WHITE MATTER CHANGES ASSOCIATED WITH COMPUTERIZED COGNITIVE TRAINING IN HEALTHY AGING

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As our population grows ever older, the physical and mental declines associated with age contribute to a lower quality of life and present an escalating burden to our health care system. Academic researchers and private companies are both striving to identify the cause of age-related declines and develop interventions to alleviate them. Several important cognitive abilities, such as processing speed, memory, and executive function, are particularly vulnerable to the effects of age; as is the integrity of white matter in tracts like the genu, splenium, cingulum, fornix, superior longitudinal fasciculus, and uncinate fasciculus that support these higher order cognitive functions. The current study analyzed data from a randomized controlled clinical trial that measured cognition and white matter DTI in older adults before and after either 50 hours of laboratory-based online brain training using Posit Science's *BrainHQ* application, or 50 hours of playing casual online video games (the active control condition). Deterministic white matter tractography was used to measure FA in the six tracts mentioned above. We found only marginal evidence that BrainHQ training increased FA in the left cingulum. We did observe improvements

to processing speed and executive function for the BrainHQ group above and beyond the active control condition. We also found that both groups improved in memory. In addition, we observed correlations between baseline FA in the genu and cingulum and processing speed, and between baseline FA in the fornix and memory. These baseline correlations do not survive correction for multiple comparisons. However, when we examine the relationship between changes in FA in the aforementioned regions and changes to associated cognition, we find a significant relationship between change in FA in the fornix and change in memory performance for the BrainHQ group.

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CHAPTER 1

INTRODUCTION, BACKGROUND, AND LITERATURE REVIEW

1.1 Aging and Cognition

As we age, we display a decline in multiple areas of cognitive functioning, including processing speed (Schaie, 1996), episodic memory (Nilsson, 2003; Salthouse, 2003), inhibition (Bélanger, Belleville, & Gauthier, 2010; Hasher, Stoltzfus, Zacks, & Rypma, 1991), working memory updating (Bopp & Verhaeghen, 2018) and capacity (Bopp & Verhaeghen, 2005), spatial orientation (Schaie, 1996; Sliwinski & Hall, 1998), reasoning (Schaie, 1996), and task-switching (Verhaeghen, Steitz, Sliwinski, & Cerella, 2003). Some of these age-sensitive abilities are considered to be sub-processes of executive function, which regulates the operation of other cognitive abilities (Banich, 2009; Friedman & Miyake, 2017), and is served primarily by frontoparietal brain regions (Reineberg, Gustavson, Benca, Banich, & Friedman, 2018; Wager, Jonides, & Reading, 2004; Wager & Smith, 2003). Executive functions include updating: the constant maintenance, monitoring, and manipulation of multiple information units in working memory, task switching: the flexible shifting between different tasks or mental sets, and inhibition: the top-down rejection of certain information in favor of other more task-relevant information (Miyake & Friedman, 2012; Miyake et al., 2000). Fluid abilities, such as the executive functions described above, are most vulnerable to age-related decline (Jurado & Rosselli, 2007); whereas crystallized abilities, like vocabulary and other semantic knowledge, are relatively preserved throughout the lifespan (Park et al., 2002; Verhaeghen, 2003).

1.2 Aging and White Matter Integrity

Aging is also associated with a deterioration of both size and integrity of brain structures (Raz et al., 2005; Scahill et al., 2003). Both gray and white matter volume decrease with age (Park & Reuter-Lorenz, 2009). White matter integrity also decreases, as demonstrated by a decrease in fractional anisotropy (FA; Abe et al., 2008; Bennett, Madden, Vaidya, Howard, & Howard, 2010; Head et al., 2004; Madden et al., 2004; O'Sullivan et al., 2001; Pfefferbaum & Sullivan, 2003; Pfefferbaum et al., 2000; Salat et al., 2005; Sullivan & Pfefferbaum, 2006) and an increase in mean diffusivity (MD; Abe et al., 2008; Head et al., 2004; O'Sullivan et al., 2001; Pfefferbaum & Sullivan, 2003). White matter is made up of the axons of the neurons in our brain. FA and MD are diffusion metrics acquired through diffusion tensor imaging (DTI), an MRI technique that measures water diffusion. Isotropy is defined as uniformity in all directions in a 3-dimensional space, and occurs when water diffusion is unrestricted in all directions, as in the cerebrospinal fluid (CSF) for example. Water molecules diffuse differently depending on the brain tissue type, structure, architecture, and integrity. DTI works on the above-mentioned principles of water diffusion, and measures movement of water along axons. Water diffusion is however restricted by the structure of the neuronal axons that make up white matter, and tends to be anisotropic, flowing in one direction along the axon of an intact neuron (Soares, Marques, Alves, & Sousa, 2013). DTI measures the anisotropic movement of water in these neuronal axons. High FA is indicative of white matter structural integrity, because the directionality of axon bundles in white matter tracts allows for faster diffusion along the fibers, rather than across them. MD, on the other hand, is high in CSF where water diffusion is unrestricted and isotropic, but low in brain tissue (i.e., white matter; Soares et al., 2013; Vilanova, Zhang, Kindlmann, &

Laidlaw, 2006). High MD is therefore indicative of poor white matter integrity (Villanova et al., 2006).

As with declines in cognition, age-related declines to brain structure do not appear to affect all brain regions equally. Raz et al. (1997) and Pfefferbaum et al. (1998) found that older adults exhibited the greatest brain volume declines in prefrontal gray matter. DeCarli et al. (2005) showed the reduction in brain volume in older adults to be greatest in the frontal lobe, less in the temporal lobe, and least in the occipital and parietal lobes. This anterior-posterior gradient exists for age-related decline in white matter FA as well. O'Sullivan et al. (2001) found that the difference between white matter FA in older and younger adults was most significant in anterior tracts, less significant in middle regions of the brain, and non-significant in posterior tracts. Other studies also find evidence for an anterior-poster gradient in the decline of white matter FA (Head et al., 2004; Pfefferbaum & Sullivan, 2003; Salat et al., 2005), suggesting that the frontal lobe suffers most from aging.

1.3 Training Related Changes to Cognition

Many studies have begun exploring interventions to slow, or even reverse, the deleterious effects on cognition that are associated with aging (Stine-Morrow & Basak, 2011). Computerized cognitive training interventions have been shown to improve nonverbal memory, verbal memory, working memory, executive function, processing speed, and visuospatial skills in older adults (Lampit, Hallock, & Valenzuela, 2014). Video games have been studied extensively as one promising candidate for cognitive training because they are fun to play and have also been shown to tap onto a variety of cognitive processes (Baniqued et al., 2013; Toril, Reales, & Ballesteros, 2014).

There is also a recent surge of interest in training programs that are specifically designed to improve cognitive health. Companies like Lumosity, Posit Science, and even Nintendo have marketed such programs, which are often designed to be game-like themselves. Many studies have examined the effectiveness of different kinds of "brain training". Some studies have found that training improves the specific skill being trained, this is known as near transfer. Edwards and colleagues (2002), for example, used speed of processing training in older adults and found that it improved their Useful Field of View (UFOV) and timed instrumental activities of daily living (IADL), but did not improve performance in other cognitive domains. Other studies claim to have found far transfer, a much more desirable phenomenon by which training skills related to one cognitive domain improves performance on tasks related to a separate cognitive domain or domains.

1.3.1 Video game training

There are many different kinds of video games, and different video game genres require the utilization of different cognitive processes (Baniqued et al., 2013). Action video games in particular have been studied emphatically. Players of action video games have been shown to outperform non-gamers on a range of visuospatial tasks (Chisholm, Hickey, Theeuwes, & Kingstone, 2010; Clark, Fleck, & Mitroff, 2011; Green & Bavelier, 2003; West, Stevens, Pun, & Pratt, 2008), while non-gamers trained to play action games have shown to improve on visuospatial tasks (Green & Bavelier, 2003; Green & Bavelier, 2006a; Green & Bavelier, 2006b; Green & Bavelier, 2007; Green, Pouget, & Bavelier, 2010; Feng, Spence, & Pratt, 2007; Li, Polat, Makous, & Bavelier, 2009; Li, Polat, Scalzo, & Bavelier, 2010). The positive findings related to action games are controversial however, as studies have also failed to find effects of

training (Boot, Blakely, & Simons, 2011; Boot, Kramer, Simons, Fabiani, & Gratton, 2008) and others suffer from methodological inadequacies (Simons et al., 2016).

Strategy games have been less studied so far but may hold promise for older adults due to the complex age-sensitive cognitive processes on which they rely (Baniqued et al., 2013). Strategy games have been linked with better problem-solving skills and higher grades in adolescent adults (Adachi, & Willoughby, 2013). Younger adults who trained for 40 hr on *Starcraft*, a real-time strategy (RTS) game, exhibited a performance component that correlated with cognitive flexibility, which is fundamental to executive function (Glass, Maddox, & Love, 2013). RTS gamers have also shown faster reaction times than action gamers or non-gamers during task switching (Dobrowolski, Hanusz, Sobczyk, Skorko, & Wiatrow, 2015). Older adults who trained for 23.5 hr using another RTS game called *Rise of Nations* improved their performance on task switching, working memory, reasoning, and visual short-term memory (Basak, Boot, Voss, & Kramer, 2008), compared to a control group. In addition, gray matter volume in the prefrontal cortex, as well as in other areas underlying higher order executive functions, predicted the rate at which older adults learn RTS games (Basak, Voss, Erickson, Boot, & Kramer, 2011).

1.3.2 Laboratory-based "brain training" programs

There have been many studies conducted looking at the effects of laboratory-based cognitive training, far too many to include all of them here so I will attempt to review a selection of the most relevant and impactful. One of the earliest and largest studies to research cognitive training was the ACTIVE trial, which randomized 2832 older adult participants into either a no-contact control group, or one of three groups that underwent 10 sessions (60-75 minutes each) of either memory, reasoning, or speed of processing training (Jobe et al., 2001). The ACTIVE study found

near transfer of training for each group in its respective cognitive domain (the memory group showed improved performance on tasks relating to memory, etc.), but did not find any transfer to cognitive skills outside of the trained domain (the memory group did not show any improvement on tasks measuring reasoning or processing speed, and vice versa), nor did it find that any group improved on measures relating to everyday cognition (Ball et al., 2002). At a 5-year follow-up the authors found that participants in the three treatment conditions not only retained the benefits of training, but also reported significantly less difficulty in performing Instrumental Activities of Daily Living (IADL; Teresi, 1997) compared to participants in the no contact control condition (Willis et al., 2006). This decreased difficulty in IADL, along with the training effects for reasoning and speed (but not memory), was also shown at a 10-year follow-up (Rebok et al., 2014).

Bell, Bryson, Greig, Corcoran, and Wexler (2001) assigned 65 patients with schizophrenia or schizoaffective disorder, which have been associated with neurocognitive dysfunction in domains such as memory and executive function (Green, Kern, Braff, & Mintz, 2000), to complete either work therapy or work therapy combined with neurocognitive enhancement therapy. The work therapy group was employed and counseled at a medical center for up to 15 hours a week, while the neurocognitive enhancement therapy group also completed cognitive exercises for up to an additional 5 hours a week (20 total hours) for 26 weeks. The cognitive exercises were adapted from the Psychological Software Services CogRehab software (Bracy, 1995), and included two tasks training visual attention, two tasks training verbal memory, and a fifth task was added that trained executive function. Participants who participated in the neurocognitive enhancement therapy showed increased performance at 5 months after baseline

cognitive testing on two factors related to executive function and affect recognition (Factor 1 consisted of measures from the Wisconsin Card Sorting Test; while Factor 2 consisted of measures from the Bell Lysaker Emotion Recognition Task, Forward Span, Backward Span, Letter Number Sequencing, Digit Symbol, Digit Symbol Substitution, and Trail Making B) compared to participants who only participated in the work therapy (Bell et al., 2001). It should be noted that a follow-up paper published by the same group performed similar analyses on a larger sample size (n=131) and only reported significant improvements in Backward Span, without mentioning the other assessments (Bell, Bryson, & Wexler, 2003). It was also found that participants who completed the neurocognitive enhancement therapy maintained higher rates of employment at a 12-month follow-up than those who only completed the work therapy (Bell, Zito, Greig, and Wexler (2008).

Preiss, Shatil, Cermakova, Cimermannova, and Flesher (2013) randomized 31 patients with depression, a disorder with associated deficits in attention, executive function, and memory (Marvel and Paradiso, 2004), to either a cognitive training intervention or a standard care control group. The cognitive training group used CogniFit, an online program consisting of 21 different tasks that utilize various processes across multiple cognitive domains (CogniFit, 2008), three times a week (20-30 minute sessions) for 8 weeks. Patients who trained using CogniFit showed decreased depressive symptoms (as measured by the Beck Depression Inventory; BDI; Beck, Steer, & Brown, 1996) and improved global executive control (averaged across tasks measuring working memory, shifting, inhibition, visuomotor vigilance, divided attention, and auditory memory span; Preiss et al., 2013).

Miller and colleagues (2013) randomized 74 older adults into either a cognitive training group or a waitlist control group. The cognitive training group trained on Brain Fitness, a commercially available online program that includes over 400 exercises across six cognitive domains (short-term and long-term memory, language, spatial processing, reasoning, and calculation; Brain Fitness, 2018), for forty 20-25-minute sessions over an 8-week period. Older adults who underwent cognitive training using Brain Fitness showed significantly better delayed memory than the waitlist controls, but not better intermediate memory or language (Miller et al., 2013).

The Iowa Healthy and Active Minds Study (IHAMS; Wolinsky, Vander Weg, Howren, Jones, & Dotson, 2013; Wolinsky et al., 2011) is another large-scale clinical trial examining cognitive training in 681 older adults (ages 50 and above), and the first study mentioned so far to include an active control condition. Participants in the experimental conditions of this study trained for 10 hours using a visual processing speed task, called *Road Tour*, that was developed by Ball and Roenker (Ball, Beard, Roenker, Miller, & Griggs, 1988; Ball, Edwards, & Ross, 2007; Roenker, Cissell, Ball, Wadley, & Edwards, 2003), was also used in the ACTIVE trial (Jobe et al., 2001), and was eventually acquired by the Posit Science Corporation (Posit Science Corporation, 2010). Participants in the active control condition completed 10 hours of crossword puzzles. Immediately after training, participants in the experimental conditions outperformed those in the control condition on measures of UFOV, but not on any of the secondary outcome measures of attention and executive control (Wolinsky et al., 2011). At a one-year follow-up however, participants in the experimental conditions outperformed participants in the control

condition not only on measures of UFOV, but also on Trails A & B and a Stroop Word task (Wolinsky et al., 2013).

The Improvement in Memory with Plasticity-based Adaptive Cognitive Training (IMPACT; Smith et al., 2009; Zelinksi et al., 2011) also trained older adults using cognitive training developed by the Posit Science Corporation. This large-scale study randomized 487 older adults to complete either 40 hours of cognitive training consisting of six computer-based auditory exercises (experimental training condition) or 40 hours of educational training that involved watching videos on art, history, and literature (active control condition). The training group showed increased improvements on a variety of tasks related to memory and attention compared to the active control group (Smith et al., 2009). These improvements persisted at a three-month follow-up (Zelinski et al., 2011).

A multitude of other cognitive training studies have reported similar results to those described above. A recent meta-analysis analyzed the data from 215 training studies and found an overall net gain on cognitive outcomes for older adults ($g = .28$, $p < .01$; Basak, Qin, & O'Connell, 2020). This meta-analysis looked at single and multi-component training strategies separately and found that both significantly improved overall cognition. The study also differentiated between near transfer and far transfer and found that, although the effect sizes for overall training gains were larger for near transfer, they were still significant for far transfer. When looking at specific cognitive training strategies, the results showed that near-transfer gains from training were significant across all training types (reasoning, processing speed, episodic memory, and executive function), but far transfer was only significant for executive function and memory training (Basak et al., 2020).

The evidence suggests that computerized cognitive training programs can improve various cognitive abilities, including important processes like memory and executive function that decline with age. It is possible that exercising these vital cognitive skills by playing video games or engaging in laboratory designed brain training programs may ameliorate some of the adverse effects of age. It is also possible that the cognitive improvements exhibited after training are driven by changes in brain structure, particularly the integrity of the white matter tracts that are believed to underly these age-sensitive cognitive domains.

1.4 Training Related Changes to White Matter Integrity

A theoretical framework for cognitive plasticity has been proposed by Lövdén, Bäckman,Lindenberger, Schaefer, & Schmiedek (2010). This framework suggests that the term *plasticity* should be distinguished from the term *flexibility*. Flexibility refers to the total amount of cognitive resources an individual may have at his/her disposal. An individual with high flexibility may therefore be able to hold 7 items in their short-term memory store, while an individual with lower flexibility may only be able to hold 4. Plasticity on the other hand is the result of a reactive change in the amount of cognitive resources available. These changes occur due to a prolonged mismatch between cognitive supply and cognitive demand. Two primary examples of this type of mismatch would be: 1) brain injury, where an individual now suffers from decreased cognitive supply; and 2) cognitive training, where increased cognitive demand is now placed upon an individual. The framework goes on to state that any reactive change in functional supply can only be considered plastic when it is associated with an underlying structural change (i.e. when neural activity in certain pathways in the brain changes as a result of changes in the structural integrity of those pathways). To summarize, an individual may undergo

cognitive training, where he/she is exposed to greater cognitive demands for an extended period of time. This prolonged mismatch between cognitive supply and demand may result in increased flexibility (i.e., an increase in the total amount, or supply, of cognitive resources available), which may in turn result in increased functionality (i.e., improved performance on tasks requiring this cognitive resource). For this change in function to be considered plastic, it must have resulted from a change in structure. Therefore, the improved cognitive performance experienced by the individual would be the result of the improved integrity of the underlying brain structures that support the cognitive activity in question.

Behavioral interventions, including cognitive training, have indeed shown to improve the integrity of structures in the brain, such as white matter. Training-related white matter changes have been demonstrated in participants of varying ages, including children. Keller and Just (2009) showed that 100 hours of remedial reading instruction increased FA in the left anterior centrum semiovale in children (8-12 years old) with poor reading ability, a population that has shown to have reduced FA in left hemisphere cortical regions. Hu and colleagues (2011) found that three years of training in abacus-based mental calculation (AMC) increased children's (age = 10.48 ± 0.58 years) FA in the left occipitotemporal junction (an area related to short-term visual memory and the speed of transfer of visual information to anterior temporal regions; Catani, Jones, Donato, & Ffytche, 2003; Tusa & Ungerleider, 1985), the right premotor projection to the midanterior corpus callosum (a motor area important for the maintenance of dynamic visuospatial imagery and the planning of associated movements, which would presumably facilitate the manipulation of an abacus; Lamm, Windischberger, Leodolter, Moser, & Bauer, 2001; Passingham, 1989), and the splenium and anterior midbody at the midsagittal

corpus callosum (the corpus callosum is a large fiber tract responsible for communication between hemispheres that the authors posit would be critical for AMC, as they suggest that participants may generate spatial images in the left parietal cortex while manipulating and comparing those images using the right parietal cortex; Hu et al., 2011). Although it may seem intuitive, the evidence above indicates that training in skill acquisition at a young age can strengthen the white matter connections in the brain that facilitate the performance of the trained skill.

Brain plasticity is not limited to childhood though. Multiple studies have found training related improvements in younger adults (18-33 yr). Fifteen hours of juggling training increased FA in an area underlying the intraparietal sulcus, which is responsible for visuo-spatial cognition and working memory capacity (Scholz, Klein, Behrens, & Johansen-Berg, 2009). Eleven hours of meditation training increased FA in the genu and body of the corpus callosum, the corona radiata, and the superior longitudinal fasciculus (Tang et al., 2010). Two months of working memory training increased FA in the anterior body of the corpus callosum and areas surrounding the intraparietal sulcus, suggesting increased inter-hemispheric connectivity, which in turn is related to greater working memory capacity (Takeuchi et al., 2010). Twenty hours of neurofeedback increased FA in the corona radiata, superior longitudinal fasciculus, inferior longitudinal fasciculus, internal capsule, and cerebellum (Ghaziri et al., 2013). Finally, 100 hours of reasoning training decreased RD in the genu of the corpus callosum and the anterior corona radiata, and decreased MD in the left frontal and right parietal cortices, all areas implicated in higher order cognitive processes like reasoning and executive function (Mackey, Whitaker, & Bunge, 2012). Overall these studies in younger adults once again suggest that behavioral

interventions can increase inter-hemispheric connectivity and enhance the neural connections (for example between frontal and parietal brain regions; e.g., the superior longitudinal fasciculus) responsible for complex cognitive operations. The results of these studies should be interpreted cautiously however. Only two of the five studies mentioned here compared changes in their training groups to changes in an active control group (Ghaziri et al., 2013; Tang et al., 2010). Two others used a passive control group (Mackey at al., 2012; Scholz et al., 2009), and one used no control group at all (Takeuchi et al., 2010).

Far fewer studies have looked at training -related changes to white matter integrity in older adults (51-80 yr). One study showed that approximately 17 hours of memory training increased FA in a left frontal cluster containing portions of the anterior thalamic radiation, inferior fronto-occipito fasciculus, uncinate fasciculus, and superior longitudinal fasciculus (Engvig et al., 2012). Another study showed that 101 hours of training in various cognitive tasks increased FA and decreased MD in the genu of the corpus callosum (Lövdén et al., 2010). Antonenko and colleagues (2016) found that 3 days of object-location training reduced MD in the fornix. A fourth study showed an increase in RD (increased RD has been argued to indicate a decrease in myelination; see section below) in a left posterior parietal cluster in control participants compared to those who completed 24 hours of multidomain cognitive training (Cao et al., 2016). It should be noted however that this study did not find any significant changes in FA, MD, or AD after correcting for multiple comparisons. It should also be noted that in all four of these studies, changes in the training group were compared to changes in a passive control group or no control group at all. The lack of an active control group is a methodological shortcoming found in many

training studies and has been pointed out as a significant problem that needs to be overcome in order to truly understand the efficacy of such cognitive interventions (Simons et al., 2016).

1.5 Mechanism of White Matter Change

As we have discussed above, aging is associated with cognitive decline, particularly in higher order cognitive processes such as working memory and reasoning (e.g., Salthouse, 2010). This age-related cognitive decline is associated with decreased white matter volume and integrity in brain areas that support these functions, like the prefrontal cortex (Caserta et al., 2009). White matter volume is decreased in older adults by as much as 28% (Pakkenberg & Gundersen, 1997). As we age we also experience white matter atrophy (Lemaître et al., 2005), white matter tract disruption (Shenkin et al., 2005), damage to the blood vessels that supply our white matter (Pantoni, 2002), increased white matter inflammation (Sloane, Hollander, Moss, Rosene, & Abraham, 1999), and loss of myelination to the axons that constitute the majority of our white matter (Marner, Nyengaard, Tang, & Pakkenberg, 2003).

White matter is supplied by long and delicate arterioles, which makes it susceptible to hypoperfusion, a reduction in blood flow (Moody, Bell, & Challa, 1990). These arterioles can become twisted and coiled as we age, increasing the risk of hypoperfusion (Brown, Moody, Challa, Thore, & Anstrom, 2002; Moody, Santamore, & Bell, 1991). Collagen deposits form in the walls of the veins and venules that supply deep white matter tissue as we age, which can further reduce blood flow (Brown et al., 2002; Moody, Brown, Challa, & Anderson, 1995). The thickened venous walls resulting from collagen deposition also slow the removal of toxins, resulting in elevated toxicity and consequent damage to white matter tissue (Rennels, Blaumanis, & Grady, 1990). Age-related deterioration in vascular density (Klein & Michel, 1977) and

autoregulation function in the cerebral vascular system (van Beek, Claassen, Rikkert, & Jansen, 2008) can also lead to hypoperfusion, which can result in ischemia and subsequent damage to the neurons and glial cells that make up our white matter.

The neuronal axons that compose our white matter are covered in fatty, insulating myelin sheathes that greatly increase the speed at which electricity propagates down the axon (Baumann & Pham-Dinh, 2001). The speed of conduction is further increased by small unmyelinated nodes of Ranvier that segment the myelin sheath (Filley & Kleinschmidt-DeMasters, 2001). Increased conduction speed across axons translates to more efficient transfer of communication across neuronal networks and improved cognitive performance (e.g. increased processing speed; Kochunov et al., 2010). Splitting of the myelin sheath, myelin balloon formation, and separation of the myelin sheath from the axon have been observed in aging rats (Sugiyama et al., 2002). These rats displayed a deterioration of the paranode that anchors the myelin sheath, which may be caused by a lack of 21.5-kDa isoform of myelin basic protein or the dysregulation of cyclic nucleotide phosphodiesterase (Sugiyama et al., 2002). The ion channels at the nodes of Ranvier have shown to be reorganized in aging monkeys in such a way that would disrupt conduction (Hinman et al, 2006). In addition, internodal length increases as we age, which would also decrease conduction speed (Mukoyama, 1973). Furthermore, the threshold for axonal conduction increases and the slope of the stimulus-response curve decreases with age (Jankelowitz, McNulty, & Burke, 2007).

So far, we've discussed some possible mechanisms of white matter changes in healthy aging. Age-related pathologies such as stroke and neurodegenerative disorders like Parkinson's and Alzheimer's disease result in a myriad of neuroanatomical abnormalities that can affect the

microstructure of white matter as well. We won't discuss them all in detail here, but see Liu and colleagues (2017) for a review.

The mechanism underlying white matter change in the positive direction is not yet fully understood either. Multiple factors can contribute to changes in FA, such as changes in myelination, axon density, axonal membrane integrity, axon diameter, and intravoxel coherence of fiber orientation (Tang, Lu, Fan, Yang, & Posner, 2012; Taubert, Villringer, & Ragert, 2012; Zatorre, Fields, & Johansen-Berg, 2012). In order to better understand changes in FA, perhaps we should consider changes in radial diffusivity (RD) and axial diffusivity (AD), as these are the two most important indices associated with FA (Bennett et al., 2010; Bosch et al., 2012; Burzynska, 2010; Tang et al., 2012).

AD measures the diffusion of water parallel to axons, and changes in AD have been linked to morphological changes of the axon, such as axonal density or caliber; while RD measures the diffusion of water perpendicular to the axon, and changes in RD have been linked to changes in myelination (Kumar, Macey, Woo, & Harper, 2010; Kumar, Nguyen, Macey, Woo, & Harper, 2012; Song et al., 2002; Tang et al., 2012). There is a positive correlation between AD and axonal morphology, such that decreased AD corresponds with decreased axonal density or caliber; and a negative correlation between RD and myelination, such that increased RD corresponds with decreased myelination (Della Nave et al., 2010; Hasan et al., 2008; Kumar et al., 2008, 2010, 2012; Song et al., 2002; Sun et al., 2006).

Due to concerns about the reliability and interpretation of AD and RD (Wheeler-Kingshott & Cercignani, 2009), it has been suggested only to examine them in areas that have shown a significant change in FA (Tang et al, 2012). Training in reading (Keller & Just, 2009), abacus-

based mental calculation (Hu et al., 2011), and memory (Engvig et al., 2012) resulted in increased FA in their respective samples. A decrease in RD is believed to contribute to the increase in FA in these studies, while AD remained unchanged, suggesting that myelination (rather than axonal density/caliber) is the mechanism driving changes in white matter FA (Tang et al., 2012). It has therefore been theorized that skill learning increases neural firing, which increases myelination and results in decreased RD and increased FA (Keller & Just, 2009, Tang et al., 2012).

CHAPTER 2

WHITE MATTER TRACTS OF INTEREST

The current proposal aims to evaluate changes in six white matter tracts: the genu, the splenium, the cingulum, the superior longitudinal fasciculus (SLF), the fornix, and the uncinate fasciculus. These tracts underlie fluid cognitive abilities that decline with age, and indeed, integrity of these tracts has been shown to deteriorate with age (Hasan et al., 2009; Kennedy & Raz, 2009; Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008; Peters et al., 2014; Sarro et al., 2011; Von Der Heide, Skipper, Klobusicky, & Olson, 2013; Wu et al., 2010; Zahr, Rohlfing, Pfefferbaum, & Sullivan, 2009). Importantly, the genu, uncinate fasciculus, and tracts connecting to the cingulum (corona radiata) have all shown adaptability, and integrity of these tracts has improved as a function of training (Engvig et al., 2012; Ghaziri et al., 2013; Lövdén et al., 2010; Mackey et al., 2012; Takeuchi et al., 2010; Tang et al., 2010). Specific reasons for choosing each of these four tracts are provided below.

The corpus callosum is the largest white matter bundle in the brain, and is one of three major commissures that connect the left and right hemispheres (van der Knaap & van der Ham, 2011). The genu is the anterior portion of the corpus callosum. It contains fibers that connect the frontal lobes, which underlie higher order cognitive skills, such as executive function. Processing speed, working memory, and executive function are correlated with white matter integrity in the genu across the lifespan (Kennedy & Raz, 2009). White matter integrity (as indicated by increased FA and decreased MD) has been shown to decline in the genu as a function of age, but seems to be relatively preserved in the splenium (the posterior bridge of the corpus callosum) as we age (Head et al., 2004; Pfefferbaum & Sullivan, 2003; Qin et al., 2016; Ray et al., 2017; Salat et al.,

2005). The integrity of the genu may therefore be influenced by cognitive training, particularly in older adults who are vulnerable to structural deterioration in this region.

Some studies have found age-related declines in the splenium of the corpus callosum as well however (see Kennedy & Raz, 2009). The splenium is the posterior segment of the corpus callosum containing intra-hemispheric connections between the occipital and parietal cortices, as well as between inferior and medial temporal brain regions (Knyazeva, 2013). Because computerized cognitive training often involves the visual processing of information, it may also be pertinent to examine changes in the splenium, which connects areas of the visual cortex. Penke and colleagues (2010) argue that the splenium plays a vital role in healthy aging, as white matter integrity in this tract was correlated with higher IQ and matrix reasoning skills in older adults.

The cingulum is a major association tract that runs around the corpus callosum in a C-shape from the frontal lobe to the temporal lobe. It projects fibers from the cingulate cortex to the entorhinal cortex and to other parts of the brain. The cingulum is involved with memory (Kraus et al., 2007; Wu et al., 2010), processing speed (Bendlin et al., 2010), and executive function (Kraus et al., 2007; Sarro et al., 2011), and is therefore of interest to an aging population suffering from dysfunction in these cognitive domains. FA in the cingulum has been shown to decrease with age, while MD has shown to increase (Bendlin et al., 2010).

The SLF is a long-range association tract that connects posterior parietal cortical areas to a number of regions in the frontal lobe. The SLF links the dorsolateral-prefrontal cortex with the supramarginal gyrus, a connection that is believed to play an important role in working memory (Karlsgodt et al., 2008; Klingberg, 2006). The SLF is also associated with processing speed,

which significantly predicted FA in this tract (Kerchner et al., 2012). FA in the SLF has also been linked to performance on tasks of executive function and has been shown to decrease with age (Bendlin et al., 2010; Hummer, Wang, Kronenberger, Dunn, & Mathews, 2015).

The fornix is another C-shaped fiber bundle that lies underneath the corpus callosum and outputs from the hippocampus to form a limbic circuit that is known to be vulnerable to age-related memory deficits, such as Alzheimer's disease (Oishi & Lyketsos, 2014). The fornix plays a role in memory and learning (Sarro et al., 2011), as well as working memory and problem solving (Zahr et al., 2009). FA in the fornix has been shown to decrease with age (Zahr et al., 2009), and MD shown to increase (Bendlin et al., 2010). The fornix has been tagged as a potential biomarker for cognitive decline, as lesser white matter volume and greater AD in the fornix significantly predicted a conversion to mild cognitive impairment in older adults who were cognitively normal at baseline (Fletcher et al., 2013). FA in the fornix also fully mediated a relationship between plasma phospholipid polyunsaturated fatty acids and memory in older adults, suggesting that memory in healthy aging is supported through both diet and preserved white matter FA in the fornix specifically (Zamroziewicz, Paul, Zwilling, & Barbey, 2017). Given these findings and others, the fornix is highlighted as a critical region for cognitive training interventions, particularly those targeting memory and aging.

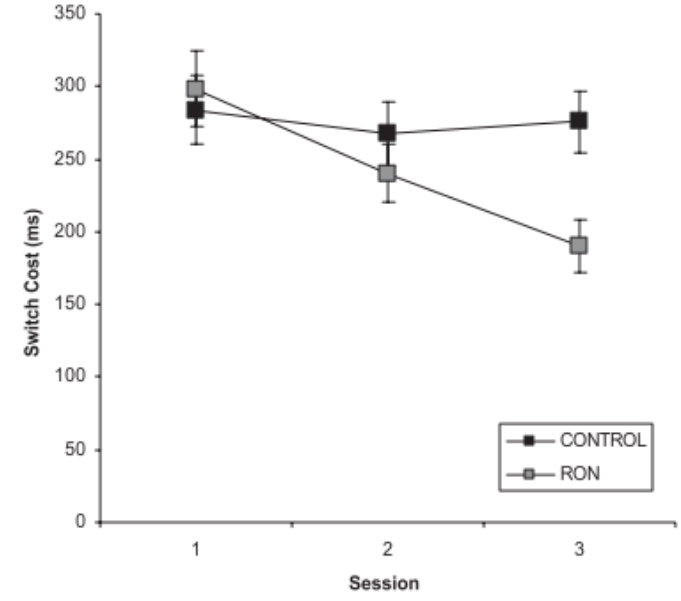
The uncinate fasciculus is another long-range association tract that connects the orbitofrontal cortex to the anterior temporal lobes. The exact role of the uncinate fasciculus is unknown, but it is also believed to play an important role in episodic memory (Von Der Heide et al., 2013). FA in the uncinate fasciculus has been shown to decrease with age (Hasan et al., 2009), while MD has shown to increase (Bendlin et al., 2010). We therefore aim to evaluate changes in multiple

types of white matter tracts: two commissural tracts that connects across hemispheres (the genu and the splenium); two association tracts that connect different areas in the same hemisphere (the SLF and the uncinate fasciculus); and two c-shaped limbic tracts that contain both commissural and association fibers (the cingulum and fornix).

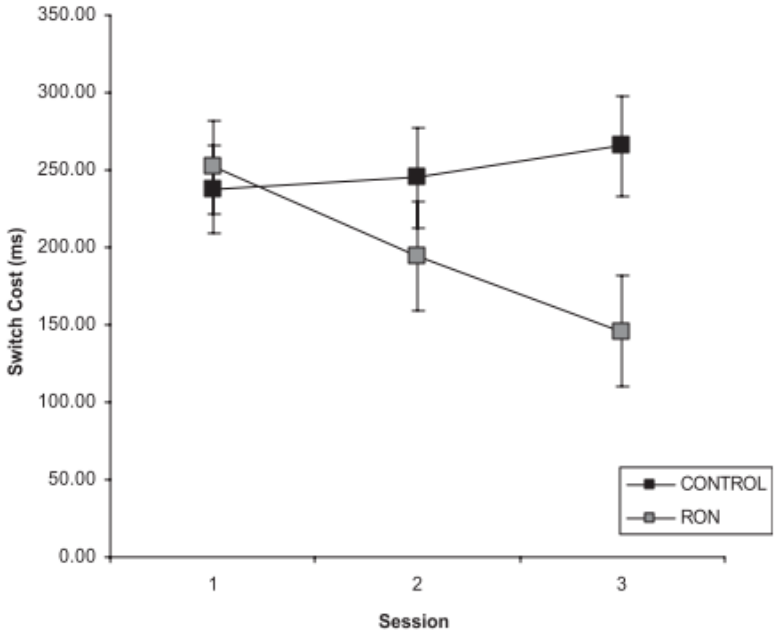
CHAPTER 3

PREVIOUS WORK

Basak and colleagues (2008) trained 19 older adults (5 males, 14 females, M_{age} = 70.05 yr, SD_{age} = 4.94 yr, $M_{education}$ = 15.42 yr, $SD_{education}$ = 3.49 yr) using a real time strategy video game called *Rise of Nations* and compared them to 20 age-matched no-contact controls (5 males, 15 females, M_{age} = 69.10 yr, SD_{age} = 6.06 yr, $M_{education}$ = 16.88 yr, $SD_{education}$ = 3.18 yr). After 23.5 hr of video game training, the experimental group improved more than the controls on task switching cost (Kramer, Hahn, & Gopher, 1999; Pashler, 2000; see Figure 3.1a), *n*-back maintenance and coordination (working memory; Verhaeghen & Basak, 2005; see Figure 3.1b), accuracy on Raven's Advanced Progressive Matrices (reasoning; Raven, 1998; see Figure 3.2), and performance on a task of visual short-term memory (Luck & Vogel, 1997; see Figure 3.3).



(a)



(b)

Figure 3.1. Taken from Basak et al. (2008). Average task switch cost in the task-switching paradigm (a) and focus switch cost in the N-back task (b) as a function of testing session for the two groups. Error bars represent plus and minus 1 standard error. CONTROL = control group; RON = the Rise of Nations group.

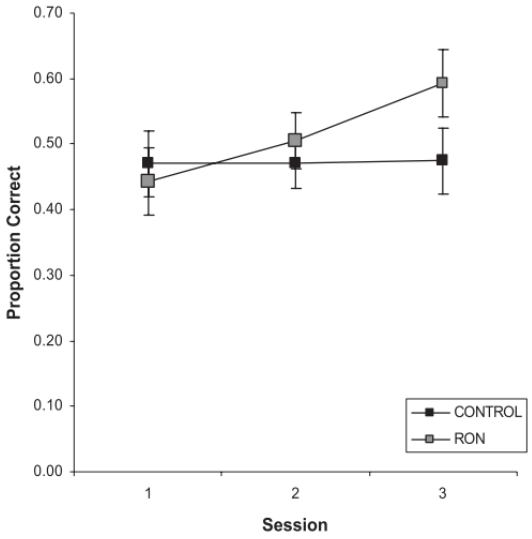


Figure 3.2. Taken from Basak et al. (2008). Accuracy in Raven's Advanced Progressive Matrices (Raven, 1990) subtests for the two groups as a function of testing sessions. Error bars represent plus and minus 1 standard error. CONTROL = control group; RON = the Rise of Nations group.

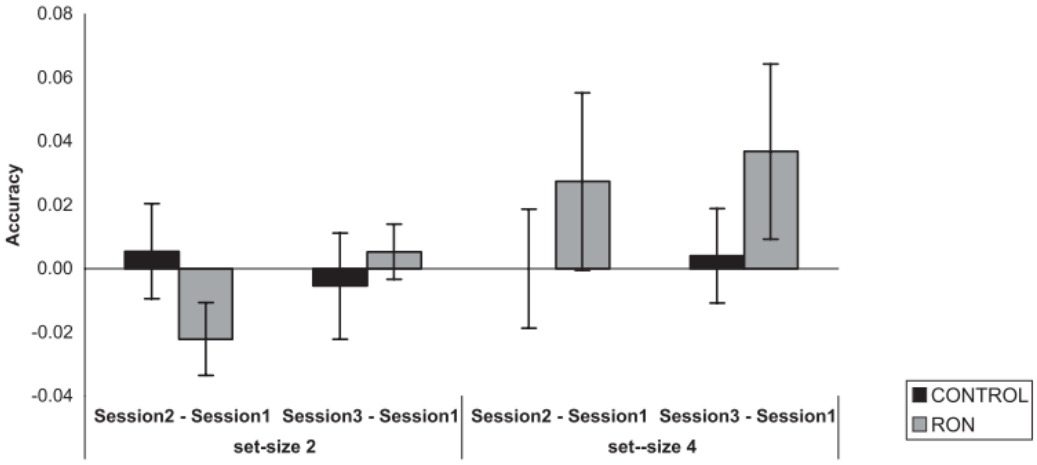


Figure 3.3. Taken from Basak et al. (2008). Improvement in the accuracy detection from Session 1 to Session 2 and Session 1 to Session 3 in the visual short-term memory task for both set sizes (2 and 4) and both groups. Error bars represent plus and minus 1 standard error. CONTROL = control group; RON = the Rise of Nations group.

Data for this dissertation were taken from a large-scale Phase II clinical trial. The results of the corresponding Phase I trial are reported by Lee and colleagues (2020), who analyzed data from 59 older adult participants. Twenty-nine participants (11 males, M_{age} = 70.41 yr, SD_{age} = 3.56 yr, $M_{education}$ = 17.00 yr, $SD_{education}$ = 3.27 yr) were assigned to a Cognitive Training (CT) condition consisting of 17 different computerized exercises, each involving mainly one of four difference cognitive domains: processing speed, attention, memory, and executive control. Thirty participants (12 males, M_{age} = 69.10 yr, SD_{age} = 3.49 yr, $M_{education}$ = 17.45 yr, $SD_{education}$ = 3.09 yr) were assigned to an Active Control (AC) condition that played 13 different casual online computer games. Using mixed-effects linear regression, the authors found significant group by time interactions for overall cognition, $t(57.72) = 2.59$, $p < .05$, processing speed, $t(42.84) = 2.54$, $p < .016$, and working memory, $t(56.59) = 2.38$, $p < .033$, in favor of the CT group.

Ray et al. (2017) collected DTI data from 31 younger adults (18 females; M_{age} = 25.84, SD_{age} = 4.52; $M_{education}$ = 16.85, $SD_{education}$ = 2.08), and 31 older adults (19 females; M_{age} = 65.84, SD_{age} = 6.77; $M_{education}$ = 15.77, $SD_{education}$ = 1.88). I preprocessed the data using FSL (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012; Smith et al., 2004). DTI images were brain extracted using the BET command (Smith, 2002) and corrected for eddy-current and motion artifacts using DTIprep (Liu et al., 2010; Oguz et al., 2014). I fit a diffusion tensor model at each voxel using the DTIFIT (Behrens et al., 2003) tool, projected each subject's FA onto a mean FA skeleton using Tract-Based Spatial Statistics (TBSS; Smith et al., 2006), and extracted regional FA values using the JHU ICBM-DTI-81 white-matter labels atlas (Mori, Wakana, Van Zijl, & Nagae-Poetscher, 2005). After correlating FA in the genu, body, and splenium of the corpus callosum with age, we found a strong negative correlation between age and FA in the genu, $r(59)$

= -.62, $p < .001$, a weaker negative correlation between age and FA in the body, $r(59) = -.52$, $p < .001$, and no correlation between age and FA in the splenium, $r(59) = -.04$, $p = .76$. This provides further evidence of the anterior-posterior gradient of age-related white matter decline and illustrates the potential importance of the genu in association with age-related cognitive decline.

Using the approach described above, we also correlated DTI and cognitive performance with learning on two different casual games, one action game called *Tank Attack 3D* and one strategy game called *Sushi-Go-Round* (miniclip.com). We found that FA in the right fornix/stria terminalis positively correlated with action game learning and FA in the left cingulum/hippocampus positively correlated with strategy game learning (Ray et al., 2017; see Figure 3.4). Both types of game learning correlated with measures of working memory (2-update switch accuracy and backward span) and visual perception/attention (cued-discrimination and subitizing speed); and strategy game learning also correlated with performance on the digit symbol substitution task (which measures perceptual processing speed).

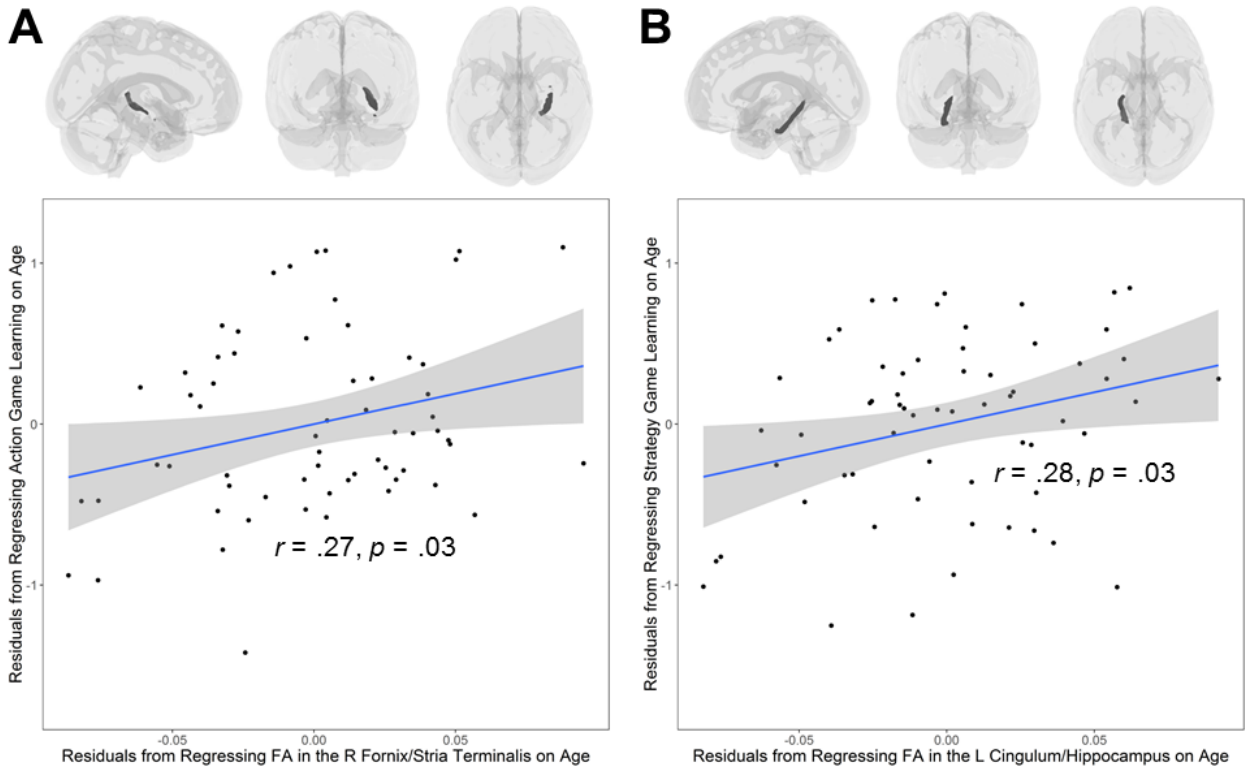


Figure 3.4. Taken from Ray et al. (2017). ROIs from the JHU ICBM-DTI-81 white-matter labels atlas (Mori, Wakana, & Van Zijl, 2005). (A) The right fornix/stria terminalis and a scatterplot showing the partial correlation between FA in this region and action game learning, after controlling for age. (B) The left cingulum/hippocampus and scatterplot showing the partial correlation between FA in this region and strategy game learning, after controlling for age.

CHAPTER 4

THE CURRENT STUDY AND HYPOTHESES

In the current study I analyze data from a randomized controlled clinical trial. The Brain Enhancement Training Towards Elders Resilience (BETTER) to Aging study is a collaborative project involving the University of Texas at Dallas, The University of Iowa, and the Posit Science Corporation. We measure older adults' cognitive performance (processing speed, memory, and executive function) and structural brain data (white matter DTI) both before and after they complete either an experimental computerized cognitive training paradigm (*BrainHQ*; designed by the Posit Science Corporation; San Francisco, California, USA) or an active control training program.

Hypothesis 1

My first hypothesis is that older adults in the BrainHQ group will show improved white matter integrity (increased FA) in one or more of the six tracts of interest (genu, splenium, cingulum, SLF, fornix, and uncinate fasciculus) after completing the laboratory-designed brain training compared to the older adults who participate in the active control training condition.

Hypothesis 2

My second hypothesis is that older adults in the BrainHQ group will demonstrate increased performance in three different cognitive domains – processing speed, memory, and executive function – compared to participants in the active control condition.

Hypothesis 3

My third hypothesis is that any observed gains in white matter integrity in the tracts of interest will correlate with a corresponding gain in cognitive performance. I hypothesize that

improved integrity in the genu, cingulum, and SLF will correlate with improvements in processing speed and executive function; and that improved integrity in the cingulum, fornix, and uncinate fasciculus will correlate with improvements in memory.

CHAPTER 5

METHODS

5.1 Participants

To be eligible to participate in the BETTER Aging Study, participants must have met the following inclusion criteria: 1) they must be at least 65 years of age; 2) they must be fluent English speakers; 3) they must possess adequate sensorimotor capacity to perform the training program, including sufficient visual capacity (able to read from a computer screen at a normal viewing distance), auditory capacity (able to understand normal speech), and motor capacity (able to control a computer keyboard and mouse); and 4) they must be cognitively normal (no signs of mild cognitive impairment or dementia) as indicated by a score of 22 or higher on the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005). Participants were excluded if they met any of the following exclusion criteria: 1) they must not self-report any medical illness, injury, or condition that would predispose them to functional and/or cognitive decline (schizophrenia; bipolar disorder; any cardiovascular conditions including, but not limited to: congenital heart disease, arrhythmia, ischemic heart disease, valvular heart disease, uncontrolled hypertension, thromboembolism, peripheral vascular disease; HIV/AIDS; sickle cell disease; CVA/Stroke; TIAs only if there are residual effects in expressive/receptive language, any sensory loss, motor impairments, or any body weakness; multiple sclerosis; Parkinson's disease; Alzheimer's disease; other dementias; brain injury within the last year; brain injury that required brain surgery or removal of brain tissue; any type of cancer diagnosed within the last 6 months; currently receiving or have received chemotherapy or radiation therapy within the last 6 months; uncontrolled diabetes; uncontrolled hypothyroidism; uncontrolled epilepsy); 2) they must not

require caregiver assistance in dressing or personal hygiene; 3) they must not self-report any severe visual deficits (including visual neglect, partial field cuts, and/o anopias) and/or severe hearing deficit that would prevent use of the computerized treatment program; 4) they must not have participated in any other type of computer-delivered cognitive training within 2 years of consent; 5) they must not self-report claustrophobia or any other contradiction to MRI scanning; 6) they must not be unable to complete a 1-hour MRI scan; 7) they must not be pregnant; 8) they must not have any implanted devices above the waist (e.g., cardiac pacemaker or auto-defibrillators, neural pacemaker, aneurysm clips, cochlear implant, metallic bodies in the eye or central nervous system, any form of wires or metal devices that may concentrate radio frequency fields); and 9) they must not present any active suicidal behaviors or ideations as assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS; Posner et al., 2008). Because the first aim of my dissertation is to examine changes to white matter integrity, I have analyzed data only from participants who have completed both a pre-training and post-training MRI scan; and whose MRI data is of high enough quality to be used in subsequent analyses.

158 older adults were consented and assessed for eligibility. 11 of these individuals were excluded for not meeting the previously stated inclusion criteria, 8 decided not to participate, 2 were lost to follow-up, and 1 was withdrawn by an investigator. Therefore, a total of 136 participants were enrolled in the study – 67 were randomly assigned to complete the BrainHQ computerized cognitive training intervention, and 69 were randomly assigned to participate in the active control condition that played casual computerized games. 11 participants left before completing their first training session (7 in the BrainHQ group and 4 in the active control group), and 3 participants did not complete their post-assessments (2 in the BrainHQ group and 1 in the

active control group). 15 participants were in the middle of training when the COVID pandemic shutdown occurred (7 in the BrainHQ group and 8 in the active control group), and complete post-training data was not able to be collected. An additional 2 subjects were excluded from analysis due to the poor quality of their imaging data (1 in the BrainHQ group and 1 in the active control group). The sample for this dissertation therefore consists of 105 older adult participants – 50 assigned to the BrainHQ group and 55 assigned to the active control condition (see Figure 5.1).

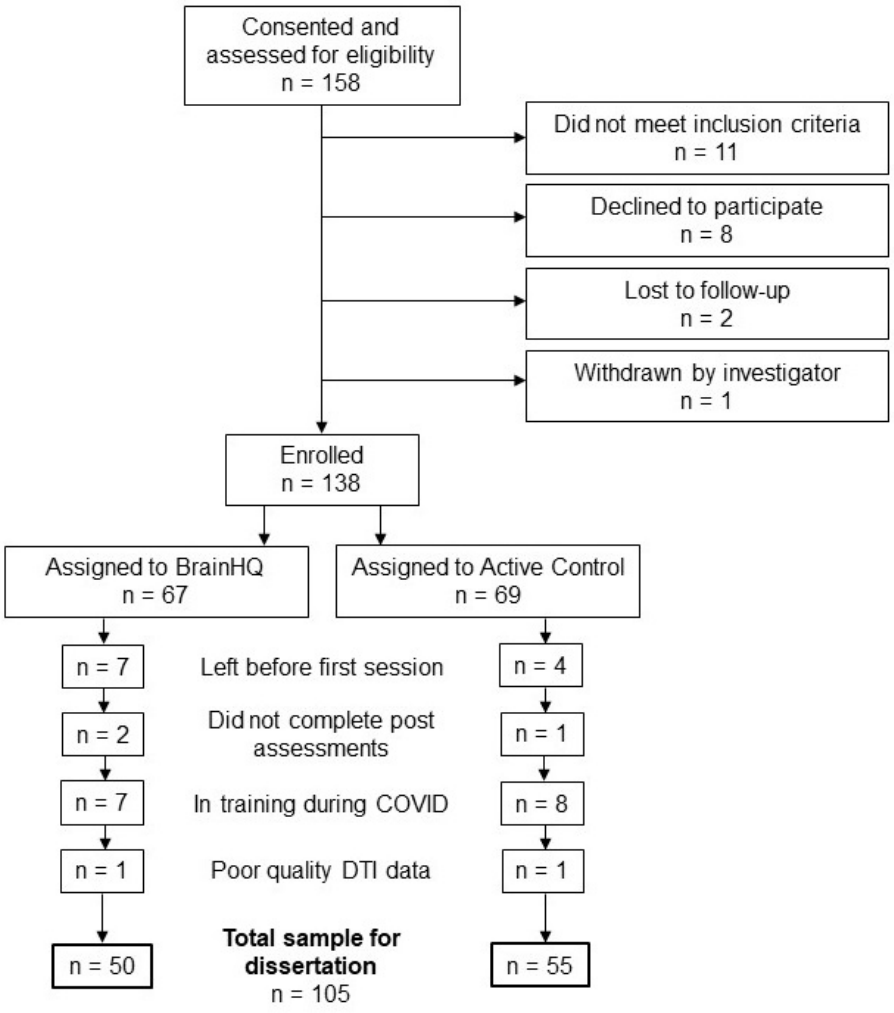


Figure 5.1. Participant recruitment, assignment, and dropout for the BETTER study.

There were 47 males and 58 females in the sample. The sample had a mean age of 72.10 years (*SD* = 4.66), and mean education of 16.74 years (*SD* = 2.41). This information, along with demographic information for each site and each experimental group, is presented in Table 5.1.

Table 5.1. Participant Demographic Information

	n	*M* Age	*SD* Age	# Males	# Females	% Males	% Females	*M* Education	*SD* Education
Total	105	72.10	4.66	47	58	44.76	55.24	16.74	2.41
Site									
Iowa	53	72.11	4.78	27	26	50.94	49.06	16.94	2.55
UTD	52	72.08	4.58	20	32	38.46	61.54	16.54	2.26
Group									
BrainHQ	50	72.22	4.71	23	27	46	54	16.72	2.40
Active Control	55	71.98	4.66	24	31	43.64	56.36	16.76	2.44

5.2 Procedure

The BETTER Aging study is a NIH-funded, parallel arm, double-blind, randomized, controlled clinical trial, with the aim of evaluating the effects of Posit Science Corporation's (San Francisco, California, USA) online brain training application, *BrainHQ,* on the cognitive abilities and brain structure/functionality of older adults. This study is being conducted in collaboration with Posit Science and the University of Iowa. In this multi-site collaborative study, older adult participants were assigned to one of two groups: 1) an experimental group that trained using *BrainHQ* brain training (BrainHQ BT), an online application designed to improve processing speed, attention, memory, and executive function; or 2) an active control group that trained using casual, online, commercially available computer games. Both groups completed the training at home and accessed the training using an identical portal via the Posit Science website.

Both groups were encouraged to complete 50 training sessions, with each session lasting approximately 45 min. In addition, participants in each group underwent an MRI scan before and after training, and participants in each group completed a ~2 hr neuropsycholgical test battery once before training, once after training, and once at a 6-month follow-up visit. The MRI included a DTI scan; and the neuropsychological session involved tasks measuring processing speed, episodic memory, and executive function.

5.3 Measurements

5.3.1 Cognitive training

Participants in both training groups were tasked with completing 50 sessions (~45 min each) of training in a location of their choosing by accessing the Posit Science website (https://app.brainhq.com) with a study-provided username and password (containing no personally identifiable information) via a laptop or desktop computer (if the participants did not have access to a personal computer, a laptop was loaned to them for the duration of the training). Participants were encouraged to complete one 45 min session a day, for 5 days a week, for 10 weeks. Flexibility in this recommended schedule was afforded to the participants. Participants were allowed to complete two sessions a day, once per week. In addition, if participants did not finish the training in the recommended 10-week period, extra time was granted to them, up to a total of 16 weeks. Training was terminated after the participants completed 50 sessions, or after 16 weeks (whichever came first), at which point participants completed a post-training MRI scan and neuropsychological assessment.

BrainHQ BT (experimental condition)

Participants in the experimental condition were directed to a portal where they completed 7 exercises per training session. These exercises use adaptive Bayesian algorithms that provide the participants with an appropriate difficulty level, and are designed to improve users' processing speed, memory, and attention. The BrainHQ BT program includes 18 different exercises in total and requires the participants to complete different exercises each session. The exercises fall into four categories: brain speed, attention, memory, and intelligence. Although the last category is titled 'Intelligence' on the BrainHQ website, perhaps a more appropriate title would be 'Executive Function', as the exercises that fall in this category target mostly working memory updating and task switching (two of the three executive functions outlined by Miyake et al., 2000).

Brain speed

1) *Visual Sweeps*

In this exercise participants saw two patterns in a row. Each pattern "sweeps" either inward or outward. After viewing both patterns, the participants were prompted to indicate which direction each pattern swept. The speed at which the patterns and their sweeping animations are shown increased upon correct responses and decreased upon incorrect responses.

2) *Sound Sweeps*

This exercise is similar to *Visual Sweeps*, but instead of visual patterns, participants were presented with two sounds that "sweep" either up in pitch or down in pitch.

3) *Fine Tuning*

In this exercise participants were shown two similar sounding syllables on the screen, for example: “ga” and “ka”. The participants then heard a short sound clip of someone speaking one of these syllables and had to identify which syllable was spoken. The spoken syllables became more ambiguous (sound more similar to each other) as participants made correct decisions, and more disparate (pronounced more clearly) as participants made incorrect decisions.

4) *Hawk Eye*

During this exercise a group of 8 birds appeared in a circle on the screen. All of the birds were identical, except one which was a different shade of color. The participants had to identify the bird that did not match the others. As the participants made correct judgements, the amount of time that birds appeared on the screen decreased. Contrariwise, as they made incorrect judgements the amount of time increased.

5) *Eye for Detail*

This exercise is similar to *Hawk Eye* in that visual stimuli were again organized in different positions around a circle. In *Eye for Detail* however, participants viewed butterflies, one at a time, as they appeared briefly in one of these positions. They saw 3 butterflies in total, two of which matched. They were then shown the three locations that the butterflies appeared and had to choose the two locations where the two matching butterflies appeared. The amount of time that the butterflies appeared on the screen decreased as the participants made correct decisions and increased as they made incorrect decisions. In the more challenging levels participants were shown images that were more difficult to discern from one another (e.g.,

similar looking flowers on a floral background), and the set size of the images shown could increase from 3 to 5.

Attention.

1) *Double Decision*

In this exercise participants completed two tasks at once. One of two vehicles appeared briefly in the center of the screen before being replaced by a blurred rectangular image. At the same time, a 'Route 66' sign also appeared briefly in one of eight peripheral positions around the center of the screen. The participant then had to decide which of the two vehicles was shown in the center of the screen, as well as indicate the position where the 'Route 66' was shown. The visual stimuli were presented for a shorter period of time as the participant made correct judgments, and was presented for a longer period of time as the participant made incorrect judgements.

2) *Target Tracker*

In this exercise participants were shown a number of objects on the screen. Those objects then began to move around the screen as other identical objects appeared and moved around as well. All the objects on the screen will freeze, at which point the participant must select the original objects from the larger array. As participants made correct selections the number of objects increased; as they made incorrect selections the number of objects decreased.

3) *Freeze Frame*

In this exercise participants were presented with an initial image. Participants were then presented with a series of images, one at a time. As each image in the series is presented, participants are given a certain amount of time to respond. Participants were instructed only to

respond if the image in the series does not match the initial image. As participants made correct decisions they were given less time to respond to each image, and as they made incorrect decisions they were given more time.

4) *Mixed Signals*

In this exercise participants heard an auditory stimulus while viewing a visual stimulus in the center of the screen. In the easiest version of this task participants heard a number while seeing a number of non-numerical objects on the screen (e.g., '#####'). They responded by hitting a 'Yes' button only if the number of objects matches the number they were told. In a more difficult version of this task the participants were shown a set of matching numerals on the screen (e.g., '2222'). While their task was still to respond 'Yes' only if the number of objects (in this case numerals) matched the number they were told, this version is more difficult as participants must inhibit the bottom-up processing evoked by reading the numbered objects. In yet another version of this task, participants were told a letter while being shown a set of 5 letters on the screen (e.g. 'zzhzz'). In this version, participants were to respond 'Yes' only if the middle letter was the same as the letter they heard. As participants responded correctly in all versions of the task, the amount of time they had to respond to the stimuli decreased. The amount of time increased if the participants responded incorrectly.

5) *Divided Attention*

In this exercise participants were shown two shapes on the screen. Depending on the difficulty version, participants then had to respond to one of six criteria: 'Same shape', 'Same color', 'Same interior', 'Different shape', 'Different color', or 'Different interior'. If the shapes met the criteria the participants were to press a 'Yes' button on the screen, if the shapes didn't

meet the criteria then the participants were to press a 'No' button on the screen. The amount of time participants had to respond decreased as they responded correctly and increased as they responded incorrectly.

Memory.

1) *To-Do List Training*

In this exercise participants were shown a 3 x 3 grid of objects. Before this grid was presented, the participants heard a list of instructions about how to interact with these objects. They were to remember the instructions and execute them in the appropriate order. As they executed the instructions correctly the number of instructions given increased. The number of instructions decreased if the participants made too many mistakes.

2) *Memory Grid*

In this exercise participants were shown a number of cards on the screen. When a participant clicked on a card a sound played. There were two cards that played the same sound. The participants had to match all the cards with matching sounds within a given number of clicks. As the participant completed the matches within the given number of clicks, the number of cards on the screen increases. The number of cards decreased if the participants failed to complete the matches in the given number of clicks.

3) *Rhythm Recall*

In this exercise participants heard a rhythm and saw a visual representation of the different tones and duration of the tones in the rhythm. The participants were then required to use the keyboard to recreate the rhythm. They could press any key on the keyboard, but they had to press different keys for different tones. They were to hold the keys for the different tones for

approximately the same amount of time that the tones played during the original rhythm. As the participants succeeded in this task, the rhythms became more complex (i.e., included a greater number of different tones). If the participants failed to recreate the rhythm, the number of tones decreased.

4) *Scene Crasher*

In this exercise participants were shown a scene filled with a certain number of objects. They were then shown a screen of static, followed by the original scene with an additional object added. The participants had to identify the object that had been added to the scene. As the participants made correct identifications, they were shown scenes with a greater number of objects. If they failed to make correct identifications, the number of objects in the scene decreased.

Intelligence (executive function).

There are four exercises included in the BrainHQ BT that are designed to improve fluid intelligence skills, such as working memory and task switching.

1) *Card Shark*

In this exercise participants were shown cards with varying amounts of information (depending on difficulty level) one at a time. Participants had to decide whether or not the current card they were viewing was the same as the card presented a certain number of steps (depending on difficulty level) back in the sequence.

2) *Auditory Ace*

This exercise is similar to *Card Shark*, except in *Auditory Ace* participants heard verbal information describing each card as opposed to seeing visual information.

3) *Juggle Factor*

In this exercise participants were shown a number of moving white circles on the screen. Numbers appeared in these circles one at a time. The circles then stopped moving and participants had to click on the circle where the number 1 appeared, then click on the circle where the number 2 appeared, and so forth until they've reconstructed the entire sequence of numbers in the correct locations. The number sequences grew longer as participants successfully reconstructed them, and grew shorter if participants failed to reconstruct them correctly.

4) *Mind Bender*

This is a task-switching exercise where participants were shown two objects that fall into one of two conditions (e.g., numbers that can be shown in either their numeric or written form). Participants had to choose one of the objects based on a rule that is different for each of the two conditions the objects can fall under (e.g., participants must pick the higher number if the numbers are shown numerically, but the lower number if the numbers are shown in their written form). The amount of time participants had to respond decreased as they made more correct judgments and increased as they made more incorrect judgments.

Commercially-available computer games (active control condition)

Participants in the active control (AC) condition accessed their training in an identical manner to participants in the BrainHQ BT condition (via a portal on the Posit Science BrainHQ website; brainhq.com). Each session was also comprised of 7 exercises (in this case games), with each exercise/game lasting 6 min. The AC training includes 13 games in total.

1) *Brick Squasher II*

The goal of this game is to destroy all of the bricks at the top of the screen by bouncing a ball off of a small platform that the participants can move horizontally at the bottom of the screen.

2) *War Ship*

This is a turn-based game, in which participants must first place a collection of ships of various sizes either vertically or horizontally in a grid-like board. They then must select spaces on an identical empty board in attempt to find the AI enemy ships. The object is to find and destroy (by selecting each space that a ship occupies) all of the AI's ships before the AI destroys all of the player's ships.

3) *Bricks Breaking Hex*

The goal of this game is to destroy all of the multi-colored bricks on the screen by selecting groups of identically-colored bricks before the participant runs out of his/her 5 lifelines.

4) *Chinese Checkers*

The goal of this game is to move all 10 of the blue marbles in the player's starting blue triangle across the board to the opponent's green triangle before the AI opponent can move all of its green marbles into your blue triangle.

5) *Lineup Four*

In this game participants alternate with the AI opponent to place chips in one of 7 columns. The chip falls to the bottommost slot in that column (each column has 6 slots) that has not already been occupied by a chip. The player's goal is to line up four of their yellow chips (horizontally, vertically, or diagonally) before the AI lines up four red chips.

6) *Crossword Puzzle*

In this game participants are shown a board made up of a number of connecting spaces that run both horizontally and vertically. They are then to fill in these spaces with words that match given descriptions.

7) *Gem Swap*

In this game participants are shown a screen full of differently shaped and colored gems. Their goal is to swap the location of adjacent gems until they make a line of at least three identical gems. As they do this their score and remaining time on an in-game timer increases (when the timer runs out the game ends).

8) *Double Klondike Solitaire*

The rules of this game are identical to regular Solitaire, but there are two decks of cards instead of one. Participants are shown 9 stacks of cards (the leftmost stack contains 1 card and each stack to the right contains one more card than the stack to the left of it), with the top card of each stack revealed. The goal is move cards from the stacks to the 8 foundation piles (two for each suit) on the top right of the screen in ascending order from ace to king. Additional cards can be revealed in triplets from the remaining cards in the deck, which are in a pile on the top-left of the screen. Cards can be moved to different stacks in descending order and alternate colors from the top card on each stack. Stacks beginning with a king can be moved to an empty stack position.

9) *Maze Race*

In this game participants move a green ball through a maze using the arrow keys, and attempt to reach flag within the maze before an AI controlled red ball reaches it.

10) *Reversi*

In this game players take turns with an AI opponent to place pieces on an 8x8 grid. The pieces are either black or white, with one color indicating the player's pieces and the other indicating the AI's pieces. Pieces can be placed adjacent to another piece of your color (horizontally, vertically, or diagonally). If you 'capture' a piece of another color between two of your pieces it turns to your color. The goal is to have the most pieces of your color on the board when there are no more moves remaining.

11) *Word Search II*

In this game letters are placed in a 15x15 grid. There are 10 words listed to the right of the screen. Players must find these words spelled out (horizontally, vertically, or diagonally) in the grid of letters.

12) *Sudoku*

In this game players are shown a 3x3 grid. Each block of this grid contains a smaller 3x3 grid (forming a 9x9 grid). Players must place numbers in each space such that no row, column, or block contains the same number twice.

13) *Tri Peaks Solitaire*

The goal of this game is to remove all the cards that make up three peaks, which are each formed with one card face down, which are on top of two other face down cards, which are on top of three other face down cards. At the bottom of these peaks are 10 cards face up. A card can be drawn from a deck of remaining cards on the bottom of the screen. Cards that come before or after the drawn cad can then be stacked onto it from the three peaks. If there are no cards from

the peaks that can stack onto the deck below, then a new card can be drawn from that deck. Cards from the peaks will be revealed as the cards below them are removed.

5.3.2 Neuropsychological and cognitive assessments

I. Processing Speed

1) *Pattern Comparison* (Salthouse, 2004)

In this task that measures processing speed, participants are given a sheet with 30 sets of two similar patterns on either side of a blank line. The patterns are abstract (don't resemble any shapes or symbols the participants would encounter in everyday life) and are formed of a collections of straight lines. The pattern on the left side of the line will either be identical or non-identical to the pattern on the right side of the line. The participants decide whether the patterns are identical (same) by writing an "S" on the blank line, or whether they are non-identical (different) by writing a "D" on the line. They are given 30 seconds to complete as many of the 30 sets as they can. They repeat this twice. The number of patterns that they complete correctly are totaled for the participant's score.

2) *Letter Comparison* (Salthouse, 2004)

This task is similar to the *Pattern Comparison* Task, except in *Letter Comparison* participants are given a sheet with 21 sets of two similar letter sequences on either side of a blank line. The letter sequences will be non-sensical –they will not include any vowels, and will therefore not appear word-like. The participants are again given 30 seconds to compare the sequences in as many sets as they can by writing an "S" for identical sets and a "D" for non-identical sets. They repeat this twice. The number of letter sequences that are completed correctly are totaled for the participant's score.

3) *Digit Symbol Coding* (Wechsler, 1987)

In this task participants are shown 9 boxes at the top of a sheet of paper. The top section of these boxes include the numbers 1-9, and the bottom section of the boxes include a unique symbol associated with each number in the top section. The remainder of the sheet of paper contains 140 boxes (presented in rows of 20) that include the number in the top section, but not the symbol in the bottom section. The participants are given two minutes to fill in the bottom section of each box (going in order from left to right, top to bottom) with the correct symbol that corresponds to the number in the top section of the box. The number of boxes that are filled in correctly are totaled for the participant's score.

II. Episodic Memory

1) *Face Name*

In this task (created in our lab) participants first view a series of faces, one at a time. Each face will have a corresponding name under it. The participants will view each face/name pair twice, and are instructed to remember as many as they can. Participants are then tested on their memory for these face/name pairs by being presented with another series of faces. The face/name pairs in the test phase can be either old or new. An old face/name pair is defined as a face the participant saw before with the same name under it. A new face/name pair is defined as either a face the participant hasn't seen before, or a face they have seen before, but with a different name under it. The participants are given 4 seconds to respond to each face/name pair, and are instructed to press the 'Z' key on the keyboard for old face/name pair and the 'M' key on the keyboard for a new face/name pair. Both accuracy and reaction time can be assessed in this task.

2) *Selective Reminding Task* (*SRT*; Buschke, 1973, 1974)

At the beginning of this task the experimenter reads 12 words aloud to the participant. The participant must then repeat as many words as he/she can remember to the experimenter. After the participant is done, the experimenter will remind the participant of the words he/she missed and then ask the participant to repeat all 12 words (or as many as he/she can remember) again. This process is repeated either 12 times, or until the participant is able to recall all 12 words correctly twice in a row, whichever comes first. The participant is then cued with the first two letters of each of the twelve words and asked to recall which word they belong to. The participant is then given a multiple choice test with 12 questions. There are four possible answers to each question, each being a word that is similar in length/quality to one of the 12 words previously studied. There is only one correct answer to each question, that being one of the 12 original words. The participant is asked to recall the 12 words one final time after a 30-minute delay. There are multiple indexes of performance that can be derived from this task (see Buschke, 1973).

III. Executive Function

1) *N-back* (Kane & Engle, 2002)

In this working memory task participants are shown a series of letters on the computer screen, one at a time. During the first part of this task, participants must decide whether the current letter they are seeing is the same letter as the one they saw immediately before. If it is the same (e.g., they are presented with an 's' and then another 's') the participants are to press the 'Z' key on the keyboard. If the letter is different than the previous letter (e.g., they are presented with an 's' and then an 'f') the participant is to press the '/' key on the keyboard. During the

second part of this task, participants must compare the current letter they are seeing with the letter two back in the sequence. Accuracy and reaction time for both 1-back and 2-back conditions are recorded.

2) *Visual Short Term Memory* (VSTM; Luck & Vogel, 1997)

In this task participants are presented with 4 objects side by side in the center of the computer screen. The objects will disappear and then another object will appear below the original display. If this new object was part of the original display the participants are to press the 'Z' key on the keyboard. If this object was not present in the original display the participants are to press the '/' key on the keyboard. In the first part of this task, participants will be presented with different colored squares. In the second part of this task, participants will be presented with a variety of white-colored shapes. In the third part of this task, participants will be presented with a variety of different colored shapes. Accuracy and reaction time are recorded and averaged across all three blocks.

3) *Flanker*

In this version of the Flanker paradigm (Eriksen & Eriksen, 1974) participants are presented with 5 stimuli on the screen. The center stimuli will always be an arrow pointing left or right ('<', '>') or a dash ('-'), the remaining four stimuli will be either an arrow pointing left or right ('<', '>') or a dash ('-'). The participant is told to pay attention to the center arrow and press the 'Z' key on the left side of the keyboard if the arrow is pointing to the left ('<') or the 'M' key on the right side of the keyboard if the arrow is pointing to the right ('>'). Accuracy and reaction time are measured for congruent (center arrow goes in the same direction as peripheral arrows), incongruent (center arrow goes in opposite direction as peripheral arrows), and neutral

(there are no peripheral arrows) trials. An inhibition cost can be calculated by subtracting reaction time across congruent trials from reaction time across incongruent trials.

4) *Task Switching*

This task was created in lab and is administered during an fMRI scan. In this task participants are shown a single digit on the screen and are asked to make one of two judgments via button presses. If the digit appears on a blue background the participant must decide whether the digit is higher or lower than 5 (the digit will never be "5"). If the digit appears on a red background the participant must decide whether the digit is odd or even. In single blocks participants will see the digit in only one of the two background colors. In dual blocks the color of the background will switch throughout the task so that the participant must switch back and forth between task demands. A local switch cost was calculated for each participant by subtracting his/her RT on nonswitch trials (when the background color of the previous digit is the same as the background color of the current digit) from his/her RT on switch trials (when the background color of the previous digit was different from the background color of the current digit).

5.3.3 DTI

Participants at the University of Texas at Dallas site were scanned using a Philips Achieva 3 Tesla MRI magnet (Philips Medical Systems, Andover, MA). DTI scans were performed using a single-shot spin-echo echo planar imaging sequence with the following parameters: repetition time = 5450 ms; echo time = 91 ms; flip angle = 90°; matrix = 100 × 99; field of view = 220 mm × 220 mm; slice thickness = 2 mm; voxel resolution = 1.96 mm × 1.96 mm × 2.20 mm; bandwidth = 3116.2 Hz/pixel; multi-band factor = 2; acceleration = 2 phase. The

diffusion-sensitizing gradients were applied along 60 non-collinear directions with a b value of 1000 s/mm2, and 10 volumes are acquired without diffusion weighting (b = 0).

Participants at the University of Iowa site were scanned using a 3.0T General Electric 750W MRI magnet with a 32-channel head coil (General Electric Company, Boston, MA). DTI scans were performed using a single-shot spin-echo echo planar imaging sequence with the following parameters: repetition time = 9000 ms; echo time = 76.3 ms; flip angle = 90°; matrix = 256 × 256; field of view = 256 mm × 256 mm; slice thickness = 2 mm; voxel resolution = 1 mm × 1 mm × 2 mm; bandwidth = 2000 Hz/pixel; multi-band factor = 2; acceleration = 2 phase. The diffusion-sensitizing gradients were applied along 60 non-collinear directions with a b value of 1000 s/mm2, and 10 volumes are acquired without diffusion weighting (b = 0).

The diffusion weighted images were preprocessed using FSL (Jenkinson et al., 2012; Smith et al., 2004). We first performed a brain extraction using the BET command (Smith, 2002) on each participant's b0 volume, with a fractional intensity threshold of 0.3, to create a mask that is then registered and applied to the rest of the volumes using FLIRT (Jenkinson, Bannister, Brady, & Smith, 2002; Jenkinson & Smith, 2001) and fslmaths. Each participant's images were then subjected to an open-source quality-control software called DTIprep (Liu et al., 2010), which performs several steps (Oguz et al., 2014), including an eddy-current and motion artifact correction. We used the Advanced Normalization Tools (ANTs; Avants et al., 2011; Avants et al., 2010) software to perform a non-linear registration between each participant's brain extracted T1 image and the MNI, and between each participant's T1 and their brain extracted b0 volume. These registrations are used at a later step to register any specific ROIs created in MNI space to each participant's b0. The corrected diffusion images were reconstructed using the DTI pipeline

in DSI Studio (http://dsi-studio.labsolver.org; Yeh, 2021). DSI Studio's deterministic tractography algorithm (Yeh, Verstynen, Wang, Fernández-Miranda, & Tseng, 2013) was then used to estimate 6 tracts – the genu, the splenium, the cingulum (left and right), the SLF (left and right), the fornix, and the uncinate fasciculus (left and right) – for each participant both before and after training.

Genu

Regions of inclusion (ROIs) and regions of avoidance (ROAs) are specified when estimating fiber tracks in DSI Studio. Each ROI and ROA is registered to each participant's b0 volume for both their pre-training and post-training scans. The first ROI specified when tracking the genu was the genu region included in the JHU ICBM-DTI-81 white-matter labels atlas (Mori et al., 2005; see Figure 5.2a). Because the genu is a commissural tract, a mid-sagittal plane was included as a second ROI to include only fibers connecting both hemispheres (see Figure 5.2b). A coronal plane placed approximately 2 mm posterior to the JHU genu ROI was included as an ROA to exclude fibers past that point (see Figure 5.2c). Two sagittal planes located lateral to the genu – one to the right approximately 5 mm, and one to the left approximately 5 mm – were also included as ROAs to exclude any crossing fibers projecting laterally from the genu (see Figure 5.2d). A fiber tract for the genu was estimated for each participant's pre-training and post-training scan separately using Yeh et al.'s (2013) deterministic algorithm with the following additional parameters: a seeding region was placed at whole brain; angular threshold = 60 degrees; step size = 1 mm; anisotropy threshold = 0.2; tracks with a length of less than 20 mm were discarded; and a total of 1,000,000 seeds were placed (an example genu tract is shown in Figure 5.3).

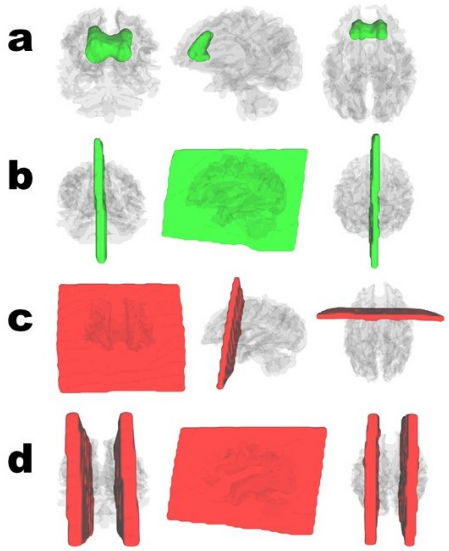


Figure 5.2. The ROIs and ROAs specified when tracking the genu in DSI Studio. ROIs are shown in green, and ROAs are shown in red. a) Genu region from the JHU atlas (Mori et al., 2005). b) A mid-sagittal plane. c) A coronal plane ~ 2 mm posterior to the JHU genu. d) Two sagittal planes, one placed ~ 5 mm to the left of the JHU genu, and one placed ~ 5 mm to the right of the JHU genu.

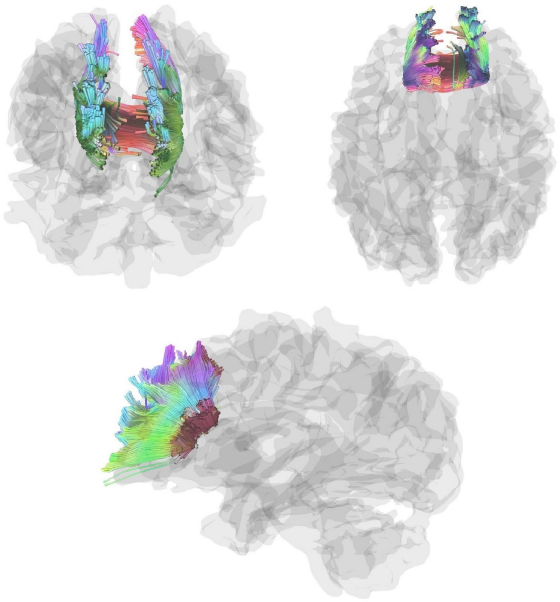


Figure 5.3. An example of a genu fiber tract estimated using DSI Studio in 3 views: coronal view looking at the front of the head (top left); axial view looking down at the top of the head (top right); and sagittal view looking at the left side of the head (bottom).

Splenium

We used the splenium region of the JHU atlas (Mori et al., 2005) as the first ROI when tracking the splenium (see Figure 5.4a). A mid-sagittal plane was again used to include only fibers connecting the two hemispheres (see Figure 5.4b). A coronal plane was placed approximately 10 mm anterior to the JHU splenium as a third ROI to include only fibers projecting into the occipital lobe (see Figure 5.4c). Another coronal plane was placed approximately 2mm anterior to the JHU splenium as an ROA to exclude fibers past that point (see Figure 5.4d). One 8 cubic voxel ROI centered approximately 20 mm to the right of the anterior splenium at x = 64, y = 93, z = 88; and a second centered approximately 20 mm to the left of the anterior splenium at x = 114, y = 93, z = 88 were also included as ROAs due to exclude crossing fibers projecting into these regions (see Figure 5.4e). A fiber tract for the splenium was estimated for each participant's pre-training and post-training scan separately using Yeh et al.'s (2013) deterministic algorithm with the following additional parameters: a seeding region was placed at whole brain; angular threshold = 60 degrees; step size = 1 mm; anisotropy threshold = 0.2; tracks with a length of less than 20 mm were discarded; and a total of 1,000,000 seeds were placed. An example splenium tract is shown in Figure 5.5.

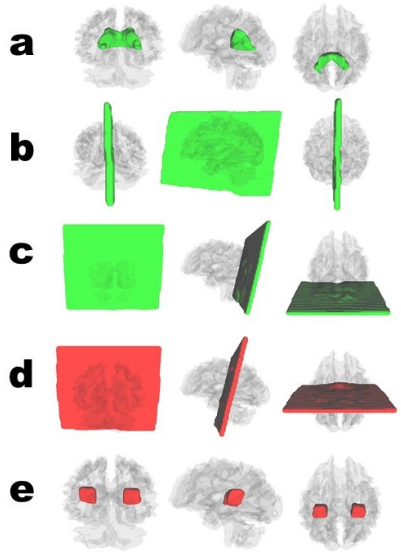


Figure 5.4. The ROIs and ROAs specified when tracking the splenium in DSI Studio. ROIs are shown in green, and ROAs are shown in red. a) Splenium region from the JHU atlas (Mori et al., 2005). b) A mid-sagittal plane. c) A coronal plane ~ 10 mm posterior to the JHU splenium. d) A coronal plane ~ 2 mm anterior to the JHU splenium. e) Two 8 cubic voxels, one centered ~ 20 mm to the right of the anterior splenium, and one centered ~ 20 mm to the left of the anterior splenium.

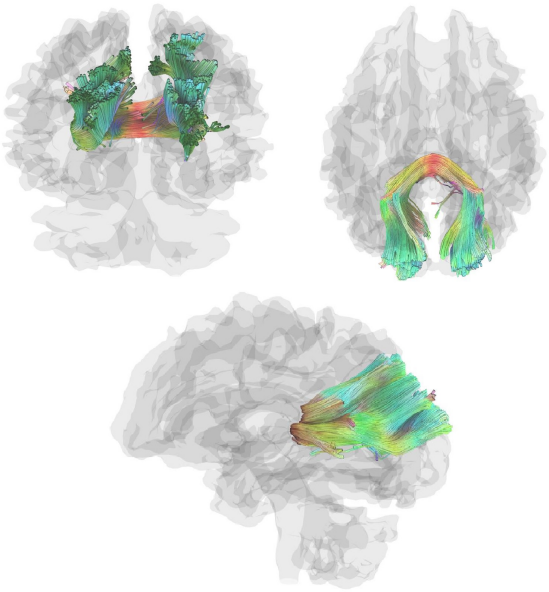


Figure 5.5. An example of a splenium fiber tract estimated using DSI Studio in 3 views: coronal view looking at the back of the head (top left); axial view looking down at the top of the head (top right); and sagittal view looking at the left side of the head (bottom).

Cingulum

The left and right cingulum were tracked separately. The left cingulum region of the JHU atlas (Mori et al., 2005) was used as an ROI for the left cingulum and the right cingulum region of the JHU atlas was used as an ROI for the right cingulum (see Figure 5.6a). A mid-sagittal plane was again included for both the left and right cingulum, but this time as an ROA since the cingulum is an association tract and not a commissural tract (see Figure 5.6b). A sagittal plane placed approximately 10 mm to the left of the JHU cingulum was included as an ROA for the left cingulum, and a sagittal plane placed approximately 10 mm to the right of the JHU cingulum was included as an ROA for the right cingulum (see Figure 5.6c). To exclude crossing fibers projecting dorsally from the cingulum into the top of the head, a custom ROA was created using the JHU atlas to trace around the dorsal surface of the cingulum (see Figure 5.6d). A fiber tract for the left and right cingulum were estimated for each participant's pre-training and post-training scan separately using Yeh et al.'s (2013) deterministic algorithm with the following additional parameters: a seeding region was placed at whole brain; angular threshold = 30 degrees; step size = 1 mm; anisotropy threshold = 0.2; tracks with a length of less than 20 mm were discarded; and a total of 1,000,000 seeds were placed. Examples of both the left and right cingulum tracts are shown in Figure 5.7.

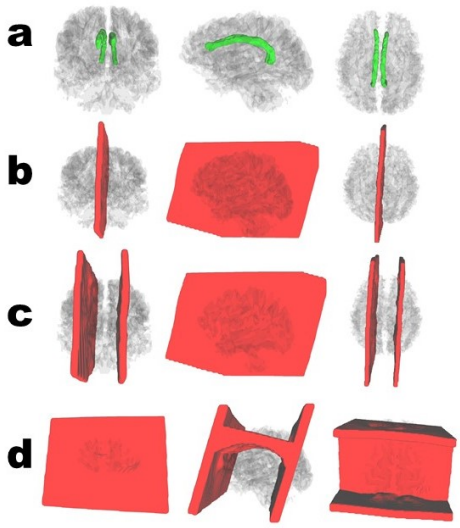


Figure 5.6. The ROIs and ROAs specified when tracking the left and right cingulum in DSI Studio. ROIs are shown in green, and ROAs are shown in red. a) Left and right cingulum regions from the JHU atlas (Mori et al., 2005). b) A mid-sagittal plane. c) A sagittal plane ~ 10 mm left from JHU cingulum, and a sagittal plane ~ 10 mm right of JHU cingulum. d) Custom region created using the JHU atlas to trace around the dorsal surface of the cingulum.

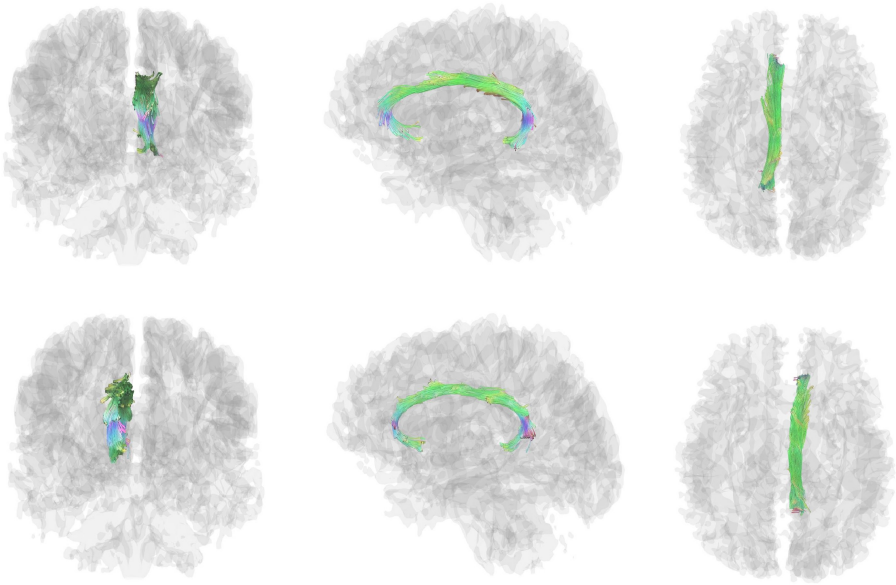


Figure 5.7. An example of a left (top) and right (bottom) cingulum fiber tract estimated using DSI Studio in 3 views: coronal view looking at the front of the head (left); sagittal view looking at the left side of the head (middle), and axial view looking down at the top of the head (right).

Superior Longitudinal Fasciculus (SLF)

The left and right SLF were tracked separately. The left SLF region of the JHU atlas (Mori et al., 2005) was used as an ROI for the left SLF and the right SLF region of the JHU atlas was used as an ROI for the right SLF (see Figure 5.8a). A mid-sagittal plane (approximately 21 mm thick) was used as an ROA for both the left and right SLF (see Figure 5.8b). A coronal plane placed approximately 10 mm anterior to the JHU SLF regions was used as an ROA for both the left and right SLF (see Figure 5.8c); and an axial plane placed approximately 10 mm inferior to the JHU SLF regions was also used as an ROA for both the left and right SLF (see Figure 5.8d). A fiber tract for the left and right SLF were estimated for each participant's pre-training and post-training scan separately using Yeh et al.'s (2013) deterministic algorithm with the following additional parameters: a seeding region was placed at whole brain; angular threshold = 60 degrees; step size = 1 mm; anisotropy threshold = 0.2; tracks with a length of less than 20 mm were discarded; and a total of 1,000,000 seeds were placed. Examples of both the left and right SLF tracts are shown in Figure 5.9.

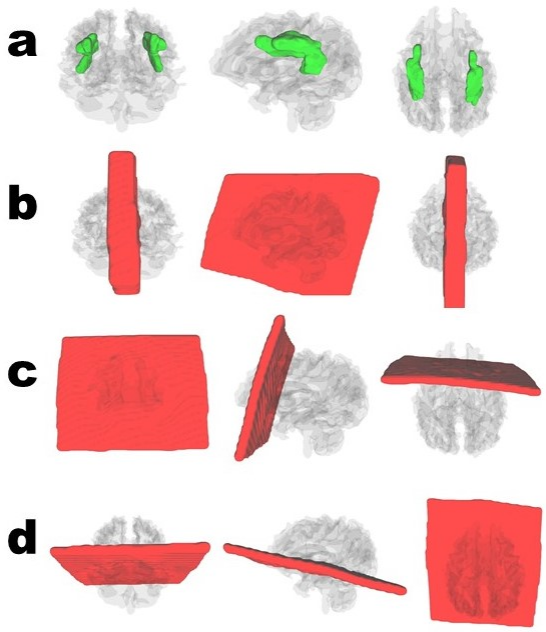


Figure 5.8. The ROIs and ROAs specified when tracking the left and right SLF in DSI Studio. ROIs are shown in green, and ROAs are shown in red. a) Left and right SLF regions from the JHU atlas (Mori et al., 2005). b) A mid-sagittal plane (~ 21 mm thick). c) A coronal plane ~ 10 mm anterior from JHU SLF. d) Axial plane ~ 10 mm inferior to JHU SLF.

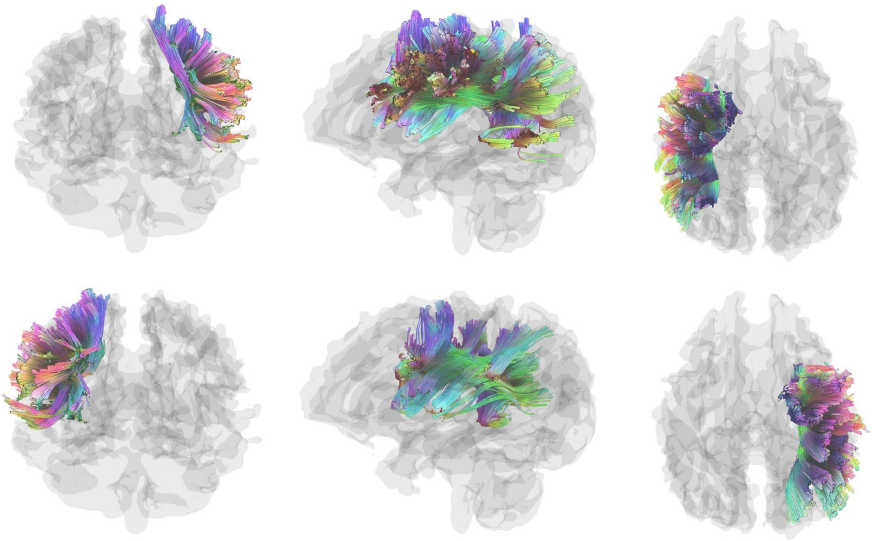


Figure 5.9. An example of a left (top) and right (bottom) SLF fiber tract estimated using DSI Studio in 3 views: coronal view looking at the front of the head (left); sagittal view looking at the left side of the head (middle), and axial view looking down at the top of the head (right).

Uncinate Fasciculus (UF)

The left and right UF were tracked separately. The left UF region of the JHU atlas (Mori et al., 2005) was used as an ROI for the left UF and the right UF region of the JHU atlas was used as an ROI for the right UF (see Figure 5.10a). A mid-sagittal plane was used as an ROA for both the left and right UF (see Figure 5.10b). A coronal plane placed approximately 5 mm posterior to the JHU UF was used as an ROA for both the left and right UF (see Figure 5.10c); and an axial plane placed approximately 15 mm superior to the JHU UF was also used as an ROA for both the left and right UF (see Figure 5.10d). A fiber tract for the left and right UF were estimated for each participant's pre-training and post-training scan separately using Yeh et al.'s (2013) deterministic algorithm with the following additional parameters: a seeding region was placed at whole brain; angular threshold = 60 degrees; step size = 1 mm; anisotropy threshold = 0.2; tracks with a length of less than 20 mm were discarded; and a total of 1,000,000 seeds were placed. Examples of both the left and right UF tracts are shown in Figure 5.11.

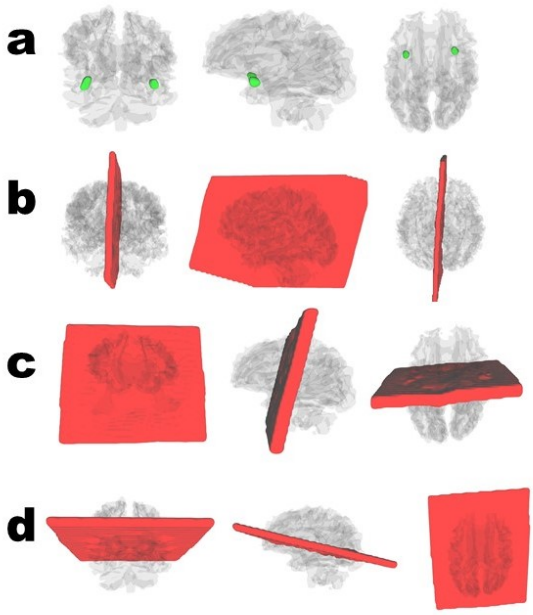


Figure 5.10. The ROIs and ROAs specified when tracking the left and right UF in DSI Studio. ROIs are shown in green, and ROAs are shown in red. a) Left and right UF regions from the JHU atlas (Mori et al., 2005). b) A mid-sagittal plane (~ 21 mm thick). c) A coronal plane ~ 5 mm posterior from JHU UF. d) Axial plane ~ 15 mm superior to JHU SLF.

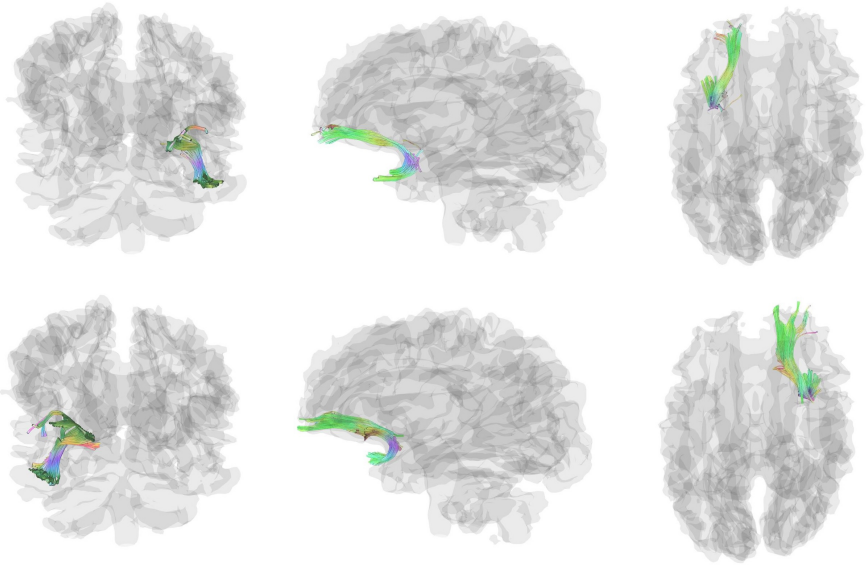


Figure 5.11. An example of a left (top) and right (bottom) UF fiber tract estimated using DSI Studio in 3 views: coronal view looking at the front of the head (left); sagittal view looking at the left side of the head (middle), and axial view looking down at the top of the head (right).

Fornix

We found the fornix region in the JHU atlas (Mori et al., 2005) to be a bit too restrictive for our sample, so we made a custom "fornix" ROI by creating a 10-voxel cube at the anterior point of the JHU fornix – the cube is centered at x = 89, y = 125, z = 80 (see Figure 5.12a). Two axial planes – one placed approximately 10 mm superior to the JHU fornix, and one place approximately 15 mm inferior to the JHU fornix – were included as ROAs (see Figure 5.12b). A coronal plane placed approximately 15 mm anterior to the JHU fornix was included as an ROA (see Figure 5.12c). Two sagittal partial planes (located on the anterior half of the brain) were placed laterally to the JHU fornix – one to the left approximately 15 mm, and one to the right approximately 15 mm – and were included as ROAs (see Figure 5.12d). Lastly, a custom ROA was created by placing a coronal plane approximately 20 mm posterior to the JHU fornix, and extending part of that plane forward (from approximately 2mm superior to the JHU fornix to the top of the brain) to approximately 5 mm posterior to the JHU fornix (see Figure 5.12e). A fiber tract for the fornix was estimated for each participant's pre-training and post-training scan separately using Yeh et al.'s (2013) deterministic algorithm with the following additional parameters: a seeding region was placed at whole brain; angular threshold = 30 degrees; step size = 1 mm; anisotropy threshold = 0.2; tracks with a length of less than 20 mm were discarded; and a total of 1,000,000 seeds were placed. An example fornix tract is shown in Figure 5.13.

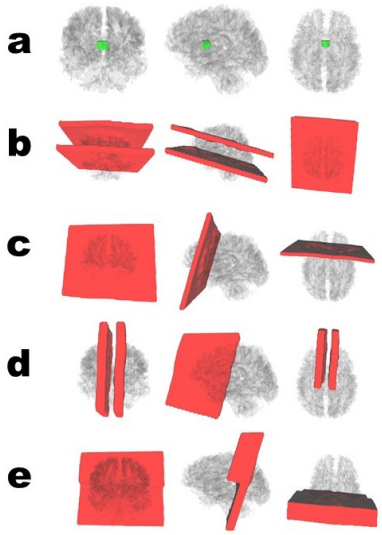


Figure 5.12. The ROIs and ROAs specified when tracking the fornix in DSI Studio. ROIs are shown in green, and ROAs are shown in red. a) 10 cubic voxel centered at anterior tip of JHU fornix. b) An axial plane ~ 10 mm superior to JHU fornix and an axial plane ~ 15 inferior to JHU fornix. c) A coronal plane ~ 15 mm anterior to JHU fornix. d) 2 sagittal anterior partial planes ~ 15 mm lateral to JHU fornix on left and right. e) Custom coronal plane ~ 5 mm posterior to JHU fornix on superior half, and ~ 20 mm posterior to JHU fornix on inferior half.

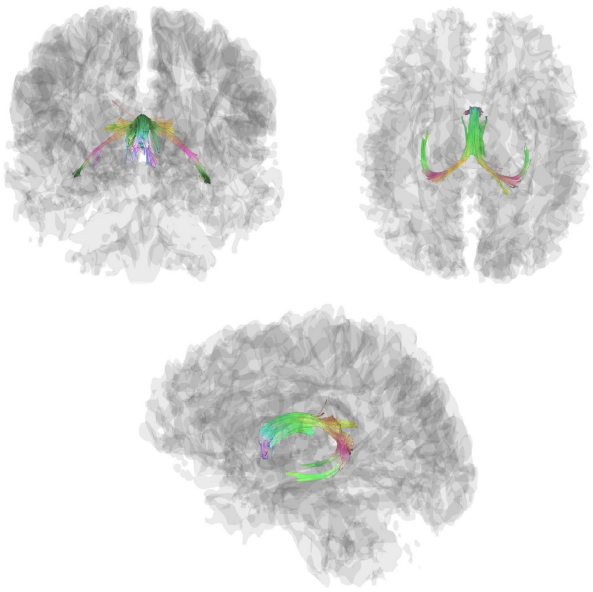


Figure 5.13. An example of a fornix fiber tract estimated using DSI Studio in 3 views: coronal view looking at the front of the head (top left); axial view looking down at the top of the head (top right); and sagittal view looking at the left side of the head (bottom).

CHAPTER 6

ANALYSIS AND RESULTS

6.1 Demographic Variables

All statistical tests were performed using R (R Core Team, 2015), and all multiple comparison corrections were performed using Benjamini and Hochberg's (1995) False Discovery Rate (FDR) approach. We performed t-tests to see if there were any baseline differences in age or education between the two research sites (the University of Iowa and the University of Texas at Dallas) or the two training groups (the BrainHQ group and the Active Control group), and chi-square tests to see if there were baseline differences in gender. There was no baseline difference in age between site, $t(102.94) = 0.04$, $p = .97$, or group, $t(101.82) = -0.26$, $p = .80$. There was no baseline difference in education between site, $t(101.95) = 0.86$, $p = .39$, or group, $t(102.36) = 0.09$, $p = .93$. There was also no baseline difference in gender between site, $\chi^2(1, N = 105) = 1.43$, $p = .23$, or group, $\chi^2(1, N = 105) = 0.11$, $p = .75$.

6.2 White Matter FA

We again conducted t-tests to determine if there was a baseline difference in FA between sites and groups for each tract. We also conducted 2 x 2 ANOVAs for each tract to examine the interaction between group (BrainHQ and Active Control) and time (pre-training and post-training). Any main effects or interactions significant at $p < .05$, or at $p < .10$, were followed up with pairwise t-tests using the FDR method to correct for multiple comparisons.

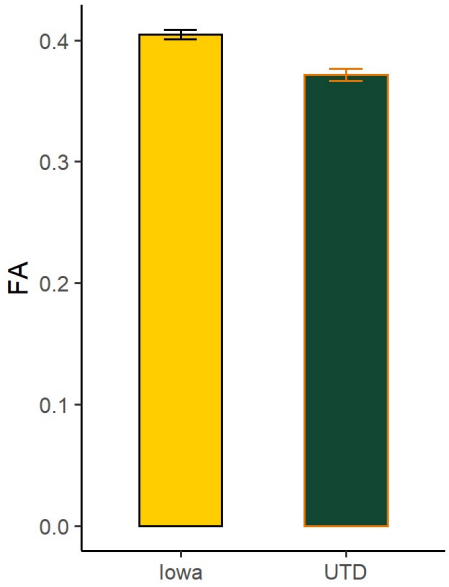


Figure 6.1. Mean baseline FA in the **genu** at each training site. Error bars represent 95% confidence intervals.

6.2.1 Genu

We did not find a baseline difference between FA in the genu between groups, $t(97.97) = 0.004$, $p = .99$, however we did observe a baseline difference between research sites, $t(95.33) = 10.38$, $p < .001$, such that FA in the genu was higher for participants at the University of Iowa ($M = .405$, $SD = .01$) compared to those at the University of Texas at Dallas ($M = .372$, $SD = .02$; see Figure 6.1). The 2 x 2 ANOVA revealed no effect of group, $F(1, 103) = 0.004$, $p = .95$, nor time, $F(1, 103) = 1.97$, $p = .16$, nor an interaction between the two, $F(1, 103) = 0.08$, $p = .78$ (see Figure 6.2).

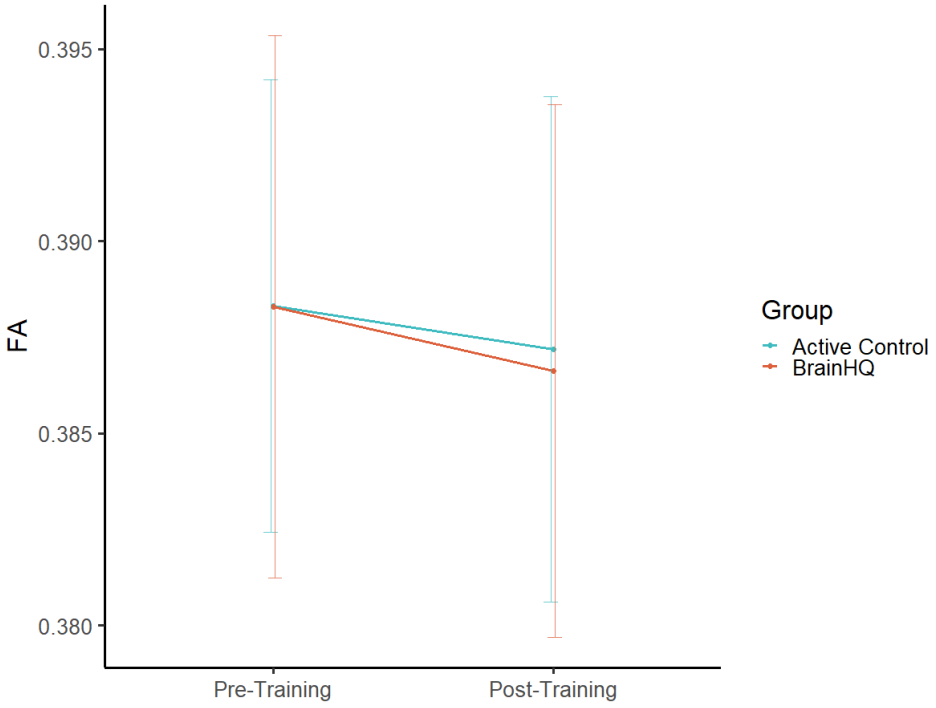


Figure 6.2. Mean FA in the **genu** for each experimental condition both before and after completing 50 hours of training in either the BrainHQ group or the Active Control group. Error bars represent 95% confidence intervals.

6.2.2 Splenium

We did not find a baseline difference between FA in the splenium between research sites, $t(90.39) = -0.51$, $p = .61$, nor experimental groups, $t(101.99) = 0.50$, $p = .62$. The 2 x 2 ANOVA revealed no effect of group, $F(1, 103) = 0.13$, $p = .72$, nor time, $F(1, 103) = 0.39$, $p = .54$, nor an interaction between the two, $F(1, 103) = 0.09$, $p = .76$ (see Figure 6.3).

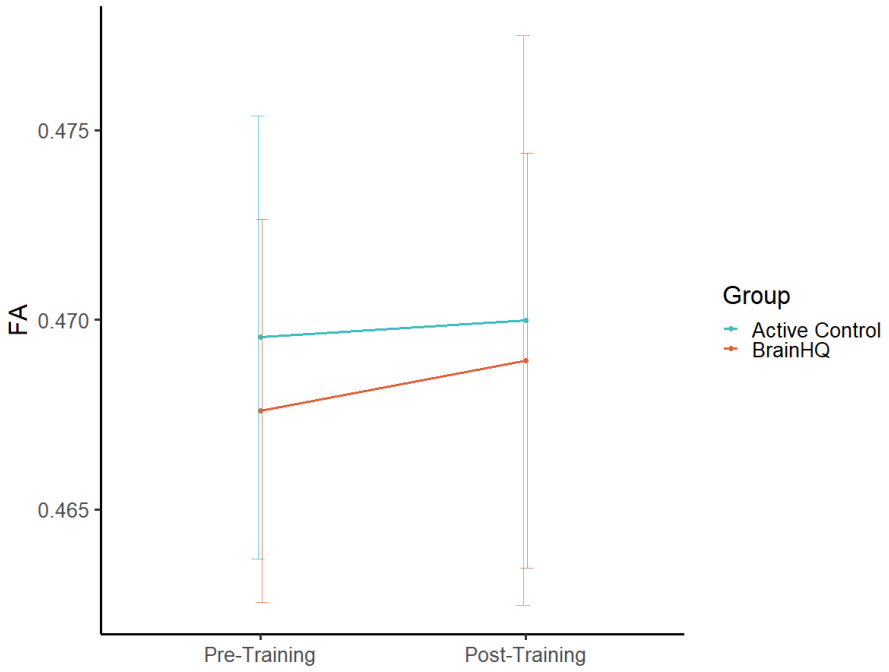


Figure 6.3. Mean FA in the **splenium** for each experimental condition both before and after completing 50 hours of training in either the BrainHQ group or the Active Control group. Error bars represent 95% confidence intervals.

6.2.3 Cingulum

Left Cingulum

We did not find a baseline difference between FA in the left cingulum between groups, $t(100.54) = 0.72$, $p = .48$, however we did observe a baseline difference between research sites, $t(88.52) = 4.06$, $p < .001$, such that FA in the left cingulum was higher for participants at the University of Iowa ($M = .41$, $SD = .02$) compared to those at the University of Texas at Dallas ($M = .39$, $SD = .03$; see Figure 6.4). The 2 x 2 ANOVA revealed no effect of group, $F(1, 103) = 0.03$, $p = .86$, however there was a marginal effect of time, $F(1, 103) = 3.18$, $p = .08$, $\eta_p^2 = .03$ and a marginal interaction between group and time at an alpha of .10, $F(1, 103) = 2.91$, $p = .09$, $\eta_p^2 = .03$. If we look at Figure 6.5, we see an effect of time for the Active Control condition, such that FA in the left cingulum decreased between pre-training ($M = .404$, $SD = .02$) and post-

training (M = .399, SD = .02), $t(54) = 2.41$, p = .02; and no effect of time for the BrainHQ group, where FA in the left cingulum appears to remain stable between pre-training (M = .401, SD = .02) and post training (M = .401, SD = .02), $t(49) = 0.06$, p = .95.

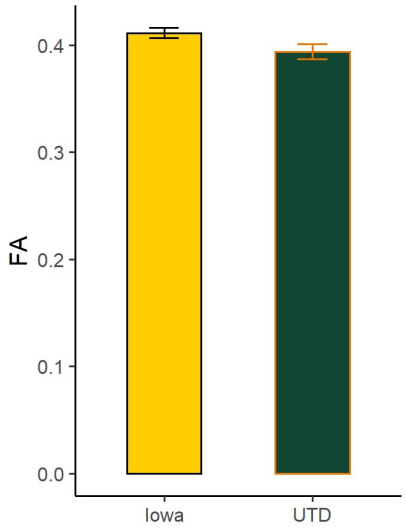


Figure 6.4. Mean baseline FA in the **left cingulum** at each training site. Error bars represent 95% confidence intervals

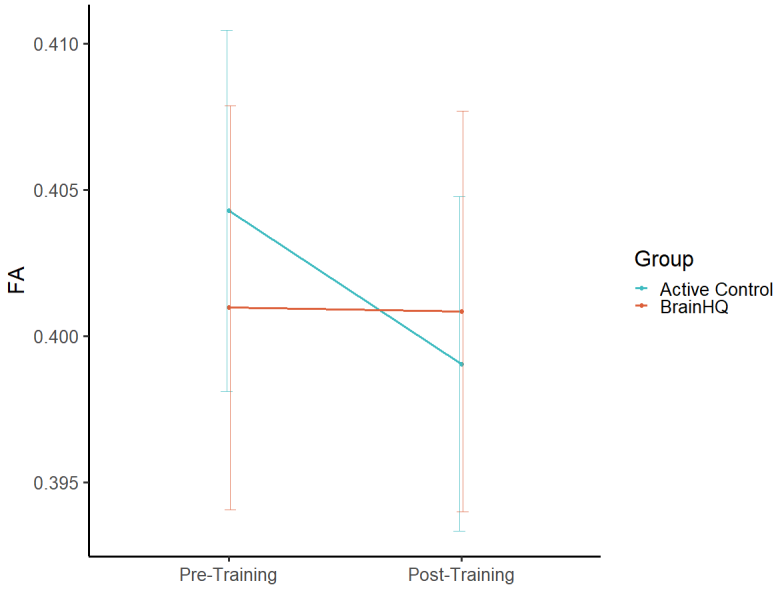


Figure 6.5. Mean FA in the **left cingulum** for each experimental condition both before and after completing 50 hours of training in either the BrainHQ group or the Active Control group. Error bars represent 95% confidence intervals.

It should be noted that neither the marginal main effect of time ($p_{corrected}$ = .69), nor the marginal interaction between group and time ($p_{corrected}$ = .82) survive multiple comparison correction. However, we decided to follow-up on these uncorrected, marginally significant effects with additional analyses. Because we observed a baseline difference in FA in the left cingulum between research sites, we decided to include research site as a variable of interest and perform a 2 (group) x 2 (time) x 2 (site) ANOVA. We found a main effect of site, $F(1, 101) = 14.17$, $p < .001$, $\eta_p^2 = .12$, and a group by time by site interaction, $F(1, 101) = 5.97$, $p = .02$, $\eta_p^2 = .06$ (see Table 6.1 for the full results of the ANOVA).

Table 6.1. Results of a 2 (Group) x 2 (Time) x 2 (Site) ANOVA using FA in the left cingulum as the dependent variable

Effect	df_n	df_d	F	p	η_p^2
Group	1	101	< .001	.99	< .001
Site	1	101	14.17	< .001***	.12
Time	1	101	3.77	.06†	.04
Group*Site	1	101	0.54	.46	.005
Group*Time	1	101	2.87	.09†	.03
Site*Time	1	101	2.86	.09†	.03
Group*Site*Time	1	101	5.97	.02*	.06

Note.† p is significant only at $\alpha = .10$, * $p < .05$, *** $p < .001$

If we look at the effects of group and time for each research site separately (see Figure 6.6) we see a main effect of time at the University of Iowa, $F(1, 51) = 12.15$, $p = .001$, $\eta_p^2 = .19$, but no main effect of group, $F(1, 51) = 0.38$, $p = .54$, and no group by time interaction, $F(1, 51) = 0.52$, $p = .47$. At the University of Texas at Dallas we see a group by time interaction, $F(1, 50) = 5.82$, $p = .02$, $\eta_p^2 = .10$, but no main effects for group, $F(1, 50) = 0.21$, $p = .65$, or time, $F(1, 50) = 0.02$, $p = .89$. At the University of Iowa we see an overall decrease in FA in the left cingulum between pre-training ($M = .411$, $SD = .02$) and post training ($M = .406$, $SD = .02$), $t(52)$

= 3.45, p = .001. At the University of Texas at Dallas, FA in the left cingulum decreases between pre-training (M = .398, SD = .03) and post training (M = .392, SD = .02) for the Active Control group, $t(25)$ = 1.61, p = .12, but increases between pre-training (M = .389, SD = .02) and post-training (M = .395, SD = .03) for the BrainHQ group, $t(25)$ = -1.87, p = .07. The decrease in FA for the Active control group is not quite significant however, and the increase for the BrainHQ group is only marginally significant at an alpha of .10.

Figure 6.6. Mean FA in the **left cingulum** at each training site for each experimental condition both before and after completing 50 hours of training in either the BrainHQ group or the Active Control group. Error bars represent 95% confidence intervals.

Because we observed a group by time interaction at the University of Texas at Dallas site, which had significantly lower FA in the left cingulum, but not at the University of Iowa site, which had significantly higher FA in the left cingulum, we hypothesized that training might be affecting those with lower and higher FA differentially. We separated the sample into three

groups: participants with FA in the bottom 33.33 percentile were placed in a "Low FA" group, participants with FA in the middle 33.33 percentile were placed in a "Middle FA" group, and participants with FA in the top 33.33 percentile were placed in a "High FA" group. We performed another 2 (Group) x 2 (Time) x 2 (FA) ANOVA to look at the interaction between group and time in these three different groups of individuals. We found a significant FA by time interaction, $F(2, 99) = 8.62$, $p < .001$, $\eta_p^2 = .15$ (see Table 6.2 for full results of the ANOVA).

Table 6.2. Results of a 2 (Group) x 2 (Time) x 2 (FA) ANOVA using FA in the left cingulum as the dependent variable

Effect	df_n	df_d	F	p	η_p^2
Group	1	99	0.62	.43	.006
FA	2	99	128.55	< .001***	.72
Time	1	99	3.52	.06†	.03
Group*FA	2	99	0.28	.76	.006
Group*Time	1	99	2.18	.14	.02
FA*Time	2	99	8.62	< .001***	.15
Group*FA*Time	2	99	0.04	.96	.001

Note.† p is significant only at $\alpha = .10$, *** $p < .001$

When we look at the effects of group and time on the low, medium, and high FA groups separately (see Figure 6.7) we see a main effect of time for the low FA group, $F(1, 33) = 4.20$, $p = .049$, $\eta_p^2 = .11$, but no effect of group, $F(1, 33) = 0.03$, $p = .88$, and no group by time interaction, $F(1, 33) = 0.45$, $p = .51$. We see no effect of group, $F(1, 33) = 1.51$, $p = .23$, nor time, $F(1, 33) = 2.58$, $p = .12$, nor a group by time interaction, $F(1, 33) = 1.20$, $p = .28$, for the medium FA group. For the high FA group, we again see a main effect of time, $F(1, 33) = 13.32$, $p < .001$, $\eta_p^2 = .29$, but no effect of group, $F(1, 33) = 0.01$, $p = .91$, and no group by time interaction, $F(1, 33) = 0.64$, $p = .43$. In the low FA group, we see an overall increase in mean FA in the left cingulum across the two training groups between pre-training ($M = .377$, $SD = .01$) and post-training ($M = .382$, $SD = .02$), $t(34) = -2.13$, $p = .04$. Meanwhile, in the high FA group,

overall mean FA in the left cingulum decreases between pre-training (M = .429, SD = .01) and post training (M = .419, SD = .01), $t(34) = 3.75$, $p < .001$.

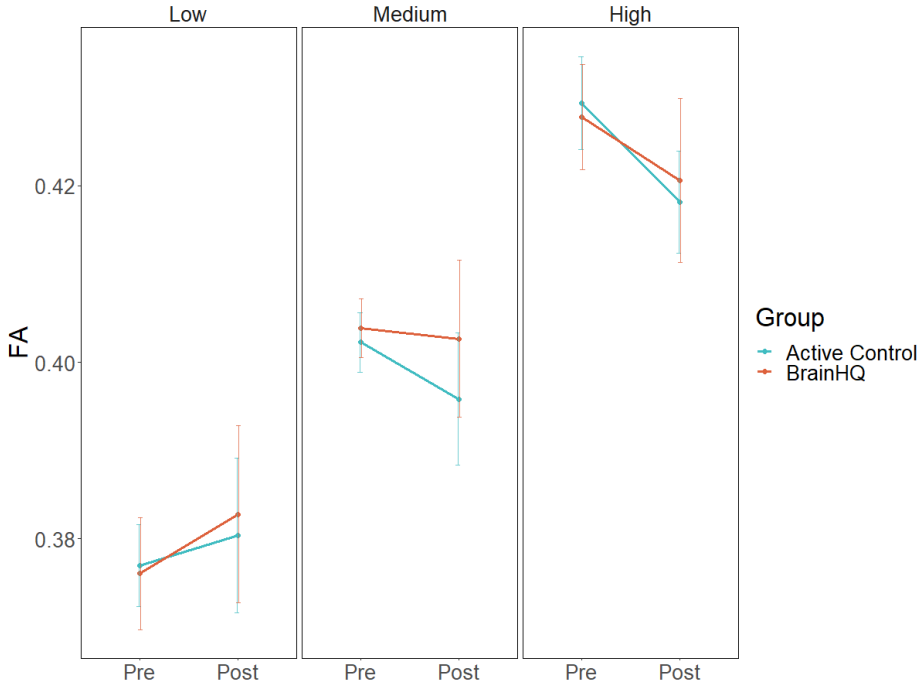


Figure 6.7. Mean FA in the **left cingulum** for the low, medium, and high FA groups for each experimental condition both before and after completing 50 hours of training in either the BrainHQ group or the Active Control group. Error bars represent 95% confidence intervals.

Right Cingulum

We did not find a baseline difference between FA in the right cingulum between groups, $t(101.48) = -0.19$, $p = .85$, however we did observe a baseline difference between research sites, $t(100.58) = 5.09$, $p < .001$, such that FA in the right cingulum was higher for participants at the University of Iowa (M = .394, SD = .02) compared to those at the University of Texas at Dallas (M = .376, SD = .02; see Figure 6.8). The 2 x 2 ANOVA revealed no effect of group, $F(1, 103) = 0.11$, $p = .74$, nor time, $F(1, 103) = 0.45$, $p = .51$, nor an interaction between the two, $F(1, 103) = 0.12$, $p = .73$ (see Figure 6.9).

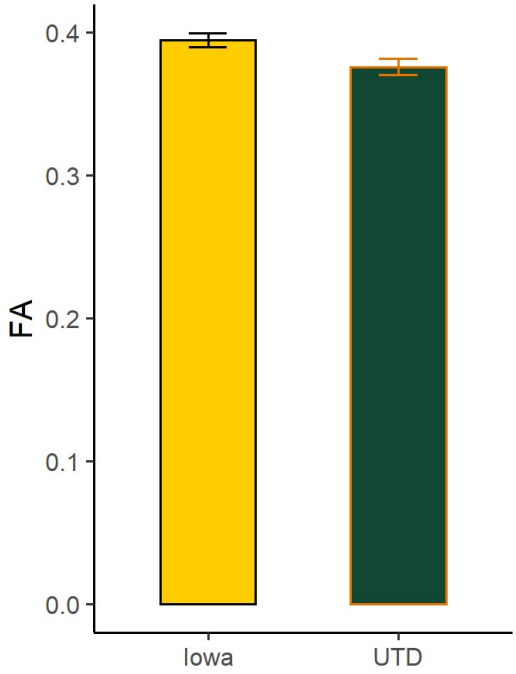


Figure 6.8. Mean baseline FA in the **right cingulum** at each training site. Error bars represent 95% confidence intervals.

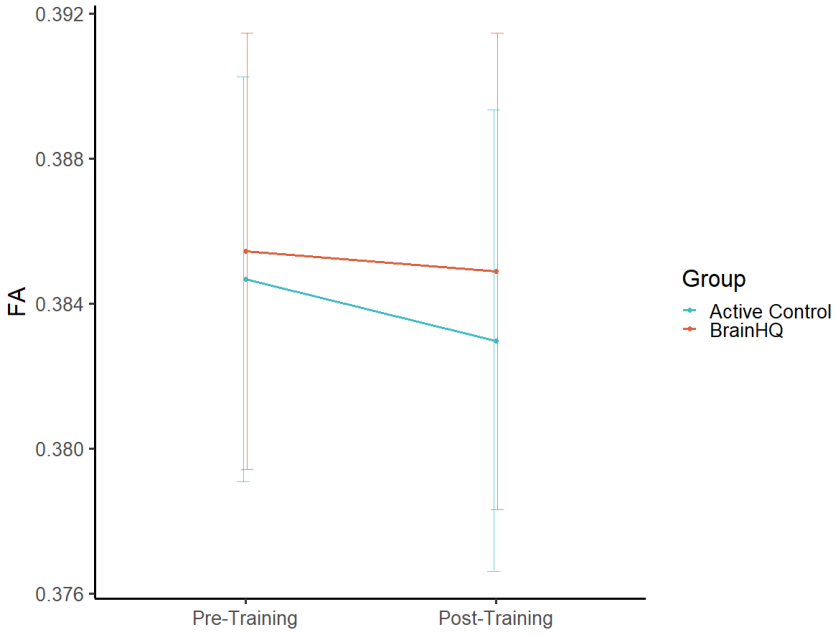


Figure 6.9. Mean FA in the **right cingulum** for each experimental condition both before and after completing 50 hours of training in either the BrainHQ group or the Active Control group. Error bars represent 95% confidence intervals.

6.2.4 Superior Longitudinal Fasciculus (SLF)

Left SLF

We did not find a baseline difference between FA in the left SLF between groups, $t(99.10) = 0.16$, $p = .87$, however we did observe a baseline difference between research sites, $t(99.64) = 9.28$, $p < .001$, such that FA in the left SLF was higher for participants at the University of Iowa ($M = .379$, $SD = .01$) compared to those at the University of Texas at Dallas ($M = .354$, $SD = .01$; see Figure 6.10). We found a main effect of time, $F(1, 103) = 6.97$, $p = .01$, $\eta_p^2 = .06$, but no effect of group, $F(1, 103) = 0.03$, $p = .86$, and no group by time interaction, $F(1, 103) = 0.001$, $p = .97$ (see Figure 6.11). After correcting for multiple comparisons, the main effect of time is only marginally significant at an alpha of .10 ($p_{corrected} = .09$). We see an overall decrease in mean FA in the left SLF between pre-training (M = 3.66, SD = .02) and post-training (M = .365, SD = .02), $t(104) = 2.65$, $p = .009$.

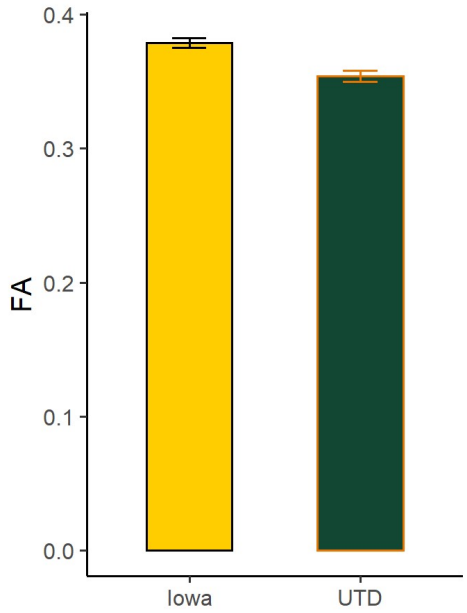


Figure 6.10. Mean baseline FA in the **left SLF** at each training site. Error bars represent 95% confidence intervals.

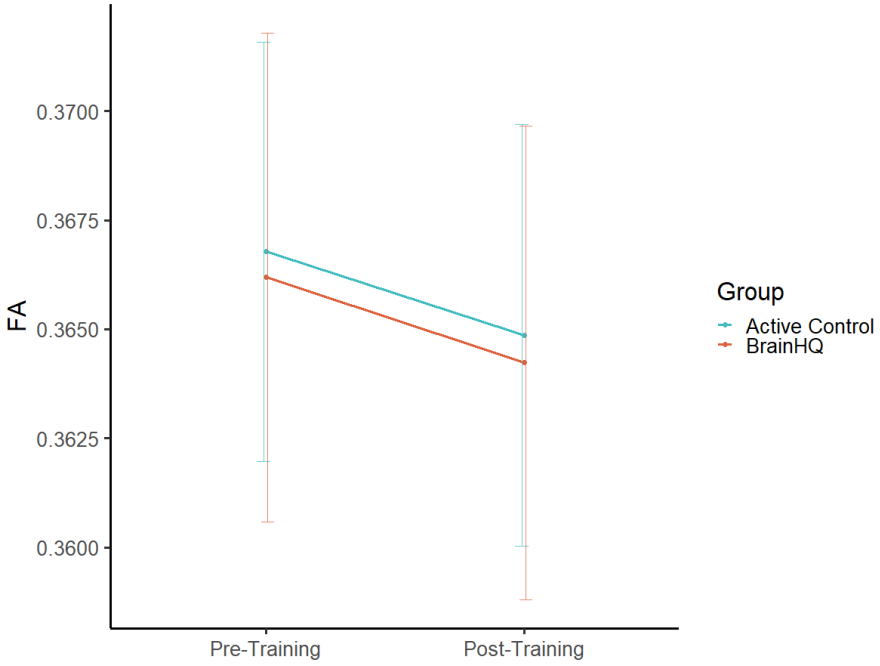


Figure 6.11. Mean FA in the **left SLF** for each experimental condition both before and after completing 50 hours of training in either the BrainHQ group or the Active Control group. Error bars represent 95% confidence intervals.

Right SLF

We did not find a baseline difference between FA in the right SLF between groups, $t(99.74) = 0.56$, $p = .58$, however we did observe a baseline difference between research sites, $t(99.73) = 17.61$, $p < .001$, such that FA in the right SLF was higher for participants at the University of Iowa ($M = .384$, $SD = .01$) compared to those at the University of Texas at Dallas ($M = .341$, $SD = .01$; see Figure 6.12). The 2 x 2 ANOVA revealed no main effect of group, $F(1, 103) = 0.12$, $p = .73$, nor a main effect of time, $F(1, 103) = 0.02$, $p = .89$, nor an interaction between the two, $F(1, 103) = 2.29$, $p = .13$ (see Figure 6.13).

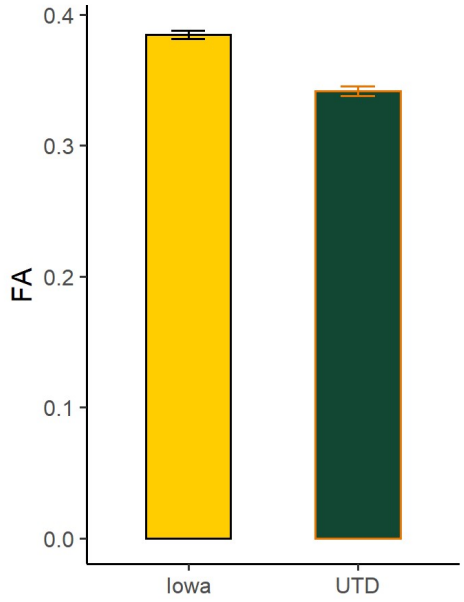


Figure 6.12. Mean baseline FA in the **right SLF** at each training site. Error bars represent 95% confidence intervals.

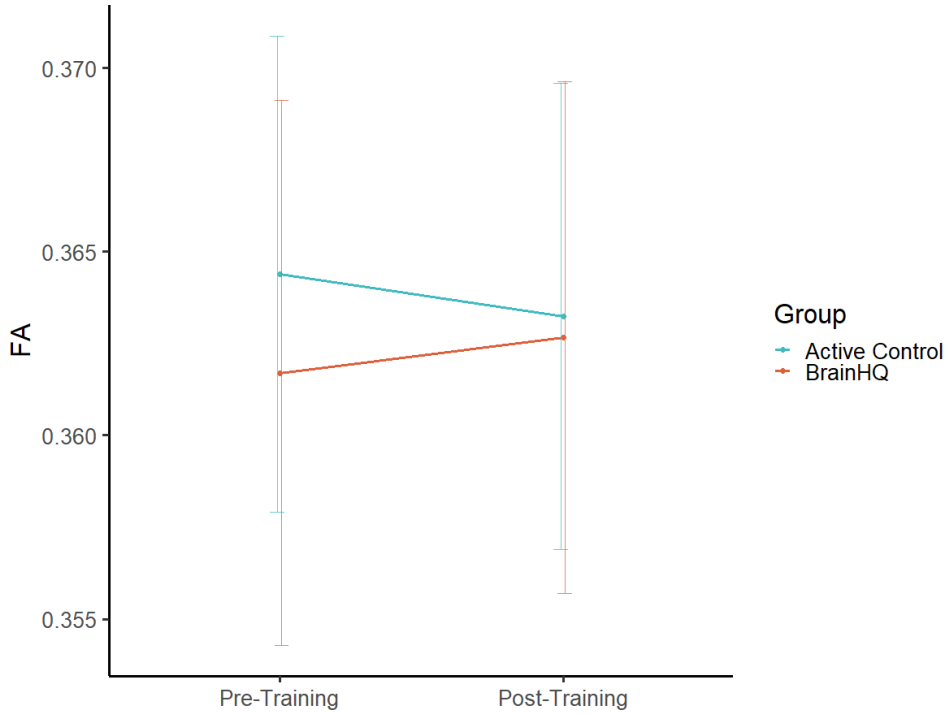


Figure 6.13. Mean FA in the **right SLF** for each experimental condition both before and after completing 50 hours of training in either the BrainHQ group or the Active Control group. Error bars represent 95% confidence intervals.

6.2.5 Uncinate Fasciculus (UF)

Left Uncinate Fasciculus

We did not find a baseline difference between FA in the left UF between groups, $t(101.36) = -0.58$, $p = .56$, however we did observe a baseline difference between research sites, $t(76.84) = -3.61$, $p < .001$, such that FA in the left UF was higher for participants at the University of Dallas at Texas ($M = .354$, $SD = .02$) compared to those at the University of Iowa ($M = .341$, $SD = .01$; see Figure 6.14). The 2 x 2 ANOVA revealed no main effect of group, $F(1, 102) = 0.32$, $p = .58$, nor a main effect of time, $F(1, 102) = 0.12$, $p = .73$, nor an interaction between the two, $F(1, 102) = 0.006$, $p = .94$ (see Figure 6.15).

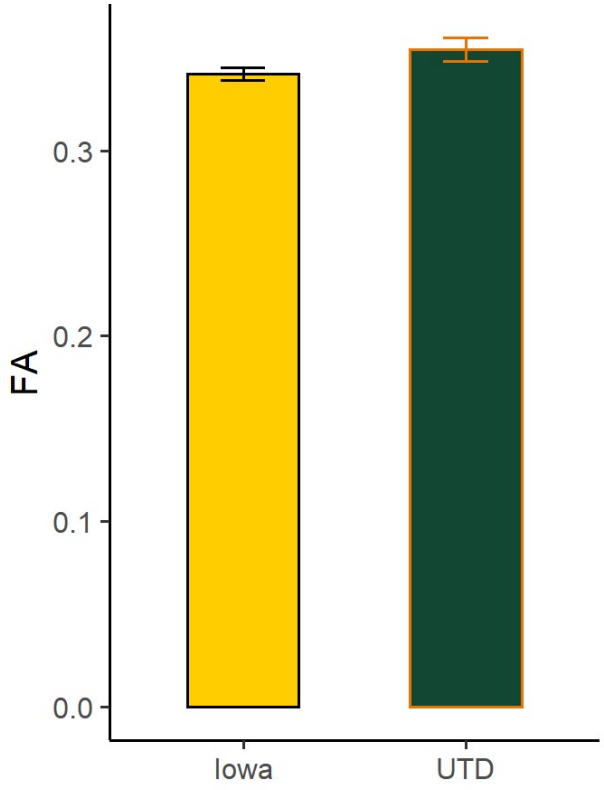


Figure 6.14. Mean baseline FA in the **left UF** at each training site. Error bars represent 95% confidence intervals.

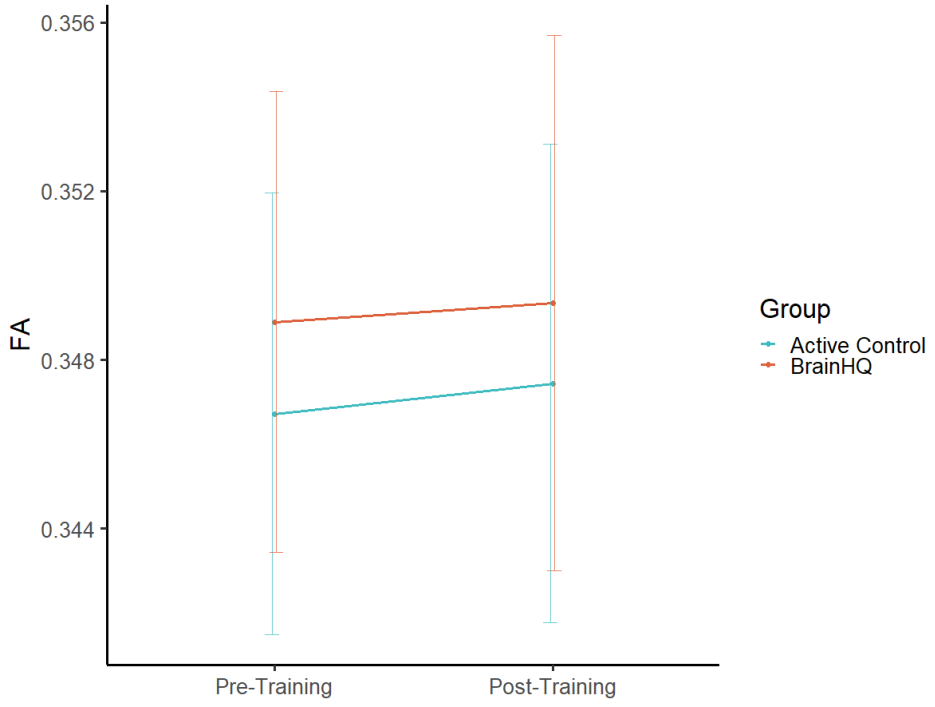


Figure 6.15. Mean FA in the **left UF** for each experimental condition both before and after completing 50 hours of training in either the BrainHQ group or the Active Control group. Error bars represent 95% confidence intervals.

Right Uncinate Fasciculus

We did not find a baseline difference between FA in the right UF between groups, $t(100.29) = 0.77$, $p = .44$, however we did observe a baseline difference between research sites, $t(75.21) = 2.26$, $p = .03$, such that FA in the right UF was higher for participants at the University of Iowa ($M = .351$, $SD = .01$) compared to those at the University of Texas at Dallas ($M = .342$, $SD = .02$; see Figure 6.16). The 2 x 2 ANOVA revealed no main effect of group, $F(1, 102) = 0.08$, $p = .78$, nor a main effect of time, $F(1, 102) = 1.59$, $p = .21$, nor an interaction between the two, $F(1, 102) = 1.43$, $p = .24$ (see Figure 6.17).

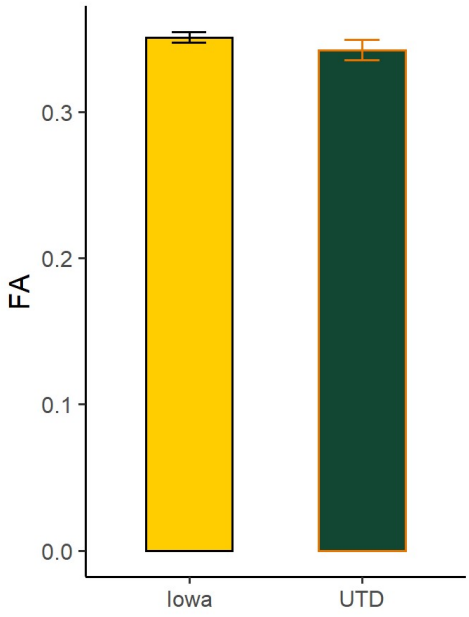


Figure 6.16. Mean baseline FA in the **right UF** at each training site. Error bars represent 95% confidence intervals.

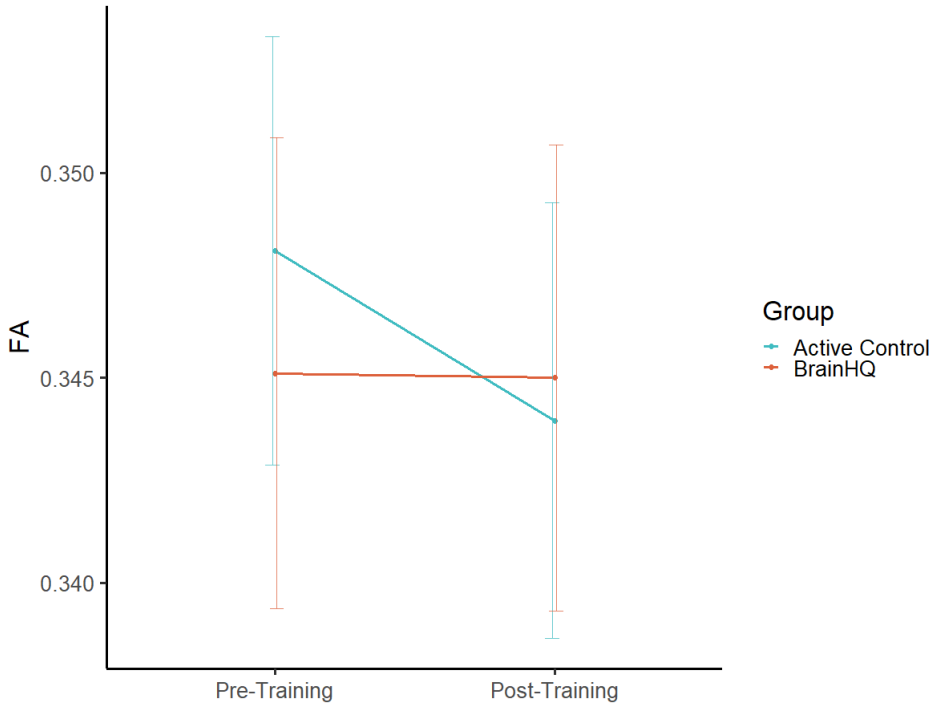


Figure 6.17. Mean FA in the **right UF** for each experimental condition both before and after completing 50 hours of training in either the BrainHQ group or the Active Control group. Error bars represent 95% confidence intervals.

6.2.6 Fornix

Fornix

We did not find a baseline difference between FA in the fornix between groups, $t(101.26) = 1.59$, $p = .11$, however we did observe a baseline difference between research sites, $t(99) = 2.60$, $p = .01$, such that FA in the fornix was higher for participants at the University of Iowa ($M = .316$, $SD = .02$) compared to those at the University of Texas at Dallas ($M = .306$, $SD = .02$; see Figure 6.18). The 2 x 2 ANOVA revealed no main effect of group, $F(1, 103) = 2.48$, $p = .12$, nor a main effect of time, $F(1, 103) = 2.75$, $p = .10$, nor an interaction between the two, $F(1, 103) = 0.13$, $p = .72$ (see Figure 6.19).

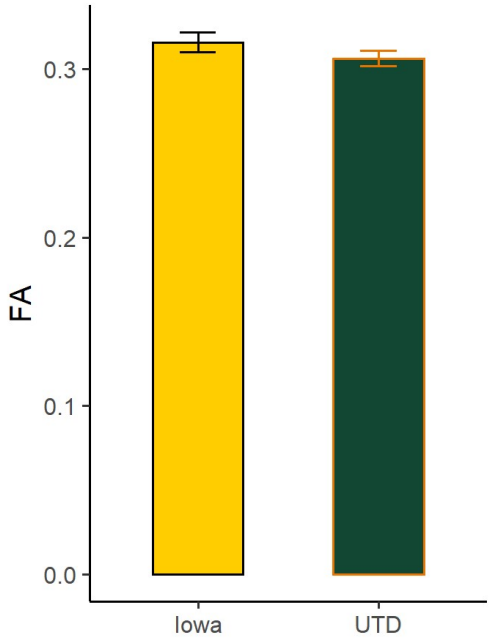


Figure 6.18. Mean baseline FA in the **fornix** at each training site. Error bars represent 95% confidence intervals.

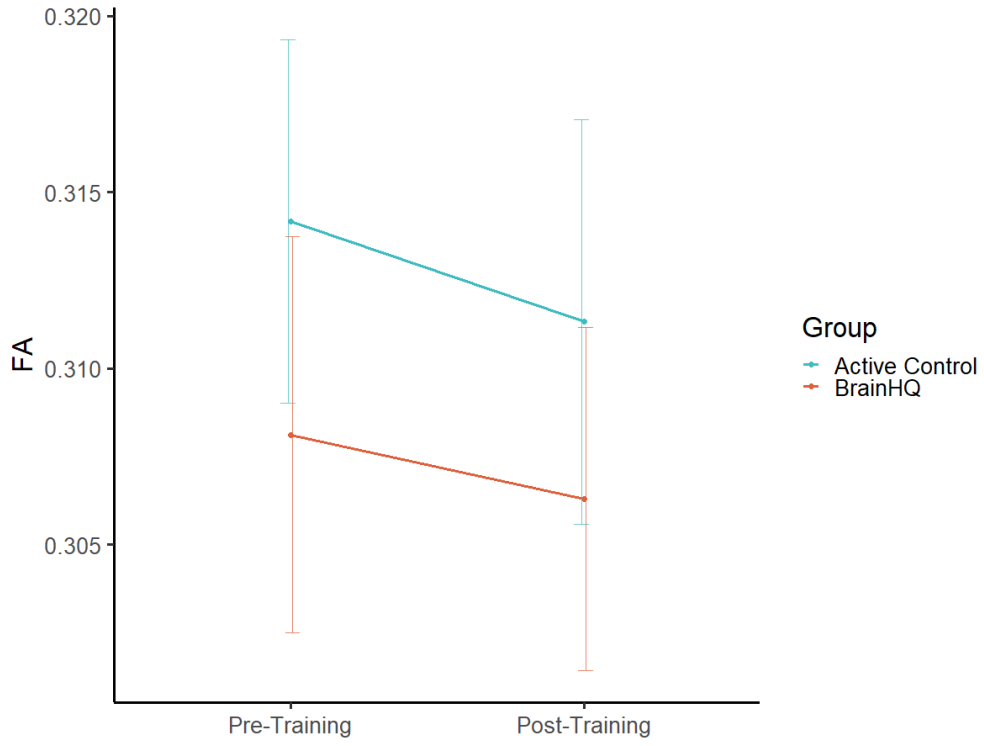


Figure 6.19. Mean FA in the **fornix** for each experimental condition both before and after completing 50 hours of training in either the BrainHQ group or the Active Control group. Error bars represent 95% confidence intervals.

6.3 Behavioral Measures of Cognition

We created construct scores for our three cognitive outcomes of interest – processing speed, memory, and executive function. We again performed t-tests to examine any baseline differences in these outcomes between research sites or training groups. We then examined the group by time interactions on each of these outcomes with another series of 2 x 2 ANOVAs. Any main effects or interactions significant at $p < .05$, or at $p < .10$, were followed up with pairwise t-tests using the FDR method to correct for multiple comparisons.

6.3.1 Processing Speed

We created a processing speed construct score for each participant at each time point by averaging across the z-scores for the digit symbol substitution task (DSST), the pattern

comparison task, and the letter comparison task. There was no baseline difference in processing speed between sites, $t(101.45) = 1.54$, $p = .13$. There was a marginally significant baseline difference in processing speed between training groups however, $t(102.84) = 1.95$, $p = .05$, such that the Active Control group showed higher processing at pre-training ($M = -0.04$, $SD = 0.73$) than the BrainHQ group ($M = -0.31$, $SD = 0.67$; see Figure 6.20). The 2 x 2 ANOVA showed no main effect of group, $F(1, 103) = 1.13$, $p = .29$. There was a main effect of time though, $F(1, 103) = 42.19$, $p < .001$, $\eta_p^2 = .29$, and a significant group by time interaction, $F(1, 103) = 5.00$, $p = .03$, $\eta_p^2 = .05$.

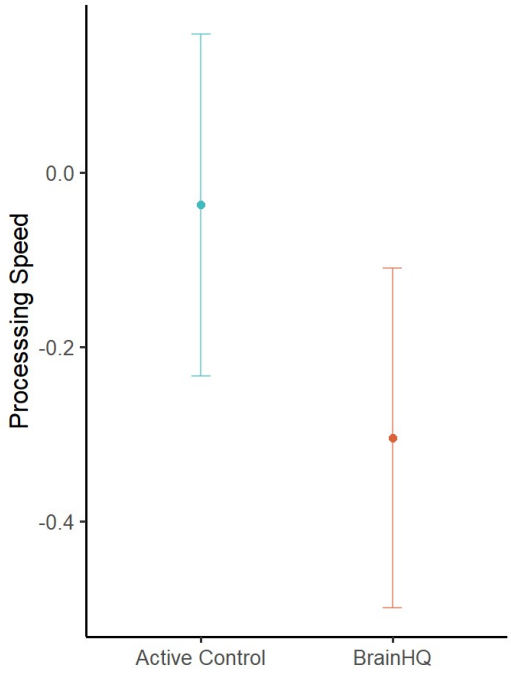


Figure 6.20. Mean baseline **processing speed** for each training group. Error bars represent 95% confidence intervals.

After correcting for multiple comparisons, the main effect of time ($p_{corrected} < .001$) remained significant, but the group by time interaction ($p_{corrected} = .08$) became only marginally significant at an alpha of .10. We can see from Figure 6.21 that both the Active Control group

(M_{pre} = -0.04, SD_{pre} = 0.73, M_{post} = 0.18, SD_{post} = 0.83), $t(54)$ = -3.14, p = .003, and the BrainHQ group (M_{pre} = -0.31, SD_{pre} = 0.69, M_{post} = 0.15, SD_{post} = 0.88), $t(49)$ = -5.92, $p < .001$, showed increased processing speed from pre-training to post-training. This increase was larger for the BrainHQ group, which showed an improvement of 0.66 SD, than for the Active Control group, which showed an improvement of 0.30 SD.

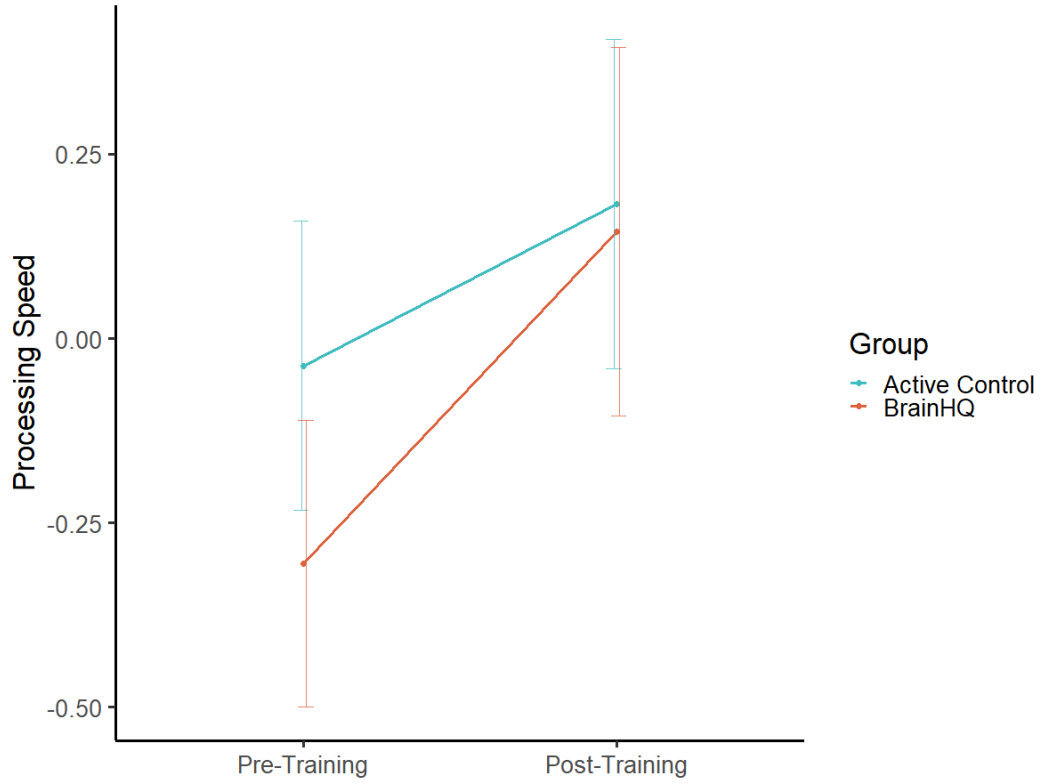


Figure 6.21. Mean **processing speed** for each experimental condition both before and after completing 50 hours of training in either the BrainHQ group or the Active Control group. Both groups show an increase in processing speed, however the increase is larger for the BrainHQ group. Error bars represent 95% confidence intervals.

6.3.2 Memory

To create a memory construct score, we first created a story recall task (SRT) composite score by adding total recall, long-term retrieval, long term storage, short-term recall, consistent

long-term retrieval, cued recall, multiple choice, and 30-minute delay, and then subtracting random long-term retrieval, number of reminders, number of intrusions, number of cued recall intrusions, and number of 30-minute delay intrusions (see Buschke & Fuld, 1974 for SRT scoring information). We then reverse coded the reaction time measures for the face name task and the visual short-term memory task (VSTM) so that more positive numbers would relate to better performance. We then averaged across the z-scores for the SRT composite score, the reverse-coded face name reaction times, accuracy on the face name task, the reverse-coded VSTM reaction times, and accuracy on the VSTM task to create the memory construct score.

We found no baseline difference in memory between training groups, $t(102.95) = 0.59$, $p = .56$; but we did find a marginally significant baseline difference between research sites, $t(102.60) = 1.69$, $p = .09$, such that memory is higher at baseline at the University of Iowa ($M = -0.02$, $SD = 0.5$) compared to the University of Texas ($M = -0.18$, $SD = 0.46$; see Figure 6.22). The 2 x 2 ANOVA showed a significant main effect of time, $F(1, 103) = 27.46$, $p < .001$, $\eta_p^2 = .21$, but no main effect of group, $F(1, 103) = 0.05$, $p = .82$, and no group by time interaction, $F(1, 103) = 0.76$, $p = .38$. The main effect of time survived multiple comparison correction ($p_{corrected} < .001$). In Figure 6.23 we can observe an overall increase in memory of 0.43 SD from pre-training ($M = -0.10$, $SD = 0.49$) to post-training ($M = 0.11$, $SD = 0.53$) across both training groups, $t(104) = -5.21$, $p < .001$. This increase was again larger for the BrainHQ group, which showed an improvement of 0.52 SD, than the Active Control group, which showed an improvement of 0.35 SD.

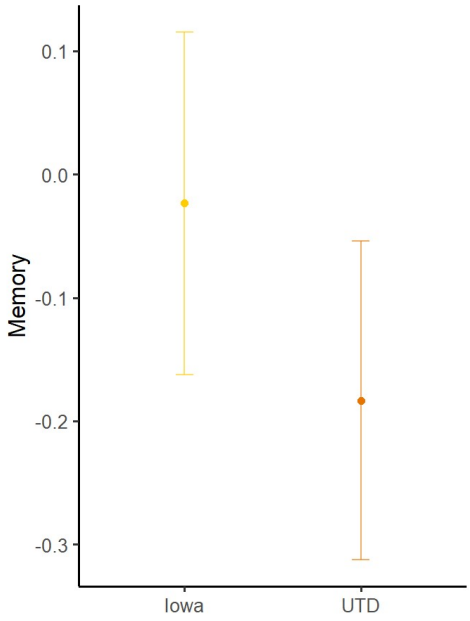


Figure 6.22. Mean baseline **memory** for each research site. Error bars represent 95% confidence intervals.

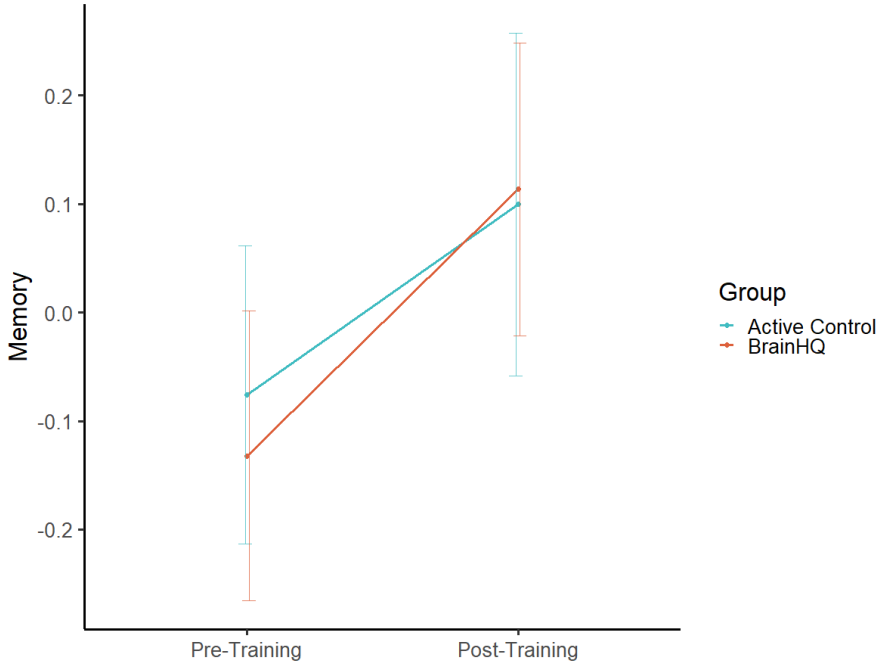


Figure 6.23. Mean **memory** for each experimental condition both before and after completing 50 hours of training in either the BrainHQ group or the Active Control group. A significant increase in memory can be observed for both training groups. Error bars represent 95% confidence intervals.

6.3.3 Executive Function

To create an executive function construct score we first created an updating cost from the n-back task by subtracting reaction time on the single block of the task (where participants do not have to update any items in their working memory) from reaction time on the dual block of the task (where participants must continuously update two different items in their working memory). We also calculated this cost for accuracy by subtracting accuracy on the dual block from accuracy on the single block. We then reverse coded both costs so that positive values relate to better performance.

Next, we calculated an inhibition cost by subtracting reaction time during the congruent trials of the flanker task from reaction time during the incongruent trials of the flanker task. We calculated this cost for accuracy as well by subtracting accuracy on the incongruent trials by accuracy on the congruent trials. Both costs were again reverse coded.

Finally, we calculated a global switch cost by subtracting reaction time on the single task blocks of the task switching task from reaction time on the dual task blocks of the task switching task. We calculated this cost for accuracy as well by subtracting accuracy on the dual task blocks from accuracy on the single task blocks. We again reverse coded both costs. We then averaged across the z-scores for all reverse-coded cost measures (both accuracy and reaction time costs for updating, inhibition, and switching – the three executive functions described by Miyake et al, 2000) to create our executive function construct score.

We didn't observe any baseline differences in executive function between training groups, $t(87.94) = 0.65$, $p = .52$, or research sites, $t(101.35) = 0.91$, $p = .36$. We did not find a main effect of group, $F(1, 103) = 0.53$, $p = .47$. We did see a marginal effect of time, $F(1, 103) =$

2.98, $p = .09$, $\eta_p^2 = .03$, and a significant group by time interaction, $F(1, 103) = 7.47$, $p = .007$, $\eta_p^2 = .07$. The group by time interaction remains significant after correcting for multiple comparisons ($p_{corrected} = .02$), but the main effect of time does not ($p_{corrected} = .26$). We can see from Figure 6.24 that the Active Control group showed a decrease in executive function between pre-training($M = -0.0002$, $SD = 0.38$) and post-training ($M = -0.04$, $SD = 0.41$) and the BrainHQ group showed an increase in executive function between pre-training ($M = -0.06$, $SD = 0.53$) and post-training ($M = 0.13$, $SD = 0.49$). The decrease of 0.11 SD in executive function displayed by the Active Control group was not significant, $t(54) = 0.76$, $p = .45$, but the increase of 0.36 SD shown by the BrainHQ group was significant, $t(49) = -2.95$, $p = .005$.

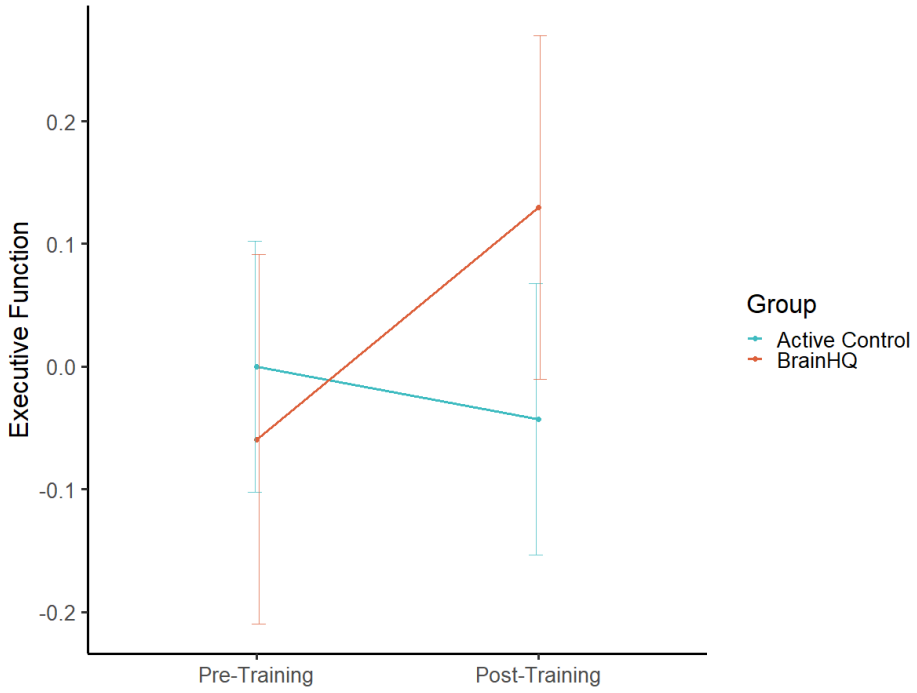


Figure 6.24. Mean **executive function** for each experimental condition both before and after completing 50 hours of training in either the BrainHQ group or the Active Control group. The BrainHQ group shows a significant increase in executive function, and the Active Control group shows a non-significant decrease. Error bars represent 95% confidence intervals.

6.4 Brain-Behavior Correlations

We decided to look at brain-behavior correlations in two different ways. We first decided to look at correlations between baseline FA in the white matter tracts and baseline performance on the cognitive constructs hypothesized to be related to those tracts. Second, we subtracted all pre-training values for white matter FA and cognition for participants in the BrainHQ training group from their post-training values to calculate the change in time for each measure. We then looked at the correlations between change in white matter FA and change in behavioral performance on the cognitive tasks for participants in the BrainHQ group only for tracts that showed a significant (before multiple comparison correction and at alpha of .10) relationship with cognition at baseline. We computed Pearson's product-moment correlations in R to examine these relationships.

6.4.1 Baseline Correlations

We hypothesized that FA in the genu would correlate with processing speed and executive function. We find a marginally significant correlation between baseline FA in the genu and baseline processing speed, $r(103) = .19$, $p = .05$ (see Figure 6.25). This correlation does not survive multiple comparison correction however ($p_{corrected} = .79$). We do not see a correlation between baseline FA in the genu and baseline executive function, $r(103) = .15$, $p = .13$.

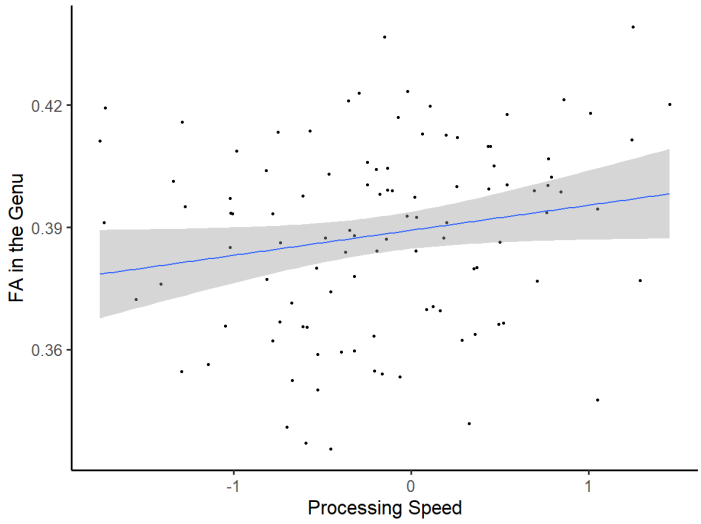


Figure 6.25. Relationship between baseline FA in the genu and baseline processing speed.

We hypothesized that FA in the cingulum would correlate with processing speed, executive function, and memory. We find a marginally significant correlation between baseline FA in the left cingulum and baseline processing speed, $r(103) = .18$, $p = .06$, $p_{corrected} = .95$ (see Figure 6.26), and a significant correlation between baseline FA in the right cingulum and baseline processing speed, $r(103) = .20$, $p = .04$, $p_{corrected} = .64$ (see Figure 6.27). Neither relationship survives multiple comparison correction however. We did not see a correlation between baseline FA in the left cingulum and executive function, $r(103) = .02$, $p = .87$, nor between baseline FA in the right cingulum and executive function, $r(103) = .02$, $p = .87$. We did not find a relationship between baseline FA in the left cingulum and baseline memory either, $r(103) = .12$, $p = .22$, nor between baseline FA in the right cingulum and baseline memory, $r(103) = .08$, $p = .43$.

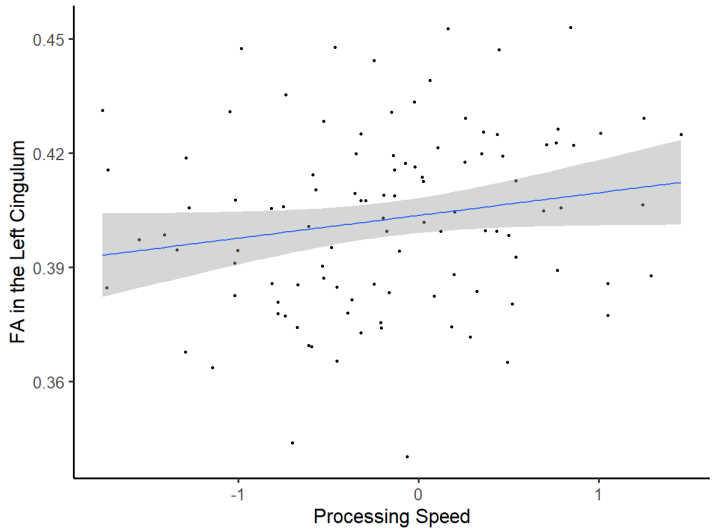


Figure 6.26. Relationship between baseline FA in the left cingulum and baseline processing speed.

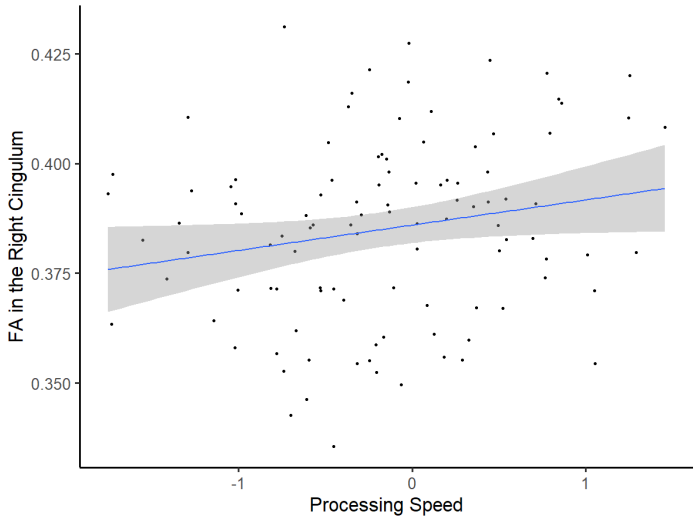


Figure 6.27. Relationship between baseline FA in the right cingulum and baseline processing speed.

We hypothesized that FA in the SLF would correlate with processing speed and executive function. We did not find a correlation between baseline FA in the left SLF and baseline processing speed, $r(103) = .10$, $p = .30$, nor between baseline FA in the right SLF and

baseline processing speed, $r(103) = .11$, $p = .25$. We also did not find a correlation between baseline FA in left SLF and executive function, $r(103) = .09$, $p = .38$, nor between baseline FA in the right SLF and executive function, $r(103) = .10$, $p = .29$.

We hypothesized that FA in the uncinate fasciculus and FA in the fornix would correlate with memory. We don't find a correlation between baseline FA in the left uncinate fasciculus and baseline memory, $r(102) = .02$, $p = .82$, nor between baseline FA in the right uncinate fasciculus and memory, $r(103) = -.04$, $p = .63$. Finally, we do see a correlation between baseline FA in the fornix and baseline memory, $r(103) = .21$, $p = .04$ (see Figure 6.28); but again, this relationship does not survive multiple comparison correction, $p_{corrected} = .53$.

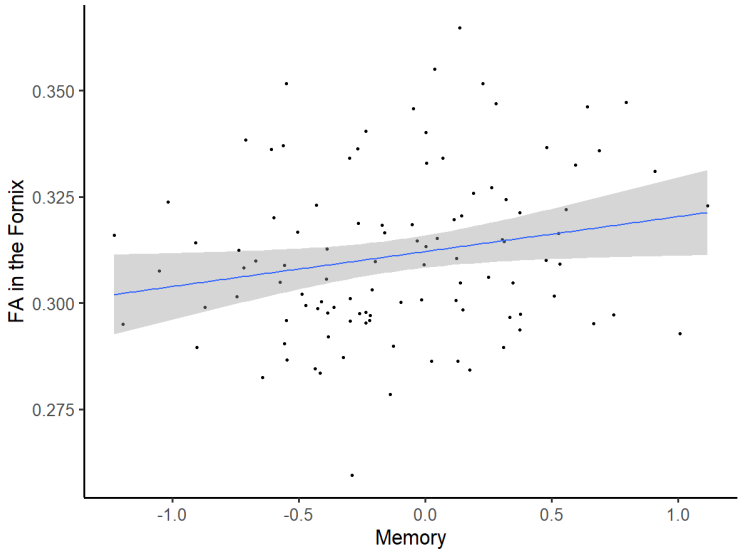


Figure 6.28. Relationship between baseline FA in the fornix and baseline memory.

6.4.2 Correlations Between Change Scores

The genu showed a marginally significant relationship with processing at baseline before correcting for multiple comparisons, but we did not observe a correlation between change in FA

in the genu and change in processing speed for individuals in the BrainHQ group, $r(48) = .03$, $p = .83$. The left and right cingulum showed a relationship with processing speed before multiple comparison correction as well, but we did not find a correlation between change in processing speed and change in FA in the left cingulum, $r(48) = -.07$, $p = .61$, or right cingulum, $r(48) = -.05$, $p = .71$. We observed a correlation between FA in the fornix and memory at baseline (before multiple comparison correction). We also found a correlation between change in FA in the fornix and change in memory for participants in the BrainHQ group, $r(48) = .36$, $p = .01$, and this relationship does survive correction for multiple comparisons, $p_{corrected} = .04$ (see Figure 6.29).

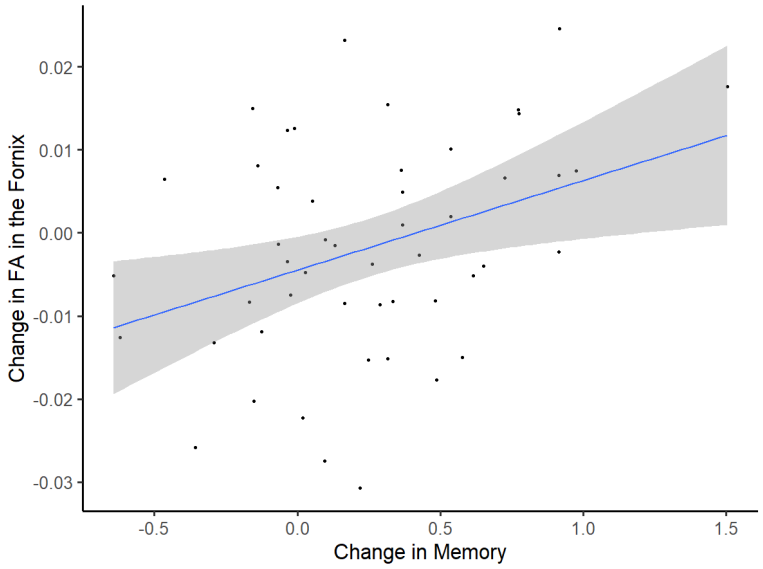


Figure 6.29. Relationship between change in FA in the fornix and change in memory performance for the BrainHQ group.

CHAPTER 7

DISCUSSION

There have been very few studies looking at cognitive training related changes to white matter in older adults. This project analyzed data from a Phase II randomized controlled clinical trial that significantly improves on past studies. The study by Engvig and colleagues (2012) included 41 older adult participants, the studies by Lövdén and colleagues (2010) and Antonenko and colleagues (2016) both only included 25 participants. The current sample consists of 105 older adult participants, giving us far greater power to detect small and medium sized effects. Engvig and colleagues (2012) and Lövdén and colleagues (2010) both used passive control conditions, allowing for evaluation of training-related change to practice effects. Antonenko and colleagues (2016) did not use any control condition, therefore their results do not allow us to dissociate between training effects and practice effects. The BETTER study used an extremely stringent and well-matched active control condition, in which participants played casual games that involved attention, memory, and reasoning. In addition, the current study uses a deterministic algorithm (Yeh at al., 2013) to estimate the specific white matter tracts of interest for each participant at each time point. This method should increase the accuracy and reliability of our measurements compared to other approaches that use generic ROIs or perform analyses on skeletonized tracts that represent a space common to all participants in the sample.

We did not find any strong evidence to support the first hypothesis that white matter FA would increase after 50 hours of computerized cognitive training. We did see a marginal (and uncorrected) effect in the left cingulum, where FA decreased for the active control condition, but remained stable for the BrainHQ group. White matter in the cingulum has been shown to support

all three of our cognitive outcomes of interest – processing speed, memory, and executive function (Bendlin et al., 2010; Kraus et al., 2007). When we looked at research sites separately, we found an overall decrease in FA in the left cingulum at the University of Iowa (whose participants showed higher FA in this area); and we found a significant group by time interaction at The University of Texas at Dallas (whose participants showed relatively lower FA in this area at baseline), such that FA increased after 50 hours of training in BrainHQ, but not after 50 hours of playing casual online games. To evaluate if the group by time interactions related to site differences, but not to individual differences in baseline FA, we divided participants into three groups (low, medium, and high) based on their baseline FA in the left cingulum. We found that, irrespective of the type of training, the low FA group showed a significant increase in FA after training, but the high FA group showed a decrease in FA. It is therefore possible that cognitive training effects individuals differentially based on pre-existing conditions, such as baseline white matter integrity. Computerized cognitive training may be more beneficial for individuals with lower white matter integrity, than those who already have high white matter integrity. Moreover, our results suggest that the significant effects of BrainHQ training on increased FA in left cingulum in the Dallas site cannot be attributed to lower FA at baseline. Given that neither age nor education were significantly different across the sites, we cannot attribute the significant results from Dallas site to these variables. It is however possible that other lifelong factors or experiential factors may influence these site differences. Our immediate conclusion is that BrainHQ training has positive impact on white matter integrity of the left cingulum, a region previously implicated in videogame learning (Ray et al., 2017), but only for the Dallas site.

We did find evidence to support the second hypothesis. Participants who completed 50 hours of BrainHQ training showed an increase in processing speed above and beyond that shown by participants who played casual online games for 50 hours (although it should be noted that this effect was only significant at an alpha of .10 after correcting for multiple comparisons). Both groups showed a significant increase in memory after 50 hours of training. Participants also showed increased executive function after 50 hours of BrainHQ training, but not after 50 hours of casual video game training. We therefore provide evidence that completing 50 hours of computerized cognitive training using BrainHQ can improve processing speed and executive function above and beyond 50 hours of training in a stringent active control condition.

We found some evidence to support the third hypothesis that changes in white matter FA correlate with changes in behavioral performance on cognitive tasks. To evaluate these relationships, we first established the tracts that showed correlations with cognition at baseline. This allowed us to have a theorized hypothesis about change and restrict our analyses to a limited number of correlations. Our working hypothesis is that only if the white matter integrity of a tract and cognition are related at baseline, we would expect coupling of these changes esp. for BrainHQ group. We found that baseline FA in the genu and cingulum were correlated with baseline processing speed, and that baseline FA in the fornix was correlated with baseline memory. Although these relationships do not survive correction for multiple comparison, we followed them up by looking at correlations between changes in FA in these regions and changes in performance in their associated cognitive domains. We found that increases in FA in the fornix were significantly associated with gains in memory in the BrainHQ group. Change in white matter integrity in the fornix and change in memory performance was also reported by

Antonenko and colleagues (2016), who argue that this relationship provides further support for the role of the fornix in memory and learning.

The BETTER study addresses many of the methodological concerns mentioned by Simons and colleagues (2016) and adheres to the "gold standards" outlined in their paper. The BETTER study still suffers from several limitations, however. We observed differences in baseline FA in many regions between training sites. One explanation for this could be a sampling bias between the two recruitment locations such that a large city like Dallas could provide a more diverse sample, whereas a smaller college town like Iowa City may provide a more homogenous sample. We did not find any baseline differences in our demographic variables, although we did not look at race or ethnicity, nor did we look at individual differences in health variables in this paper. These may be important variables to explore in future analyses that could provide some insight into whether a sampling bias may be the cause for the baseline differences observed in FA.

Another explanation for the baseline differences in FA between sites may have to do with the different MRI scanners used at each site, and the differing DTI scan parameters used for each scanner. We attempted to match parameters as closely as possibly between research sites, but as you can see in the Methods chapter, there are still numerous differences between the DTI scan parameters for each site. This limitation may be hard to overcome in future studies where data collection is occurring at multiple research sites, as MRI scanners are extremely expensive, and institutions are limited by the equipment currently available. If possible though, future multi-site studies should attempt to use similar scanners, or at the very least match the parameters of their DTI scans as closely as possible.

The framework by Lövdén and colleagues (2010) mentioned in Chapter 1 suggests that cognitive plasticity can only occur when behavioral changes in cognition are supported by an underlying structural change in the brain. It is therefore perplexing to observe behavioral changes in our sample without any accompanying changes to white matter integrity. It is possible that we focused on the wrong white matter tracts, perhaps a whole brain approach like TBSS would be more appropriate. Perhaps the resolution of our diffusion data was not sufficient to detect subtle changes in white matter structure, or perhaps DTI in general is not sensitive or reliable enough to detect these changes. Future studies should also look at gray and white matter volume, as well as functional connectivity, in addition to DTI.

Future studies should also examine different cognitive training paradigms. As mentioned in Chapter 1, video games have been studied as one promising candidate for cognitive training, as they are designed to be engaging and often involve many of the cognitive skills that are vulnerable to age-related decline (Baniqued et al., 2013). There are many kinds of video games, but strategy games, which have shown to improve task switching, working memory, and executive function (Basak et al., 2008; Glass et al., 2013), may hold particular promise as a training tool for older adults who suffer declines in these cognitive domains.

In summary, we were not able to show that computerized cognitive training improved white matter structure in the brain. We were able to show that it improved behavioral performance in processing speed, memory, and executive function – three important cognitive components that are known to decline with age. We did not show that these behavioral changes in cognition were supported by underlying structural changes in the brain. However, we did find further evidence to support the relationship between the fornix and memory, which has been

shown in past studies. More research is needed to understand the complex relationship between brain and behavior. In addition, we did show some evidence that training may affect individuals differentially based on pre-existing white matter integrity. Future studies should consider individual differences such as these, and incorporate them as variables of interest when building future theoretical models.

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BIOGRAPHICAL SKETCH

Nicholas Ray was born in Houston, Texas in 1989. He graduated from North Allegheny High School in Pittsburgh, Pennsylvania in 2007. His plunge into research began as an undergraduate research assistant at the Pennsylvania State University in Dr. Judith Kroll's laboratory at the Center for Language Science (CLS). Upon graduation he was offered a position as lab manager and research technician for the CLS, where he worked for two years under the tutelage of Dr. Giuli Dussias. During his time with the CLS, he collected data from many participants and learned the basics of several cognitive neuroscience techniques, including eye tracking, EEG (specifically ERP), and fMRI. He was co-author on one of the ERP projects in which he was involved, and presented the data for said project at the 2013 Psychonomic Society Annual Meeting.

It was at the CLS that he was introduced to the concept of Bilingual Advantage, a theory proposing that bilingual individuals incur cognitive benefits from the complex processes involved with maintaining multiple languages at once (i.e., constantly switching between languages; inhibiting one or more languages in order to produce another; etc.). While it might not seem directly connected at first, the theory of Bilingual Advantage started him down a path that would eventually lead to his interest in cognitive training. If speaking multiple languages could potentially strengthen connections in the brain and improve cognitive performance, then why couldn't other mentally taxing activities − like playing video games for example?

It was this question that brought Nicholas to The University of Texas at Dallas (UTD) to study under Dr. Chandramallika Basak at the Center for Vital Longevity. Dr. Basak has published several important papers looking specifically at the effects of strategy video game

training on older adult cognition. Since joining Dr. Basak's laboratory as a PhD candidate, Nicholas has involved himself in a multitude of projects. He spent much of his time learning to perform diffusion tensor imaging (DTI) analyses, and performed the DTI analysis for a study published in *Psychophysiology* in 2016. He is first author on a project evaluating the relationship between white matter integrity (as measured by DTI), cognition, and two types of video game learning (action and strategy). Preliminary data for this project were presented at the 2016 Cognitive Neuroscience Society Annual Meeting, and the final results were published in *Restorative Neurology and Neuroscience* in 2017. He also presented preliminary data for a project looking at strategy game training related white matter changes in older adults at the Cognitive Neuroscience Society Annual Meeting in March 2017. For the past two years Nicholas has managed a NIH-funded phase II clinical trial examining the effects of cognitive training on older adults' cognition. Many of the details of this study are presented here in this dissertation.

In addition to research, Nicholas has continually taken classes since enrolling at UTD. These classes have covered a wide range of important topics (statistics, cognitive psychology, memory, neuroanatomy, etc.) that have helped to shape his current understanding of the field of cognitive neuroscience. He has also continually served as a teaching assistant since enrolling at UTD. He has assisted mostly with Experimental Projects in Psychology, where students are tasked with designing, implementing, and writing up a simple behavioral study. As such, his responsibilities included grading and providing feedback for writing assignments, meeting with students in and out of class (to discuss various topics, such as experimental design and data analysis), and guest lecturing. He has also assisted with Cognitive Psychology, where he met with students, led review sessions, proctored and graded exams, and provided guest lectures.

CURRICULUM VITAE

NICHOLAS R. RAY

The Center for Vital Longevity
School of Behavioral & Brain Sciences
The University of Texas at Dallas

EDUCATION

The University of Texas at Dallas, Richardson, Texas
Ph.D. in Cognition and Neuroscience — August 2021

The University of Texas at Dallas, Richardson, Texas
M.S. in Applied Cognition and Neuroscience — May 2018

The Pennsylvania State University, University Park, Pennsylvania
Bachelor of Arts in Psychology — December 2011
Bachelor of Arts in Crime, Law, and Justice
Minor in Spanish

Universidad de Sevilla, España
Visiting Student (through CIEE program) — Spring 2010

AWARDS

Travel Support Award — 2019
The University of Texas at Dallas
School of Behavioral and Brain Sciences

Travel Support Award — 2017
The University of Texas at Dallas
School of Behavioral and Brain Sciences

Travel Support Award
2016 The University of Texas at Dallas
School of Behavioral and Brain Sciences

PUBLICATIONS

Ray, N. R., O'Connell, M. A., Nashiro, K., Smith, E. T., Qin, S., & Basak, C. (2017). Evaluating the relationship between white matter integrity, cognition, and varieties of video game learning. *Restorative Neurology and Neuroscience*, *35*(5), 437-456.

Qin, S., Ray, N. R., Ramakrishnan, N., Nashiro, K., O'Connell, M. A., & Basak, C. (2016). Illusory conjunctions in visual short-term memory: Individual differences in corpus callosum connectivity and splitting attention between the two hemifields. *Psychophysiology*, *53*(11), 1639-1650.

INVITED TALKS

Cognition, DTI, & Video Game Learning — October
12, 2017 Cognitive Psychology Undergraduate Lecture (Guest Lecturer)
The University of Texas at Dallas

Evaluating the Relationship Between White Matter Integrity, Cognition, and Video Game Learning

October 6, 2017 Cognition and Neuroscience Annual Retreat
The University of Texas at Dallas

Evaluating the Relationship Between White Matter Integrity, Cognition, and Video Game Learning
September 8, 2017 Dallas & Austin Area Memory Meeting
The University of Texas at Austin

PRESENTATIONS

Ray, N. R. & Basak, C. (2019, November). *The birdwatch game and its relationship with working memory and other executive functions.* Poster presented at the Psychonomic Society Annual Meeting, Montréal, Canada.

Ray, N. R., Nashiro, K., O'Connell, M. A., Qin, S., Smith, E., & Basak, C. (2017, March). *Real-time strategy game training effects white matter integrity in older adults.* Poster presented at the Cognitive Neuroscience Society Annual Meeting, San Francisco, CA.

O'Connell, M. A., Ray, N. R., Qin, S., Nashiro, K., Basak, C. (2017, January). *Age-related differences in the relationship between structural integrity and task-related functional connectivity in a cognitive control task.* Poster presented at the Dallas Aging & Cognition Conference, Dallas, TX.

Ray, N. R., O'Connell, M. A., Nashiro, K., Smith, E., Qin, S., Basak, C. (2016, April). *Evaluating the relationship between white matter integrity, cognition, and varieties of video game learning.* Poster presented at the Cognitive Neuroscience Society Annual Meeting, New York, New York.

Roman, P. E., Ray, N. R., Contemori, C., Kaan, E., & Dussias, P. E. (2013, November). *The role of verb bias and plausibility in the resolution of temporarily ambiguous sentences: An ERP study with English speakers.* Poster presented at the Psychonomic Society Annual Meeting, Toronto, Canada.

ACADEMIC/PROFESSIONAL EXPERIENCE

Ph.D. Candidate/Research Assistant/Teaching Assistant, The University of Texas at Dallas

The School of Behavioral and Brain Sciences
The Center for Vital Longevity August 2014 - Present
Lifespan Neuroscience and Cognition (LiNC) Laboratory
Advisor: Dr. Chandramallika Basak

Responsibilities: Attending graduate courses; Employed as teaching assistant to the university; Behavioral and MRI data collection and analysis for ongoing projects in the LiNC Lab at the Center for Vital Longevity; Training and supervising undergraduate research assistants on data collection, data coding, and data analysis.

Research Technologist/Lab Manager, The Pennsylvania State University

Center for Language Science and The Department of Spanish, Italian, & Portuguese
July 2012 - July 2014
Mentor: Dr. Giuli (Paola) Dussias

Responsibilities: Involved in multiple projects using behavioral, event related potential (ERP), and eye tracking techniques; Behavioral, ERP, and eye-tracking data collection; Traveling abroad to collect valuable bilingual eye-tracking and behavioral data; Behavioral, ERP, and eye-tracking data coding using E-Prime and Microsoft Excel; ERP data cleaning using Scan 4.5; Building and debugging of eye-tracking experiments using EyeLink 1000 and Experiment Builder; Various administrative duties, including

purchasing/setting up/maintaining equipment, updating IRB protocols, recruiting participants, building and maintaining a participant database, coordinating with finance office to handle participant payment, etc.; Training and supervising undergraduate research assistants on data collection, data coding, and participant recruiting for behavioral, ERP, and eye-tracking techniques.

Research Assistant, The Pennsylvania State University
Center for Language Science August 2011 - July 2012
Mentors: Dr. Judith F. Kroll

Responsibilities: Involved in multiple projects using behavioral, ERP, and functional magnetic resonance imaging (fMRI) techniques; Behavioral, ERP, and fMRI data collection; Behavioral, ERP, and fMRI data coding using E-Prime and Microsoft Excel; ERP data cleaning using Scan 4.5; fMRI data analysis using SPM8.

PROFESSIONAL DEVELOPMENT

Training Course in fMRI Summer 2018
University of Michigan
Instructors: Dr. John Jonides, Dr. Jeanette Mumford, Dr. Luis Hernandez-Garcia, Dr. Robert Welsh, Dr. Scott Peltier, and Dr. Steve LaConte
Description: I attended a two-week intensive boot camp at the University of Michigan, where we learned about the theory and application of functional magnetic resonance imaging (fMRI). The boot camp included a daily lecture in the morning, and lab session in the afternoon, where we learned how to preprocess and analyze fMRI data in SPM8 using Matlab.

Data processing and analysis for language scientists using the R statistical package Spring 2013
Department of Psychology, The Pennsylvania State University
Instructors: Dr. Jason Gullifer and Dr. Cari Bogulski
Description: I audited a graduate level class on the R programming language. The course focused on using R for statistical analysis. I completed all course work except for the final project, which was primarily tailored to the graduate students and their individual studies.

Computing for Data Analysis January 2013 – February 2013
Coursera
Instructor: Dr. Roger Peng, *Johns Hopkins University*
Course description: I completed a 4-week online course on the R programming language. The official course description reads: "This course is about learning the fundamental computing skills necessary for effective data analysis. You will learn to program in R and to use R for reading data, writing functions, making informative graphs, and applying modern statistical methods." The class involved video lectures, graded quizzes, and challenging programming assignments.
Certificate earned: Statement of Accomplishment.

Visual world workshop January 3rd-4th, 2013
The Pennsylvania State University
Instructor: Dr. Jorge Valdes Kroff, *University of Pennsylvania*
Description: I attended a two-day workshop where we learned how to write an advanced R script for analyzing Visual World data.

ERP Methods Summer 2012

The Pennsylvania State University

Instructor: Dr. Darren Tanner, *University of Illinois at Urbana-Champaign*

Description: I attended a weekly seminar on the ERP methodology. The seminar covered a broad range of topics, including background concepts, neural origins, ERP components and interpretation, ERP recording, averaging techniques, artifacts, uses of various filtering techniques, and plotting ERP waveforms.

SPM8 Workshop June 8th, 2012

The Pennsylvania State University

Instructor: Dr. Frank Hilary

Description: I attended an all-day workshop on using SPM8, where we learned some introductory theory on the fMRI methodology, some basic commands in MATLAB, and, most importantly, how to construct and use a batch file in SPM8.

SKILLS

Computer skills

Experimental software: E-Prime, Experiment Builder
Statistical analysis: R, SPSS
MRI analysis: FSL
Eye-tracking system: EyeLink 1000
ERP/EEG system: Neuroscan

Languages

English (native language)
Spanish (intermediate proficiency)