alabama at Birmingham 701 20th Street South Birmingham, AL 35294
11. Phone No. *(with area code)* (205) 934-3789	
12. Fax No. *(with area code)* (205) 934-1301	
13. Email: dhball@uab.edu	

14. Name of Official Ferdinand Urthaler, M.D.	15. Title Chairman, IRB
16. Signature, *Ferdinand Urthaler, MD/db* Authorized for local Reproduction	17. Date 12|16|11 Sponsored by HHS

- **You are applying** for IRB review of the research described in this form.
- **To avoid delay**, respond to all items in order and include all required approvals and documents.
- **To complete the form,** click the underlined areas and type or paste in your text; double-click checkboxes to check/uncheck. For more tips, see www.uab.edu/irb/forms.
- **Mail or deliver all materials to AB 470**, 701 20th Street South, Birmingham, AL 35294-0104.

Indicate the type of review you are applying for:
☐ Convened (Full) IRB *or*
☒ Expedited—See the Expedited Category Review Sheet, and indicate the category(ies) here: ☐1 ☒2 ☒3 ☒4 ☐5 ☐6 ☒7

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1. IRB Protocol Title: <u>VINES: Visual Integrity and Neural plasticity in the Elderly (Why is processing speed training effective?: Translating neural mechanisms into community-based products)</u>

2. Investigator, Contacts, Supervisors
a. Name of Principal Investigator: <u>Lesley Ross</u>
Degree(s)/Title:<u>PhD</u>   BlazerID:<u>agorwal</u>
Dept/Div:<u>Psychology</u>   Mailing Address:<u>CH 415; 1300</u>   UAB ZIP:<u>35294-1170</u>
Phone:<u>205-975-9424</u>   Fax:<u>205-975-6110</u>   E-mail:<u>lesleyross@uab.edu</u>
b. Name of Contact Person:<u>Shernine Lee</u>   Title:<u>Program Coord. I</u>
Phone:<u>205-934-7516</u>   E-mail:<u>sklee@uab.edu</u>   Fax:<u>205-975-2295</u>
Mailing Address (if different from that of PI, above):<u>HMB 123</u>

INVESTIGATOR ASSURANCE STATEMENT & SIGNATURE
By my signature as Principal Investigator, I acknowledge my responsibilities for this Human Subjects Protocol, including:

- Certifying that I and any Co-Investigators or Other Investigators comply with reporting requirements of the UAB Conflict of Interest Review Board;

- Certifying that the information, data, and/or specimens collected for the research will be used, disclosed and maintained in accordance with this protocol and UAB policies;

- Following this protocol without modification unless (a) the IRB has approved changes prior to implementation or (b) it is necessary to eliminate an apparent, immediate hazard to a participant(s);

- Verifying that all key personnel listed in the protocol and persons obtaining informed consent have completed initial IRB training and will complete continuing IRB training each year;

- Verifying that all personnel are licensed/credentialed for the procedures they will be performing, if applicable;

- Certifying that I and all key personnel have read the *UAB Policy/Procedure to Ensure Prompt Reporting of Unanticipated Problems Involving Risks to Subjects or Others to the IRB, Institutional Officials*, *and Regulatory Agencies* and understand the procedures for reporting;

- Applying for continuing review of the protocol at least annually unless directed by the IRB to apply more frequently;

- Conducting the protocol as represented here and in compliance with IRB determinations and all applicable local, state, and federal law and regulations; providing the IRB with all information necessary to review the protocol; refraining from protocol activities until receipt of initial and continuing formal IRB approval.

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Signature of Investigator:_____ **Date:**_____

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c. List all staff who will be involved with the design, conduct, and reporting of the research, their degree(s) and job title, and any additional qualifications. Include individuals who will be involved in the consent process. *Repeat the table below for each individual.*

<u>Note.</u> *For studies involving investigational drugs, include all investigators who will be listed on FDA Form 1572 and attach a copy, if applicable. Send the IRB a copy of Form 1572 anytime you update the form with the FDA.*

Role:	☐Co- -*OR*- ☒Other –*AND/OR*- ☒Consent Process
Full Name:	**Lesley Ross**
Primary UAB Dept.: (Employer if not UAB)	**Psychology**
Degree(s) / Job Title:	**PhD/ Assistant Professor**
Additional Qualifications pertinent to the study:	**Study PI; Experience with studies and protocols of this nature; Trained developmental psychologist and expert in cognitive training and everyday outcomes in older adults**

Role:	☒Co- -*OR*- ☐Other –*AND/OR*- ☒Consent Process
Full Name:	**Kristina Visscher**
Primary UAB Dept.: (Employer if not UAB)	**Neurobiology**
Degree(s) / Job Title:	**PhD/ Assistant Professor**
Additional Qualifications pertinent to the study:	**Prior Experience in brain imaging using fMRI and EEG; experience with human research participants**

Role:	**☐Co- -OR- ☒Other –AND/OR- ☒Consent Process**
Full Name:	**Ryan Vaden**
Primary UAB Dept.: (Employer if not UAB)	**Neurobiology**
Degree(s) / Job Title:	**BS/ Research Technician**
Additional Qualifications pertinent to the study:	**Psychology background and expertise in similar lab research**

Role:	**☐Co- -OR- ☒Other –AND/OR- ☒Consent Process**
Full Name:	**Hrishikesh Dehpande**
Primary UAB Dept.: (Employer if not UAB)	**Psychology**
Degree(s) / Job Title:	**MS/Statistical Analyst**
Additional Qualifications pertinent to the study:	**Statistical expertise**

Role:	**☒Co- -OR- ☐Other –AND/OR- ☐Consent Process**
Full Name:	**Cynthia Owsley**
Primary UAB Dept.: (Employer if not UAB)	**Ophthalmology**
Degree(s) / Job Title:	**PhD/ Professor**
Additional Qualifications pertinent to the study:	**Expert in vision and visual problems**

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Role: ☒Co- -OR- ☐Other –AND/OR- <mark>☐</mark>**Consent Process**
Full Name: **Karlene Ball**
Primary UAB Dept.: **Psychology**
(Employer if not UAB)
Degree(s) / Job Title: **PhD/ Professor**
Additional Qualifications **Expert in vision and cognitive training in older adults**
pertinent to the study:

Role: ☐Co- -OR- ☒Other –AND/OR- ☒Consent Process
Full Name: **Stephen Todd**
Primary UAB Dept.: **Psychology**
(Employer if not UAB)
Degree(s) / Job Title: **MA/Research Assistant**
Additional Qualifications **Expertise with UFOV testing and training software**
pertinent to the study:

Role: ☐Co- -OR- ☒Other –AND/OR- ☒Consent Process
Full Name: **Joan Dodson**
Primary UAB Dept.: **Psychology**
(Employer if not UAB)
Degree(s) / Job Title: **MA/Graduate Assistant**
Additional Qualifications **Expertise with UFOV testing and training software**
pertinent to the study:

Role: ☐Co- -OR- ☒Other –AND/OR- ☒Consent Process
Full Name: **Shernine Lee**
Primary UAB Dept.: **Psychology**
(Employer if not UAB)
Degree(s) / Job Title: **BS/Program Coordinator**
Additional Qualifications **Expertise with UFOV testing and training software**
pertinent to the study:

Role: ☐Co- -OR- ☒Other –AND/OR- ☒Consent Process
Full Name: **Martha Graham**
Primary UAB Dept.: **Psychology**
(Employer if not UAB)
Degree(s) / Job Title: **MA/Program Manager II**
Additional Qualifications **Expertise with UFOV testing and training software**
pertinent to the study:

Role: ☒Co- -OR- ☐Other –AND/OR- ☒Consent Process
Full Name: **Virginia Wadley Bradley**
Primary UAB Dept.: **Med-Gerontology/Geriatrics/Palliative Care**
(Employer if not UAB)
Degree(s) / Job Title: **PhD/Associate Professor**
Additional Qualifications **Expertise with cognition and cognitive training in older adults**
pertinent to the study:

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Role: ☐Co- -OR- ☒Other –AND/OR- ☒Consent Process
Full Name: **Parya Fazeli**
Primary UAB Dept.: **Psychology**
(Employer if not UAB)
Degree(s) / Job Title: **MA/Graduate Assistant**
Additional Qualifications **Expertise with UFOV testing and training software**
pertinent to the study:

Role: ☐Co- -OR- ☒Other –AND/OR- ☒Consent Process
Full Name: **Wesley Burge**
Primary UAB Dept.: **Psychology**
(Employer if not UAB)
Degree(s) / Job Title: **BA/Neurobiology Research Assistant**
Additional Qualifications **Expertise with neural measures**
pertinent to the study:

Role: ☐Co- -OR- ☒Other –AND/OR- ☒Consent Process
Full Name: **Irma Jewett**
Primary UAB Dept.: **Psychology**
(Employer if not UAB)
Degree(s) / Job Title: **Research Assistant**
Additional Qualifications **Expertise with data entry**
pertinent to the study:

Role: ☐Co- -OR- ☒Other –AND/OR- ☒Consent Process
Full Name: **David Benz**
Primary UAB Dept.: **Psychology**
(Employer if not UAB)
Degree(s) / Job Title: **MA/ Research Assistant**
Additional Qualifications **Expertise with data entry and management**
pertinent to the study:

Role: ☐Co- -OR- ☒Other –AND/OR- ☒Consent Process
Full Name: **Christine Denning**
Primary UAB Dept.: **BioMedical Engineering**
(Employer if not UAB)
Degree(s) / Job Title: **BA/ Graduate Research Assistant**
Additional Qualifications **Expertise with data analysis and data collection**
pertinent to the study:

Role: ☐Co- -OR- ☒Other –AND/OR- ☐Consent Process
Full Name: **Lawrence Ver Hoef**
Primary UAB Dept.: **Dept of Neurology**
(Employer if not UAB)
Degree(s) / Job Title: **MD/Assistant Prof of Neurology**
Additional Qualifications **Neurologist; Agreed to read scans for incidental findings that**
pertinent to the study: **might indicate that participants are at risk**

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d. Is the principal investigator a student, fellow, or resident? ☐Yes ☒No
    If Yes, complete items below and obtain signature of faculty advisor or supervisor:

            Supervisor's Name: ____
          Degree(s) / Job Title: ____
     Additional Qualifications ____
        pertinent to the study:
               Telephone: ____
                 E-Mail: ____
            Signature: _____

e. Describe the principal investigator's activities related to this protocol and provisions made by the PI to devote sufficient time to conduct the protocol: **The PI is responsible for all aspects of the protocol. She has protected time as a beginning Assistant Professor to devote to this research.**

f. Is medical supervision required for this research? ☐Yes ☒No
    If Yes, who will provide the supervision?
      ☐ PI will provide -*OR*- Name:____ Telephone:____
    If other than PI, obtain signature of person providing medical supervision:
                    Signature _____

g. Describe the process that ensures that all persons assisting with the research are adequately informed about the protocol and their research-related duties and functions: **All research personnel have current IRB training, will be carefully trained regarding the study protocol, and will be trained in their research-related duties prior to study commencement. Weekly schedule research lab meetings will be used in part to update and clarify expectations for their duties. Additionally, random quality control observations will be conducted by the PI and Dr. Visscher to ensure that protocols are followed precisely.**

3. Funding

Is this study funded? ☒Yes ☐No
If No, specify that costs of the study will be covered by funds from the UAB department or other source named:____
If Yes, attach one copy of completed application or request for funding sent to sponsor, and complete a-d.
    a. Title of Grant or Contract: **Translational Research Intramural Grant Program and Dr. Ross' and Visscher's Startup Funds**
    b. PI of Grant or Contract: **Lesley Ross, PhD**
    c. Office of Grants & Contracts Administration Link or Tracking Number:____
        (*or enter "Pending" and provide upon receipt from OGCA*)
    d. Sponsor, Funding Route (*check and describe all that apply*):
      ☐ Gov't Agency or Agencies—Agency name(s):____
          ☐ Department of Defense (DoD): Identify DoD component:____
          ☐ Department of Energy (DOE)
          ☐ Department of Justice (DOJ)
          ☐ Department of Education
      ☐ NIH Coop. Group Trial—Group name:____

☐ Private Nonprofit (e.g., Foundation)—Name:____

☐ Industry, investigator-initiated—Name:____ Describe the funding arrangement:____

Note. *Western IRB* *reviews industry-sponsored protocols unless the investigator initiated the research, or the study qualifies for expedited review or involves gene therapy.*

☒ UAB Departmental/Division Funds—Specify: **UAB Center for Clinical and Translational Science; UAB Center for Aging; UAB Vision Science Research Center; UAB Center for Research on Applied Gerontology; UAB Department of Psychology; UAB Department of Neurobiology**

4. **Conflict of Interest—Human subjects research involving a disclosed financial interest is subject to IRB review following review by the Conflict of Interest Review Board.**

The following definitions are used for Item #4:

Immediate family means spouse or a dependent of the employee. *Dependent* is any person, regardless of his or her legal residence or domicile, who receives 50% or more of his or her support from the public official or public employee or his or her spouse or who resided with the public official or public employee for more than 180 days during the reporting period.

Financial Interest Related to the Research means financial interest in the sponsor, product or service being tested, or competitor of the sponsor.

For each investigator and staff member involved in the design, conduct and reporting of the research (see Items 2.a. and 2.c.) answer the questions below: **(Repeat the section below for each individual)**

Name: **Lesley Ross**

Do you or your immediate family have any of the following? (check all that apply)

☐ An ownership interest, stock options, or other equity interest related to the research of any value.

☐ Compensation related to the research unless it meets two tests:
  • Less than $10,000 in the past year when aggregated for the immediate family.
  • Amount will not be affected by the outcome of the research.

☐ Proprietary interest related to the research including, but not limited to, a patent, trademark, copyright, or licensing agreement.

☐ Board of executive relationship related to the research, regardless of compensation.

Name: **Kristina Visscher**

Do you or your immediate family have any of the following? (check all that apply)

☐ An ownership interest, stock options, or other equity interest related to the research of any value.

☐ Compensation related to the research unless it meets two tests:
  • Less than $10,000 in the past year when aggregated for the immediate family.
  • Amount will not be affected by the outcome of the research.

☐ Proprietary interest related to the research including, but not limited to, a patent, trademark, copyright, or licensing agreement.

☐ Board of executive relationship related to the research, regardless of compensation.

Name: **Ryan Vaden**

Do you or your immediate family have any of the following? (check all that apply)

☐ An ownership interest, stock options, or other equity interest related to the research of any value.

☐ Compensation related to the research unless it meets two tests:
  • Less than $10,000 in the past year when aggregated for the immediate family.
  • Amount will not be affected by the outcome of the research.

☐ Proprietary interest related to the research including, but not limited to, a patent, trademark, copyright, or licensing agreement.

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☐ Board of executive relationship related to the research, regardless of compensation.

***Name:*Hrishikesh Deshpande**

Do you or your immediate family have any of the following? (check all that apply)
☐ An ownership interest, stock options, or other equity interest related to the research of any value.
☐ Compensation related to the research unless it meets two tests:
• Less than $10,000 in the past year when aggregated for the immediate family.
• Amount will not be affected by the outcome of the research.
☐ Proprietary interest related to the research including, but not limited to, a patent, trademark, copyright, or licensing agreement.
☐ Board of executive relationship related to the research, regardless of compensation.

***Name:*Cynthia Owsley**

Do you or your immediate family have any of the following? (check all that apply)
☐ An ownership interest, stock options, or other equity interest related to the research of any value.
☐ Compensation related to the research unless it meets two tests:
• Less than $10,000 in the past year when aggregated for the immediate family.
• Amount will not be affected by the outcome of the research.
☐ Proprietary interest related to the research including, but not limited to, a patent, trademark, copyright, or licensing agreement.
☐ Board of executive relationship related to the research, regardless of compensation.

***Name:* Stephen Todd**

Do you or your immediate family have any of the following? (check all that apply)
☐ An ownership interest, stock options, or other equity interest related to the research of any value.
☐ Compensation related to the research unless it meets two tests:
• Less than $10,000 in the past year when aggregated for the immediate family.
• Amount will not be affected by the outcome of the research.
☐ Proprietary interest related to the research including, but not limited to, a patent, trademark, copyright, or licensing agreement.
☐ Board of executive relationship related to the research, regardless of compensation.

***Name:*Karlene Ball**

Do you or your immediate family have any of the following? (check all that apply)
☒ An ownership interest, stock options, or other equity interest related to the research of any value.
☒ Compensation related to the research unless it meets two tests:
• Less than $10,000 in the past year when aggregated for the immediate family.
• Amount will not be affected by the outcome of the research.
☒ Proprietary interest related to the research including, but not limited to, a patent, trademark, copyright, or licensing agreement.
☐ Board of executive relationship related to the research, regardless of compensation.

***Name:*Joan Dodson**

Do you or your immediate family have any of the following? (check all that apply)
☐ An ownership interest, stock options, or other equity interest related to the research of any value.
☐ Compensation related to the research unless it meets two tests:
• Less than $10,000 in the past year when aggregated for the immediate family.
• Amount will not be affected by the outcome of the research.
☐ Proprietary interest related to the research including, but not limited to, a patent, trademark, copyright, or licensing agreement.
☐ Board of executive relationship related to the research, regardless of compensation.

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Name: Shernine Lee

Do you or your immediate family have any of the following? (check all that apply)
- [ ] An ownership interest, stock options, or other equity interest related to the research of any value.
- [ ] Compensation related to the research unless it meets two tests:
  - Less than $10,000 in the past year when aggregated for the immediate family.
  - Amount will not be affected by the outcome of the research.
- [ ] Proprietary interest related to the research including, but not limited to, a patent, trademark, copyright, or licensing agreement.
- [ ] Board of executive relationship related to the research, regardless of compensation.

Name: Martha Graham

Do you or your immediate family have any of the following? (check all that apply)
- [ ] An ownership interest, stock options, or other equity interest related to the research of any value.
- [ ] Compensation related to the research unless it meets two tests:
  - Less than $10,000 in the past year when aggregated for the immediate family.
  - Amount will not be affected by the outcome of the research.
- [ ] Proprietary interest related to the research including, but not limited to, a patent, trademark, copyright, or licensing agreement.
- [ ] Board of executive relationship related to the research, regardless of compensation.

Name: Virginia Wadley Bradley

Do you or your immediate family have any of the following? (check all that apply)
- [ ] An ownership interest, stock options, or other equity interest related to the research of any value.
- [ ] Compensation related to the research unless it meets two tests:
  - Less than $10,000 in the past year when aggregated for the immediate family.
  - Amount will not be affected by the outcome of the research.
- [ ] Proprietary interest related to the research including, but not limited to, a patent, trademark, copyright, or licensing agreement.
- [ ] Board of executive relationship related to the research, regardless of compensation.

Name: Paryia Fazeli

Do you or your immediate family have any of the following? (check all that apply)
- [ ] An ownership interest, stock options, or other equity interest related to the research of any value.
- [ ] Compensation related to the research unless it meets two tests:
  - Less than $10,000 in the past year when aggregated for the immediate family.
  - Amount will not be affected by the outcome of the research.
- [ ] Proprietary interest related to the research including, but not limited to, a patent, trademark, copyright, or licensing agreement.
- [ ] Board of executive relationship related to the research, regardless of compensation.

Name: Wesley Burge

Do you or your immediate family have any of the following? (check all that apply)
- [ ] An ownership interest, stock options, or other equity interest related to the research of any value.
- [ ] Compensation related to the research unless it meets two tests:
  - Less than $10,000 in the past year when aggregated for the immediate family.
  - Amount will not be affected by the outcome of the research.
- [ ] Proprietary interest related to the research including, but not limited to, a patent, trademark, copyright, or licensing agreement.
- [ ] Board of executive relationship related to the research, regardless of compensation.

Name: **Irma Jewett**

Do you or your immediate family have any of the following? (check all that apply)

☐ An ownership interest, stock options, or other equity interest related to the research of any value.
☐ Compensation related to the research unless it meets two tests:
  • Less than $10,000 in the past year when aggregated for the immediate family.
  • Amount will not be affected by the outcome of the research.
☐ Proprietary interest related to the research including, but not limited to, a patent, trademark, copyright, or licensing agreement.
☐ Board of executive relationship related to the research, regardless of compensation.

Name: **David Benz Christine Denning**

Do you or your immediate family have any of the following? (check all that apply)

☐ An ownership interest, stock options, or other equity interest related to the research of any value.
☐ Compensation related to the research unless it meets two tests:
  • Less than $10,000 in the past year when aggregated for the immediate family.
  • Amount will not be affected by the outcome of the research.
☐ Proprietary interest related to the research including, but not limited to, a patent, trademark, copyright, or licensing agreement.
☐ Board of executive relationship related to the research, regardless of compensation.

Name: **Christine Denning**

Do you or your immediate family have any of the following? (check all that apply)

☐ An ownership interest, stock options, or other equity interest related to the research of any value.
☐ Compensation related to the research unless it meets two tests:
  • Less than $10,000 in the past year when aggregated for the immediate family.
  • Amount will not be affected by the outcome of the research.
☐ Proprietary interest related to the research including, but not limited to, a patent, trademark, copyright, or licensing agreement.
☐ Board of executive relationship related to the research, regardless of compensation.

Name: **Lawrence Ver Hoef**

Do you or your immediate family have any of the following? (check all that apply)

☐ An ownership interest, stock options, or other equity interest related to the research of any value.
☐ Compensation related to the research unless it meets two tests:
  • Less than $10,000 in the past year when aggregated for the immediate family.
  • Amount will not be affected by the outcome of the research.
☐ Proprietary interest related to the research including, but not limited to, a patent, trademark, copyright, or licensing agreement.
☐ Board of executive relationship related to the research, regardless of compensation.

If you checked any of the above, a financial interest disclosure has to be submitted to or currently be on file with the CIRB. A completed CIRB Evaluation has to be available before the IRB will conduct its review. **Dr. Ball's Memorandum of Understanding is on file at the CIRB.**

5. Locations Involved

a. Describe the facilities available for the conduct of the research. For research on UAB campus, include building names and room numbers: **This research will be conducted at the: (1) Civitan International Research Center: Magnetic Resonance Imaging**

Facility, as well as Suite 111 in CIRC (including rooms 111A and 111B), the (2) Holley Mears Building (rooms 180 and 184), and the 916 Building suite of cubicles 1-9.

b. Indicate all "performance sites" that will provide space, services, facilities, potential or actual participants, or other support for this protocol.
- ☐ The Kirklin Clinic (TKC)
- ☐ University of Alabama Hospital (UAHosp)
- ☐ The Children's Hospital of Alabama (TCHA)
- ☐ Callahan Eye Foundation Hospital (CEFH)
- ☐ UAB Highlands
- ☐ Jefferson County Dept. of Health (JCDH)
- ☐ Birmingham Veterans Affairs Medical Center (BVAMC)
- ☐ General Clinical Research Center (GCRC)—inpatient
- ☐ General Clinical Research Center (GCRC)—outpatient
- ☐ General Clinical Research Center (GCRC) at The Kirklin Clinic (TKC)
- ☐ Other (i.e., Any performance site not listed above, including those covered by subcontracts related to this protocol)—Describe:____

c. Is this study a clinical trial requiring clinical services at one of the performance sites listed in Item b above?   ☐Yes ☒No
If Yes, Fiscal Approval Process (FAP)-designated units complete a FAP submission and send to fap@uab.edu. For more on the UAB FAP, see www.uab.edu/ohr.

d. Is this a field study?   ☐Yes ☒No
If Yes, describe the community and include information about how the community will be involved in the design, implementation and analysis of the research. This would include focus groups, training local facilitators/community health advisors:____

e. Is the study to be undertaken within a school, business, or other institution that does not have an institutional review board?   ☐Yes ☒No
If Yes, attach a statement of any contacts with and approvals from the appropriate institution officials.
Note. *Documentation of all such approvals must be received by the UAB OIRB before IRB approval will be issued.*

f. Has this protocol or project been reviewed by another IRB, similar review board, or departmental review committee(s) that authorizes the use of its patient populations?   ☐Yes ☒No
If Yes, provide name of the review board(s):____   and for each board listed, enter either the date of latest approval(s) or "PENDING":____ or reasons not approved:____. *If this protocol is subsequently rejected or disapproved by another review board, the UAB IRB must be notified promptly.*
Attach copies of approvals/disapprovals.

g. Will any of the participants be from the Birmingham Veterans Affairs Medical Center?   ☐Yes ☒No
If Yes, attach VA IRB approval or notification from the VA Research and Development Department that the study has been submitted to the VA IRB for review.

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h. Will the study be conducted at or recruit participants from the Jefferson County Department of Public Health (JCDH)? ☐Yes ☒No
If Yes, attach notification that the protocol has been approved by JCDH or the Alabama Department of Public Health IRB.

6. Multi-Site Studies

a. Is the investigator the lead investigator of a multi-site study? ☐Yes ☒No
b. Is UAB a coordinating site in a multi-site study? ☐Yes ☒No
c. If you answered **Yes** to *a* or *b*, describe the management of information obtained in multi-site research that might be relevant to the protection of participants. Include, at a minimum, the following items:
   - IRB approvals from other sites
   - Unanticipated problems involving risks to participants or others. (For example, if there is an unanticipated problem involving risks to participants or others, which site is responsible for reporting it?)
   - Interim results.
   - Protocol modifications.

7. Drugs: Will any drugs or supplements be used/studied in this protocol? ☐Yes ☒No
If Yes, attach the Drug Review Sheet.

8. Devices: Will any devices be studied in this protocol or used for a purpose other than for which they were approved by the FDA? ☐Yes ☒No
If Yes, attach the Device Review Sheet.

9. Special Approvals

a. Does this project involve the use of radioisotopes? ☐Yes ☒No
If Yes, attach documentation of approval from the Radiation Safety Division.

b. Does this project include patients with contagious infections (e.g., mumps, measles, chickenpox, TB, meningitis)? ☐Yes ☒No
If Yes, attach documentation of approval from Chairman of the Infection Control Committee of the appropriate facilities.

c. Does this project involve obtaining remnant biopsy or surgical material from the Department of Pathology or any other source? ☐Yes ☒No
If Yes, attach documentation of approval from the entity or individual providing the materials (e.g., the UAB Division of Anatomic Pathology Release of Pathologic Materials).

d. Does this project require obtaining any remnant clinical laboratory specimens, body fluids, or microbiological isolates from the Department of Pathology or any other source? ☐Yes ☒No
If Yes, attach documentation of approval from the entity or individual providing the materials (e.g., the UAB Division of Laboratory Medicine Release of Pathologic Materials).

e. Does this project use stored (existing) specimens from a repository? ☐Yes ☒No
If Yes, attach documentation of approval for use of specimens, and describe how existing specimens are labeled:＿＿＿

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10. Use of Specimens

Does this project involve collecting specimens from participants and storing them for future research? ☒Yes ☐No

If Yes, complete a-h. If no, skip to Item 11

a. How will specimens be obtained, processed, distributed, and stored?

A saliva sample will be obtained (via spitting in a cup, swabbing a check or (rarely) collecting a blood sample) from each participant when they come to the CRAG for their baseline visit. Samples will be stored with the participants' permission and will be identified only with the unique study ID (and not the participants' names). Samples will be stored in locked cabinet within Dr. Ross' lab.

b. How will specimens be labeled (e.g., unique identifier, medical record number, Social Security number, name, date of birth)?

Specimens will be labeled with a unique subject ID. No identifying information will be used in conjunction with the specimens.

c. How will clinical data associated with the specimens be collected and stored?
There is no clinical data associated with the specimens.

d. What participant-identifying information will be collected and linked to the specimens?

Only unique subject IDs will be used for linking the specimens. No identifying information will be provided on the specimens.

e. What steps will be taken to maximize the confidentiality of linked identifiers? For example, procedures could include using a password-protected computer database to link identifiers, with limited personnel knowledgeable of the password, or coded identifiers released without the ability to link to clinical data (also called "stripped" or "anonymized" specimens).

The master list linking participant names and code numbers will be stored separately from the specimens and results of the genetic testing. The list will be kept in password protected computer at Dr. Ross' lab.

f. Will specimens be shared with other investigators in the future? ☐Yes ☒No

If Yes, what identifiers, clinical information and demographic information will be shared; or will the specimens be stripped of identifiers (i.e., anonymized)? Also **if yes**, outline your procedure for assuring IRB approval for release and use prior to release of specimens.

Note. *Investigators who receive and/or use these specimens must document approval from the appropriate IRB(s) before the specimens may be released.*

g. Will biological samples be stored for future use? ☒Yes ☐No

If Yes, indicate whether they will be used for the disease under study in this protocol or research on other diseases.

This study does not investigate a specific disease; however, the samples may be used for future research regarding aging, cognition and everyday functioning.

h. Is genetic testing planned? ☐Yes ☒No

If Yes, describe the planned testing here and see "DNA/Genetic Testing" in the Guidebook for consent requirements.

DNA/Genetic samples will be collected to investigate the relationship between brain function and genes related to cognition. Participants will provide a buccal swab or saliva sample for genetic testing. Only in extreme cases (such as if the participant could not provide saliva due to dry mouth) will we request a blood sample. In this unusual situation, the blood will be collected in a special visit to UAB by a certified specialist at UAB. Samples will be stored with the participant's permission for future research on cognition and everyday functioning. Samples will be identified with a study code number and not the participant's name. Samples will be stored within a locked cabinet within Dr. Ross' laboratory. This is a study with healthy individuals and is not part of a clinical trial. None of the information obtained in this study is placed in the patient's medical record.

11. Gene Therapy
Does this project involve gene therapy or administering recombinant materials to humans?   ☐Yes ☒No
If Yes, submit the Gene Therapy Project Review Panel Report –OR- If this is a vaccine trial that is exempt from the NIH Guidelines For Research Involving Recombinant DNA Molecules, submit the Protocol Oversight Review Form For Clinical Vaccine Trials.

12. HIPAA Privacy and Security
Will the PI or others obtain, review, or make other use of participants' "personal health information" (i.e., information, whether oral or recorded in any form or medium that (a) is created or received by a health care provider and (b) relates to past, present, or future physical or mental health or condition of an individual; or provision of health care; or payment for provision of heath care)?   ☒Yes ☐No

If Yes, complete a-e as described.
a. Will the data/information be stored or managed electronically (on a computer)?
                                                                                                     ☒Yes ☐No

b. Is the principal investigator requesting that the UAB IRB waive patient HIPAA authorization from another institution or entity (e.g., insurance company, collaborating institution).   ☐Yes ☒No
If Yes, attach copy of privacy notices from institution/entity, and provide the name of institution/entity:

c. Indicate which, if any, of the listed entities below would provide information or maintain health information collected for this protocol and/or where health information that been collected will be stored/maintained.
☐ The Kirklin Clinic
☐ University of Alabama Hospital
☐ The Children's Hospital of Alabama
☐ Callahan Eye Foundation Hospital
☐ UAB Highlands
☐ Jefferson County Department of Health
☐ School of Dentistry
☐ School of Health Professions

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- ☒ School of Medicine
- ☐ School of Nursing
- ☐ School of Optometry
- ☐ University of Alabama Health Services Foundation
- ☐ UAB Health Centers
- ☐ Viva Health
- ☐ Ophthalmology Services Foundation
- ☐ Valley Foundation
- ☐ Medical West - UAB Health System Affiliate
  Health System Information Systems:
- ☐ HealthQuest
- ☐ Cerner Millennium (Lab, Radiology, UED, Surgery)
- ☐ EMMI - Master Member Index
- ☐ Horizon - IPV (IVR/CDA/CRIS)
- ☐ CareFlow Net
- ☐ Eclipsys (PIN)
- ☐ IMPACT
- ☐ None—**If None, skip to Item 13.**

d. Indicate which of the listed identifiers would be associated/linked with the protected health information (PHI) used for this protocol.
- ☒ Names
- ☒ Geographic subdivisions smaller than a State
- ☒ Elements of dates (except year) related to an individual
- ☒ Telephone numbers
- ☐ Fax numbers
- ☐ Email addresses
- ☐ Social security numbers
- ☐ Medical record numbers
- ☐ Health plan beneficiary numbers
- ☐ Account numbers
- ☒ Certificate/license numbers
- ☐ Vehicle identifiers and serial numbers
- ☐ Device identifiers and serial numbers
- ☐ Biometric identifiers
- ☐ Web universal resource locators (URLs)
- ☐ Internet protocol address numbers
- ☐ Full-face photographic images
- ☐ Any other unique identifying number—Describe: _____
  Note. Codes are not identifying as long as the researcher cannot link the data to an individual
- ☐ None—**If None, skip to Item 13.**

e. Choose one plan to describe your use of the personal health information:
- ☐ The data collected meet the specifications for a "limited data set" —Attach Data Use Agreement or Business Associate Agreement

- ☒ Research staff will obtain authorization from each patient to use the information —Attach Patient Authorization form, complete except for patient name and IRB protocol number

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☐ PI requests Waiver of Patient Authorization to use the information
—Attach Waiver of Authorization and Informed Consent form

PROPOSED RESEARCH
- The IRB will not accept grant applications and/or sponsor's protocols in lieu of the items as outlined below.
- Do not separate responses from items. Instead, insert your response to each item below the item, keeping the information in the order of this form.
- Number each page of the Human Subjects Protocol (i.e., Page *X* of *Y*).

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13. Purpose—in nontechnical, lay language
Summarize the purpose and objectives of this protocol, including any related projects, in one short paragraph.

This proposal explores neural activity associated with a test of visual processing speed, the Useful Field of View (UFOV). Cognitively/physically intact older adults will be randomized to a computerized cognitive/visual Speed of Processing training group, a Cognitively Stimulating Activities (e.g., crossword puzzles, reasoning problems, etc.) group, or a No-contact Control group (equal number of participants per three groups). We will compare neural activity (fMRI) in response to UFOV stimuli both before and after training for each group. Using methods to distinguish fMRI activity with different temporal profiles, we will explore (1) the function of neural activity in the visual cortex and (2) how speed of processing training impacts this activity as compared to the No-contact Control group and the Cognitively Simulating Activities group.

14. Background—in nontechnical, lay language
Summarize in 2-3 paragraphs past experimental and/or clinical findings leading to the formulation of this study. Include any relevant past or current research by the Principal Investigator. For drug and device studies summarize the previous results (i.e., Phase I/II or III studies).

Older adults are the fastest growing segment of the US population. As such, methods to maintain this population's health, wellbeing, and independence are of increasing concern, especially from a public health and long-term care standpoint. Cognitive abilities are linked to wellbeing and are of the utmost importance when assessing an adult's ability to function independently. Processing speed is a key fluid ability thought to be a large contributing factor to cognitive aging/slowing (processing speed theory). Although aspects of cognition may decline with age, such as processing speed, the brain remains plastic throughout the normal aging process. Researchers seeking to capitalize on this neural plasticity have developed cognitive training programs that seek to translate improved cognitive function to everyday activities to maintain the independence and wellbeing of older adults. One particular such program, Speed of Processing training, has demonstrated great promise in maintaining mobility, improving mental and physical health, and improving driving safety, and maintaining abilities to perform Instrumental Activities of Daily Living, IADLs (such as using the telephone and making change).

Although research has demonstrated improved cognitive processing speed and transfer to everyday activities, little is known about the mechanisms behind this transfer of training. By understanding the mechanisms of training, we may be able to improve and translate these training effects to other interventions. This is the first study of its kind to evaluate the neural changes from Speed of Processing speed in this population using fMRI methods and a social- (Cognitively Stimulating Activities group) and no-contact control groups. Additionally, other cognitive measures postulated to mediate this training, such as visual search and attention, will be investigated through behavioral data collection at pre- and post-training.

15. Participants (Screening and Selection)

a. How many participants are to be enrolled at UAB? <mark>**300**</mark>
If multi-center study, total number at all centers: <u>**NA**</u>

b. Describe the characteristics of anticipated or planned participants.
Sex:<u>**Male (50%) and Female**</u>
Race/Ethnicity:<u>**Race and ethnic composition will reflect the Birmingham Metropolitan area**</u>
<u>**older adult population (i.e., 30% African American based on our previous experience/studies).**</u>
Age:<u>**65-95**</u>
Health status: <u>**Cognitively and physically intact older adults (Telephone Interview of Cognitive**</u>
<u>**Status-Modified; TICS-M)**</u>

Note. If data from prior studies indicate differences between the genders or among racial/ethnic groups in the proposed research or if there are no data to support or to negate such differences, Phase 3 clinical trials will be required to include sufficient and appropriate entry of gender and racial/ethnic subgroups so that trends detected in the affected subgroups can be analyzed. If ethnic, racial, and gender estimates are not included in the protocol, a clear rationale must be provided for exclusion of this information. If prior evidence indicates that the results will not show gender or racial differences, researchers are not required to use gender or race/ethnicity as selection criteria for study participants. They are, however, encouraged to include these groups. See Section II. Policy of the NIH POLICY AND GUIDELINES ON THE INCLUSION OF WOMEN AND MINORITIES AS SUBJECTS IN CLINICAL RESEARCH – Amended, October, 2001) for further details.

c. From what population(s) will the participants be derived?
<u>**Participants will be recruited from the Center for Research on Applied Gerontology Recruitment**</u>
<u>**Database (IRB Protocol # X050502007). Participants in this database have consented to be**</u>
<u>**contacted about future Center studies. Flyers may also be distributed to Birmingham area sites**</u>
<u>**(including churches, Senior Centers, and ads). In addition, older adult subjects will be recruited**</u>
<u>**through Dr. Visscher's research group. The flyer is also attached in this application packet.**</u>
Describe your ability to obtain access to the proposed population that will allow recruitment of the necessary number of participants:
<u>**Demographic data is stored in the recruitment database (IRB Protocol # X050502007).**</u>
<u>**Participants in this database who have consented to be contacted regarding future studies will be**</u>
<u>**contacted regarding this study if they are currently 65 or older and have previously received a**</u>
<u>**poor score on the UFOV (Useful Field of View) test. These potential participants will be contacted**</u>
<u>**to verify their age and interest in participating in the study. Those who wish to participate will be**</u>
<u>**asked a serious of questions regarding their health and ability to undergo fMRI. Those who are**</u>
<u>**still interested and able to participate will be scheduled for a screening/baseline behavioral**</u>
<u>**assessment and mailed an informed consent. Flyers will also be used if additional recruitment is**</u>
<u>**needed outside of the main database.**</u>
Describe the inclusion/exclusion criteria:
     <u>Inclusion Criteria:</u> <u>**The following inclusion criteria are necessary for this project to reduce**</u>
<u>**variability, to ensure non-problematic participation in the magnet environment, and to address**</u>
<u>**magnet safety concerns:**</u>
- <u>**Right handed individuals**</u>
- <u>**No evidence of dementia (via the TICS-M assessment)**</u>
- <u>**Aged 65-95 in good health (self-report)**</u>
- <u>**Poor baseline processing speed via the UFOV test (Risk category of 3-5 as indicated by**</u>
<u>**standard scoring guidelines via the User Manual)**</u>
- <u>**Normal or corrected-to-normal vision**</u>

- **Weight must be under 300 pounds and maximum girth less than 60 inches (for the purposes of the scanner)**
- **Normal hearing (for the purposes of following directions in the scanner)**
- **No report of current pregnancy**
- **No report of having had a previous serious head injury or neurological disorder, or loss of consciousness for more than 2 minutes**
- **No report of having hallucinations or delusions or currently taking psychoactive medications**
- **No report of having a current or past history of substance abuse**
- **No report of being claustrophobic**
- **No report of having excessive old or colorful tattoos (especially near the head), having ferromagnetic material in body, wearing a pacemaker, wearing braces or a permanent retainer**

d. If participants will comprise more than one group or stratification, describe each group (e.g., treatment/intervention, placebo, controls, sham treatment) **and** provide the number of participants anticipated in each group.
Three hundred participants will be randomized to the Speed of Processing group (1/3rd), a Cognitively Stimulating Activities group (social-contact control; 1/3rd), or a No-contact Control group (1/3rd). The control groups for this experiment are necessary to understand how the different timecourses of neural activity in response to the stimuli studied here are different between participants who have received training, who have received materials generally thought to provide stimulation to the brain, and those who have received nothing.

e. Indicate which, if any, of the special populations listed below will be involved in the protocol. Include the Special Populations Review Form (SPRF) if indicated.
☐ Pregnant Women: Attach SPRF—Pregnant Women, Fetuses, Neonates/Nonviable Neonates
☐ Fetuses: Attach SPRF—Pregnant Women, Fetuses, Neonates/Nonviable Neonates
☐ Neonates/Nonviable Neonates: SPRF—Pregnant Women, Fetuses, Neonates/Nonviable Neonates
☐ Prisoners: Attach SPRF—Prisoners
☐ Minors (<19 years old): Attach SPRF—Minors
☐ Employees or students at institution where research conducted
☐ Persons who are temporarily decisionally impaired
☐ Persons who are permanently decisionally impaired (e.g., mentally retarded)
☐ Non-English Speakers
For each box checked, describe why the group is included **and** the additional protections provided to protect the rights and welfare of these participants who are vulnerable to coercion:**NA**

f. List any persons other than those directly involved in the study who will be at risk. If none, enter "None":**None**

g. Describe the process (e.g., recruitment, chart review) that will be used to seek potential participants (e.g., individuals, records, specimens). Research recruitment by non-treating physicians/staff may require completion of Partial Waiver of Authorization for Recruitment/Screening. (See http://main.uab.edu/show.asp?durki=61981.)
Participants will come from the Recruitment Database or will be recruited via a flyer (attached)

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h. If you will use recruitment materials (e.g., advertisements, flyers, letters) to reach potential participants, attach a copy of each item. If not, identify the source (e.g., databases) from which you will recruit participants.

We will recruit primarily from the Center for Research on Applied Gerontology Recruitment Database (IRB Protocol # X050502007). We will send these potential participants a letter (attached) describing the study prior to contacting them via the phone. However, if needed, we will also use flyers in the surrounding areas (churches, senior centers, community outreach centers, etc). A copy of this flyer is attached.

i. Describe the procedures for screening potential participants.

Once potential participants have been identified, a telephone screening will take place before the participants are asked to come to the Center for Research on Applied Gerontology for further evaluation (after signed informed consent). Potential participants will answer approximately ten minutes worth of questions over the phone. These questions will include the participant's willingness and availability to complete this training study and posttest assessments. We will also administer basic questions regarding cognitive status, health and an MR safety questionnaire in order to determine whether potential participants are safe to have fMRI scan. These measures are attached.

16. Protocol Procedures, Methods, and Duration of the Study—in nontechnical language

a. Describe the study methodology that will affect the participants—particularly in regard to any inconvenience, danger, or discomfort.

Potential participants from the Center for Research on Applied Gerontology Recruitment Database (IRB Protocol # X050502007) will receive a letter detailing the current project. After a two-week period (to allow time for mailing and review of letter), potential participants will be contact via phone to determine interest and eligibility (see Phone Screening 1 measures). Eligible participants will be mailed an Informed Consent and scheduled for an in-person Screening 2/Baseline visit. Participants who are eligible will be seen at the Holley-Mears building and after the Screening 2 assessment (15 minutes) will be invited to stay and complete the Baseline behavioral measures (1.5 hours). These Baseline behavioral measures will include demographic, health, lifestyle, and cognitive assessments. Additionally, we will ask for the participants' drivers' license numbers for future use in identifying correlates of vehicular crashes. Such records are publically available in Alabama; however, we have also included the following information in the Informed Consent:

> "We will ask for your drivers' license number. If you give us the number, we will save it in a secure location, and will obtain publicly available information on your driving record. Such information will be treated as completely private and will not be shared with other entities. Any information gathered for the study will not be released to the state and will not impact your right to hold a driver's license."

We will also ask participants for a DNA so that this data can be used to investigate the impact of genetics on aging, cognition, wellbeing and health. The following information has been added to the Informed Consent:

> "We will also take a DNA or genetic sample from you at baseline in order to see if there is any relationship between brain function and genes related to brain chemistry. This can be done through spiting in a cup, swabbing the inside of your check with a Q-tip-like object, or (in rare cases) a small blood sample. The results of this study could help understand how genetics may affect aging, cognition, health and/or wellbeing."

Storage of Specimens

DNA/Genetic samples will be stored (with your permission) for future research on aging, wellbeing, and everyday functioning. Samples will be stored in a locked cabinet within Dr. Ross' laboratory. The samples will be identified with a study code number and not your name.

Please initial your choice(s) below:

___ I agree to allow my samples to be kept and used for future research on aging, wellbeing, and everyday function.

___ I do not agree to allow my samples to be kept and used for future aging, wellbeing, and everyday function research.

After, completion of the Baseline behavioral assessment, participants will then be directed to the Civitan center to undergo their baseline fMRI visit (2 hours). If completed on the same day (depending on availability of the magnet and preference of the participant), we will ensure that there is a break of at least an hour between the behavioral and fMRI visits. After completion of the Baseline fMRI visit, participants will be randomized to one of three groups (Speed of Processing training, Cognitively Stimulating Activities, or a No-contact Control). After completion of training, participants will be asked to return for a Posttest Behavioral assessment and a Posttest fMRI assessment. Please see the 'Study Design/Flow' attachment. If further recruitment is needed, flyers will also be distributed in the Birmingham metropolitan area. Flyers will instruct interested persons to contact the Center so that screening can begin. A trained tester will conduct all screening/baseline/posttest assessments. Dr. Visscher, Ryan Vaden or another trained member of Dr. Visscher's lab will undertake the fMRI aspect of this study. All measures have been attached. Breaks and refreshments will be provided as needed. Further details regarding the fMRI data collection and training groups are provided below.

fMRI: The participant will have brain imaging done using the 3 Tesla scanner in the Civitan International Research Center (CIRC). The participant will change into hospital scrubs and remove any metallic material on the body and put such material in a small locked locker. The participant will then be taken to the imaging room and comfortably positioned in a supine position on the padded magnet table. The participant will wear headphones that serve as ear protectors, stimulus presenters, and a means of communicating to the subject through the intercom. The "head coil" part of the fMRI will be placed around the participant's head. This coil has openings at the front through which the participant can see. A small mirror aimed toward the rear of the magnet is attached to the coil, and through it the participant can see stimuli presented on a computer screen. The participant will be given a button to press to indicate his/her responses to stimuli. He/she will also be given a squeeze ball to signal desire to cease the experiment. Squeezing the ball will sound an alarm and terminate the experiment immediately. If a squeeze ball is used, the participant will be taken out of the scanner.

To begin the experiment, the participant will be slid into the magnet and will be made comfortable with the use of pillows etc. The first few minutes of the scanning will be used to adjust the scanner and take anatomical images of the brain. The participant will be instructed to lie still and relax during this phase. After this first phase, the participant will be reminded of the tasks (practiced outside of the scanner) and will be asked to complete these tasks. The participant's eye movements will be tracked using an MRI compatible infrared eyetracker. The entire fMRI portion of this project will take approximately 2 hours per session.

Training: 1/3rd of the participants will be randomized to a no-contact control group. These participants will be asked to complete the screening, baseline and posttest measures only. 1/3rd of

the participants will be randomized to the Cognitively Stimulating Activities group (social-contact control) they will be asked to complete ten hours of activities such as crosswords, word finds, and Sudoku. These activities are similar to ones performed by a wide range of older adults daily and have been previously used in other IRB-approved research at the Center. Another 1/3ʳᵈ of participants will be randomized to the Speed of Processing training group. This is a standardized computer training program that asks participants to decipher between a car and truck icon and localize a peripheral target at increasing speeds and levels of difficulty. Ten hours within a five week period will be required to complete the training. Training will be conducted at the 916 Building suite of training cubicles 1-9 with 17-inch touch screen monitors. Participants will be guided by certified trainers. Breaks for all participants (throughout testing and training) will be encouraged to ensure that participants do not fatigue.

b. What is the probable length of time required for the entire study (i.e., recruitment through data analysis to study closure)?
5 years

c. What is the total amount of time each participant will be involved?
Participants in the No-contact Control group will be asked to commit to three or less hours for behavioral data collection and four hours of neural data collection. Participants in the Cognitively Stimulating Activities group and the Speed of Processing training group will be asked to also dedicate an additional ten hours of time for the training/activities. Further details are provided in 16 e.

d. If different phases are involved, what is the duration of each phase in which the participants will be involved? If no phases are involved, enter "not applicable."
Once the participates are enrolled, they will be involved in the project for approximately seven weeks (total of 2-7 visits over a seven week period).

e. List the procedures, the length of time each will take, and the frequency of repetition, and indicate whether each is done solely for research or would already be performed for treatment or diagnostic purposes (routine care) for the population. *Insert additional table rows as needed.*

Procedure	Length of Time Required of Participants	Frequency of Repetition	Research (Res) – OR- Routine Care
Telephone Screening 1	**~10-15 minutes**	**Once**	☒Res ☐Routine
In-Person Screening 2	**~10 minutes**	**Once**	☒Res ☐Routine
Baseline Behavioral Data Collection	**~1.5 hours**	**Once**	☒Res ☐Routine
Baseline/Postest fMRI Data Collection	**~2 hours**	**Twice**	☒Res ☐Routine
Training (if applicable depending on randomization)	**~10 hours (either 10 one-hour visits or 5 two-hour visits)**	**Once**	☒Res ☐Routine
Posttest Behavioral Data Collection	**~1 hour**	**Once**	☒Res ☐Routine

f. Will an interview script or questionnaire be used?　　　　　　　☒Yes ☐No
If Yes, attach a copy. – **Copies of all measures and examples of training items are included in this application.**

g. Will participants incur any costs as a result of their participation?　　☒Yes ☐No
If Yes, describe the reason for and amount of each foreseeable cost.

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Participants will incur some costs associated with travel to and from the Center for Research on Applied Gerontology and the Civitan Research Center. These costs should be nominal as we are recruiting from the local area. There will be no costs associated with parking for appointments.

h. Will participants be compensated? ☒Yes ☐No
If Yes, complete i-v:
i. Type: (e.g., cash, check, gift card, merchandise):**check**
ii. Amount or Value:
$5 for participants who are deemed 'ineligible' after the in-person screening-
$120 for No-contact Control participants

$25 per hour of fMRI collection	**4*25=$100**
$20 for behavioral data collection	**$20**

$200 for Cognitively Stimulating Activities and Speed of Processing training groups

$25 per hour of fMRI collection	**4*25=$100**
$20 for behavioral data collection	**$20**
$80 for training activities	**$80**

iii. Method (e.g., mail, at visit): **mail at conclusion of visit**
iv. Timing of Payments: (e.g., every visit, each month):**at conclusion of visit**
v. Maximum Amount of Payments per Participant: **This varies depending on the group to which group the participant is randomized. $120 for those in the No-contact Control group and $200 for those in the Cognitively Stimulating Activities group or the Speed of Processing group.**

17. Describe the potential benefits of the research.

From the Informed Consent: **You may not personally benefit from your participation in this research; however, if you qualify for the study and decide to enroll, your participation may provide valuable information to the medical and scientific community regarding the neural mechanisms of cognitive activity/training on mental and physical abilities that are important for everyday functioning and mobility. This information may form the basis for future interventions for delaying or reversing the physical and cognitive declines that accompany normal aging.**

18. Risks

a. List the known risks—physical, psychological, social, economic, and/or legal—that participants may encounter as a result of procedures required in this protocol. Do not list risks resulting from standard-of-care procedures. *Note. Risks included in this protocol document should be included in the written consent document.*
All risks associated with this protocol are minimal. Techniques used are behavioral training, functional magnetic resonance imaging (fMRI), DNA collection and eyetracking with a Eyelink 1000 video eyetracker.

fMRI is a noninvasive procedure that involves no ionizing radiation. Magnetic resonance imaging (MRI) of the brain is a standard diagnostic tool used by neurologists for many years for a large group of patients including children and older adults. fMRI represents no greater risk than standard MRI. People who have conditions that would exclude them from safely participating in MRI experiments will be excluded from the study by use of a screening protocol. Risk factors include presence of ferromagnetic material within the body or pacemakers. Uncommonly, some people have found that after moving their head rapidly in the presence of high field magnets, they experience a transient period of dizziness. We have not experienced such an effect. In principle, if someone were to bring ferromagnetic materials close to the bore of the magnet, the materials would be pulled into the magnet and could injure a person in the magnet. This possibility is avoided by having the magnet room closed by a strong shielded door when the participant is in the magnet; additionally, the access hallway to the magnet is closed and under key controlled access.

Behavioral training requires subjects to press a button or touch a screen in response to cognitive tests on a computer. No physical risks are known. Behavioral testing requires paper and pencil tests, interview questions, or computerized questions. No physical risks are known.

DNA collection can be accomplished through spitting in a cup, swabbing a check (or in unusual cases) collection of a small amount of blood. We do not anticipate having to collect any blood as the spit collection and swabbing collection have proved very effective in previous studies. Participants have the right to refuse this aspect of the study at any time. No substantial risks are known.

Psychological risks involved in these studies are minimal. There is a slight possibility that someone who was claustrophobic but did not know it might participate in an fMRI study. This is unlikely because we ask about claustrophobia in screening potential participants. If we found that a participant was uncomfortable in the scanner, they would immediately be taken out of the scanner. In addition, since each participant's structural scan is examined by a physician, there is a slight risk that the physician could find a brain abnormality, an "incidental finding", that may or may not have any functional significance. When this is communicated to the participant, the finding may disturb him or her. However, this possibility is clearly outlined in the consent form and a participant can decline to participate in the study if such knowledge would be disturbing. Psychological risks associated with behavioral tasks are minimal. Participants may feel anxiety related to their performance on the tasks. Participants will be assured that the tasks are created to be difficult for them, so they should not expect to perform perfectly. If anxiety persists, participants can stop and withdraw from the study.

Some participants may experience fatigue while participating in the testing or training program. We provide scheduled breaks and refreshments in order to prevent fatigue. Participants may request as many breaks as they would like.

b. Estimate the frequency, severity, and reversibility of each risk listed.
Physical: Risks due to ferromagnetic materials being pulled into the magnet would be potentially serious and potentially not reversible. However, such risks are highly unlikely for the reasons detailed above (18a). Other physical risks are reversible and minor.

Psychological: The risk of experiencing claustrophobia in the fMRI scanner is possible, but unlikely given the screening questionnaires. The participant can stop the scan at anytime. Any possible effects of claustrophobia are reversible. The psychological risk from finding an abnormality in the brain is unlikely. Such a finding may be benign or functionally meaningless. However, the participant will probably want to follow up on the finding with a visit to a physician.

c. Is this a therapeutic study or intervention? ☐Yes ☒No
  If Yes, complete the following items:
  i. Describe the standard of care in the setting where the research will be conducted:_____
  ii. Describe any other alternative treatments or interventions:_____
  iii. Describe any withholding of, delay in, or washout period for standard of care or alternative treatment that participants may be currently using:_____

d. Do you foresee that participants might need additional medical or psychological resources as a result of the research procedures/interventions? ☐Yes ☒No
  If Yes, describe the provisions that have been made to make these resources available.

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e. Do the benefits or knowledge to be gained outweigh the risks to participants?

⊠Yes ☐No

If No, provide justification for performing the research: _____

19. Precautions/Minimization of Risks

a. Describe precautions that will be taken to avoid risks and the means for monitoring to detect risks.

The 3T magnet in the Civitan Center is similar to a clinical magnet equipped with all the standard safety features to avoid accidental patient injury. The screening questions/protocol will ensure that those for whom the MRI procedure would be unsafe are excluded from the study. Participants will be constantly monitored and can stop the study at any time.

The training regimen described has been used in hundreds of older adults. We do not anticipate that this computer game could have adverse effects on participants. However, if any participant reports adverse effects, the training (or testing) will be ceased for that participant. If 3 or more participants report adverse effects, the training will be stopped immediately for all participants. Additionally, Dr. Lawrence Ver Hoef, a UAB Assistant Professor of Neurology, is a neurologist who has agreed to read the study scans for potential incidental findings that might indicate that a participant is at-risk.

> **If study involves drugs or devices skip Items 19.b. and 19.c., go to Item 20, and complete the Drug or Device Review Sheet, as applicable.**

b. If hazards to an individual participant occur, describe (i) the criteria that will be used to decide whether that participant should be removed from the study; (ii) the procedure for removing such participants when necessary to protect their rights and welfare; and (iii) any special procedures, precautions, or follow-up that will be used to ensure the safety of other currently enrolled participants.

A participant will be able to withdraw from the study at anytime once requested. If for any reason an unforeseen hazard arises with an individual in the magnet, the imaging session will be terminated. If such an event occurs with 3 participants, the entire study will be terminated.

c. If hazards occur that might make the risks of participation outweigh the benefits for all participants, describe (i) the criteria that will be used to stop or end the entire study and (ii) any special procedures, precautions, or follow-up that will be used to ensure the safety of currently enrolled participants.

The entire study will be terminated if an adverse event occurs with 3 participants.

20. Informed Consent

a. Do you plan to obtain informed consent for this protocol? ⊠**Yes** ☐**No**
If Yes, complete the items below.
If No, complete and include the Waiver of Informed Consent or Waiver of Authorization and Informed Consent, as applicable.

b. Do you plan to document informed consent for this protocol? ⊠**Yes** ☐**No**
If Yes, complete the items below.
If No, complete the items below **and** include the Waiver of Informed Consent Documentation.

c. How will consent be obtained? Prior to the telephone screening the participants will be given a brief oral informed consent agreeing to answer a few questions over the phone (please see telephone script). If the participant has passed this telephone screening and would like to participate in the

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study, he/she will be scheduled for further in-person screening/baseline assessments and sent an informed consent. The potential participant will have at least two weeks between the letter being sent and the in-person screening/baseline appointment. The participant will then be given a new copy of the same informed consent at his/her screening/baseline appointment. Participants will meet with one of the study staff who is trained on appropriate policies and procedures and who has gone through the UAB IRB training certification. This staff will be able to review the informed consent with the participant and address any questions/clarifications.

d. Who will conduct the consent interview? **IRB-trained study personnel listed in section 2c other than Dr. Karlene Ball (who will not be involved with the informed consent process, data collection, or data analysis).**

e. Who are the persons who will provide consent or permission? **Participants**

f. What steps will be taken to minimize the possibility of coercion or undue influence? **Participants will have ample time to review the informed consent prior to their first in-person screening/baseline appointment. Additionally, participants can address any questions or concerns regarding the study to IRB-trained staff. Participants will be informed that there is no penalty should they choose to discontinue the study, and that they are free to withdraw at anytime during the study. No individual who is a student or employee of study personnel will be allowed to participant.**

g. What language will the prospective participant or the legally authorized representative understand? **English**

h. What language will be used to obtain consent? **English**

i. If any potential participants will be, or will have been, in a stressful, painful, or drugged condition before or during the consent process, describe the precautions proposed to overcome the effect of the condition on the consent process. If not, enter "no such effect."
No such effect

j. If any project-specific instruments will be used in the consenting process, such as flip charts or videos, describe the instrument(s) here, and provide a copy of each. If not, enter "not used."
Not used

k. How long will participants have between the time they are told about the study and the time they must decide whether to enroll? If not 24 hours or more, describe the proposed time interval and why the 24-hour minimum is neither feasible nor practical. **24 hours or more**

21. Procedures to Protect Privacy
Describe the provisions included in the research to protect the privacy interests of participants (e.g., others will not overhear your conversation with potential participants, individuals will not be publicly identified or embarrassed).
Collection of testing data (via phone or in-person) will always be conducted in a closed and private room. All brain imaging and behavioral data will be identified solely by a study code number. No personal identification information will be used in publications or grant applications. Research data will only be accessible to key personnel involved in the study.

22. Procedures to Maintain Confidentiality

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a. Describe the manner and method for storing research data and maintaining confidentiality. If data will be stored electronically anywhere other than a server maintained centrally by UAB, identify the departmental and all computer systems used to store protocol-related data, and describe how access to that data will be limited to those with a need to know.
Research data from screening that contains participants' names will be kept in a locked filing cabinet within a secured and locked testing room in the Center for Research on Applied Gerontology. Any electronic data will be kept on a secured password protected and encrypted computer. All demographic, testing, and training data will be de-identified and only collated to a study ID. No identifying data (name, address, phone numbers, birthdates) will be kept with the other behavioral or fMRI data.

b. Will any information derived from this study be given to any person, including the subject, or any group, including coordinating centers and sponsors?   ☒Yes ☐No
If Yes, complete i-iii.
  i. To whom will the information be given? **Participants**
  ii. What is the nature of the information? **Incidental findings from MRI scans and/or incidental findings from any behavioral testing (e.g., vision)**
  iii. How will the information be identified, coded, etc.? **Identifying information for behavioral and MRI scans and incidental findings will be coded to maintain participant confidentiality. Only key study staff will have access to identifying information associated with the code and will be responsible for providing incidental findings to the participants (so that they may take such information to their primary care physicians).**

23. Additional Information
In the space below, provide any additional information that you believe may help the IRB review the proposed research, or enter "None."
Relevant attached documents:
- Introduction letter to be sent to potential participants from the CRAG Recruitment Database (included in original submission- not included in resubmission)
- Flyer to be used for Recruitment purposes (if needed) (included in original submission- not included in resubmission)
- Telephone Script and Measures for Telephone Screening 1 (new version included in resubmission)
- Informed Consent (new version included in resubmission)
- Behavioral In-person Screening 2 measures 1 (new version included in resubmission)
- Behavioral In-person Baseline/Posttest measures 1 (new versions included in resubmission)

- Metal screening form to be completed for MRI visits (included in original submission- not included in resubmission)
- Training logs and examples of training items (included in original submission- not included in resubmission)
- Funding Application: Copy of grant application and letter of acceptance (included in original submission- not included in resubmission)