PERSISTENT NEUROCOGNITIVE EFFECTS OF CONCUSSION IN MIDDLE-ADULTHOOD

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ABSTRACT

Eleanna Martha Lyman Varangis: Persistent Neurocognitive Effects of Concussion in Middle-Adulthood
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Past studies on the persistent effects of concussions on neurocognitive health have suggested that former athletes in younger and older adulthood are at risk for persistent cognitive impairment, functional neural inefficiency, and loss of structural neural integrity. However, few studies have focused on the effects of concussions on these measures in former athletes in middle-adulthood in order to gain a more complete picture of neurocognitive health in the lifespan of former athletes. The present study utilized a sample of former collegiate athletes to examine neurocognitive health in middle-adulthood via cognitive testing, a functional magnetic resonance imaging scan assessing neural connectivity during a memory binding task, and analysis of white matter integrity along tracts implicated in the neuropathology of concussive and neurodegenerative injury. Based on past research, former athletes with a history of concussions were hypothesized to perform worse on tasks involving high demands on cognitive control and memory, and to show impaired modulation of functional connectivity and compromised structural neural integrity. Results from these analyses showed few differences between athletes with and without a history of concussions: athletes with a history of concussions performed within the normal range on standard cognitive assessments, performed equivalently to athletes with no history of concussions on a task of memory binding, and showed no evidence of reduced white matter integrity. However, former football players with a history of concussions showed inefficient patterns of functional connectivity between a task-relevant and task-irrelevant network. Thus, concussion history may not be consistently associated with widespread neurocognitive dysfunction in middle-adulthood, but it may be associated with inefficient recruitment of cognitive neural networks during a challenging cognitive task. These results have implications for the long-term neurocognitive health of these former football athletes, and raise concerns about the effects of concussion history on more subtle expressions of reduced cognitive reserve throughout the aging process.

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LIST OF ABBREVIATIONS

AD	Alzheimer's Disease
AxD	Axial Diffusivity
ALS	Amyotrophic Lateral Sclerosis
BDI	Beck Depression Inventory
BOLD	Blood Oxygen Level Dependent
CNSVS	CNS Vital Signs
COWAT	Controlled Oral Word Association Test
CTE	Chronic Traumatic Encephalopathy
DTI	Diffusion Tensor Imaging
FA	Fractional Anisotropy
fMRI	Functional Magnetic Resonance Imaging
HVLT	Hopkins Verbal Learning Test
MCI	Mild Cognitive Impairment
MD	Mean Diffusivity
MMSE	Mini-Mental State Examination
mTBI	Mild Traumatic Brain Injury
NFL	National Football League
RD	Radial Diffusivity
ROI	Region of Interest
TBSS	Tract-Based Spatial Statistics
TRACULA	Tracts Constrained by Underlying Anatomy
WAIS	Wechsler Adult Intelligence Scale
WTAR	Wechsler Test of Adult Reading

I. INTRODUCTION

In the study of the persistent effects of concussions on neurocognitive health, there are several considerations to be made in evaluating risk for development of persistent impairment. Existing research has primarily been stratified based on cause of concussion (all-cause vs. sport-related concussion) and time since injury (acute vs. long-term effects). As such, there are four key subdivisions in the field of concussion research: acute effects of all-cause concussions, long-term effects of all-cause concussions, acute effects of sport-related concussions, and long-term effects of sport-related concussions. Over the past few decades, extensive research has probed the acute effects of all-cause and sport-related concussions, and has begun to examine the long-term effects of all-cause concussions, but it is the last category, the long-term effects of sport-related concussions, that has yet to be fully explored and arguably represents the greatest risk to current and former athletes.

Studies on the effects of acute concussion have suggested that in the short-term, symptoms of concussion can be divided into three primary categories: somatic symptoms, cognitive symptoms, and affective symptoms (McCrea et al., 2003). In most cases, these symptoms resolve within 7-10 days (McCrea et al., 2003), however recovery may be more difficult or more prolonged for individuals who have experienced concussions in the past (Collins et al., 2002; Guskiewicz et al., 2003; Schulz et al., 2004). Additionally, recently concern has been raised over whether recurrent discrete concussive injuries might result in accumulated damage in the brain, giving rise to long-term health concerns in aging (Manley et al., 2017; Omalu et al., 2005).

Studies examining the effects of a single concussive injury (regardless of cause) have been able to thoroughly characterize the effects of a single isolated injury; however, these fall short in their ability to adequately detail the effects of concussions as they occur in an athletic environment. Concussions that occur in an athletic environment are made more complicated by the fact that in many athletic environments, head impacts may be an inherent element of athletic participation, and concussive or sub-concussive events occur frequently in practice and competition (CDC, 2007; Kerr et al., 2015; Prevention, 2011). As such, athletic concussions may represent a substantially different mechanism and type of injury that could make athletes in particular more vulnerable to experiencing multiple concussions, and thus more vulnerable to the consequences of head impacts and concussive injuries.

One point of controversy in the field of concussion research is the debate over whether discrete concussions or repeated sub-concussive hits to the head are responsible for the long-term dysfunction observed in athletes with a history of participation in contact sport who have sustained concussions. Several studies have pointed towards repeated blows to the head as the culprit (Bailes, Petraglia, Omalu, Nauman, & Talavage, 2013; Baugh et al., 2012; Churchill, Hutchison, Di Battista, Graham, & Schweizer, 2017; Gavett, Stern, & McKee, 2011; McAllister & McCrea, 2017; Miyashita, Diakogeorgiou, & Marrie, 2017; Montenigro et al., 2017; R. A. Stern et al., 2011), or early exposure to contact sport (Stamm, Bourlas, et al., 2015; Stamm, Koerte, et al., 2015), while others have maintained that it is multiple unique concussive events and not subconcussive impacts that are associated with these patterns of impairment (Gysland et al., 2012; also see studies cited below). Thus, in addition to elucidating the types of deficits that can be observed in former contact sport athletes, it may also be necessary to determine whether these deficits are associated with history of specific concussive episodes, or are a result of cumulative neural injury from repetitive head impacts sustained through participation in contact sport.

Based on the current state of concussion research, it is clear that there remains much to be clarified about the scope of the long-term effects of repeat sport-related concussions or subconcussive episodes. Since we know athletes to be at heightened risk for sustaining a concussive/subconcussive injury, and since many of the long-term effects of repeat head impacts have yet to be fully explored, this is an area of critical importance in protecting former, current, and future athletes. Further, in the studies reviewed below, it is evident that there is also a gap in our study of such long-term effects: most studies on the long-term effects of concussions either study recently active younger athletes or athletes who have been retired from participation in sport for decades. While these studies provide us with important context for the long-term effects of concussions we might expect to see in former athletes, they gloss over a large period of middle-adulthood that may provide critical information about how the long-term effects of head impacts may change or develop over the lifespan.

In order to target an under-studied question in this missing age group, the present study of athletes in middle-adulthood specifically focused on the effects of concussion history and head impacts on three different indices of neurocognitive health: (Aim 1) behavioral measures of cognitive function, (Aim 2) functional connectivity between neural networks during a cognitive task, and (Aim 3) indices of white matter health and integrity. Participants in the current study were former collegiate football athletes with or without a history of participation in football (non-contact athletes and football athletes), and within the sample of football players, with and without a history of concussions (low concussion football and high concussion football). All participants (non-contact and football athletes) completed tasks measuring each primary domain of cognition (attention, working memory, inhibition, language, and memory) and a diffusion tensor imaging (DTI) scan assessing whole-brain white matter integrity, and former football athletes also completed a task of memory binding during a functional magnetic resonance imaging (fMRI) blood oxygen level-dependent (BOLD) scan measuring functional connectivity during the encoding portion of the in-scanner task. The combination of these measures enabled a more holistic view of the effects of neural insult sustained earlier in life on long-term neurocognitive health.

Below, I review the existing research assessing the long-term effects of repeat sport-related concussion on cognitive performance, neural functioning, and structural neural integrity in order to inform the present study of these indices within a sample of former athletes in middle-adulthood. First, I review literature on the persistent cognitive deficits in younger and retired athletes with a history of concussion, and discuss how domain of impairment (attention, working memory, inhibition, language, and memory) varies critically as a function of time since injury. Second, I describe literature within the field of concussion discussing the utility of fMRI as a tool for studying the long-term effects of concussion history on neural functioning and efficiency in younger and older adults with a history of concussions. Lastly, I discuss research on the effects of concussion history on white matter integrity as a function of time since injury, covering the effects observed soon after concussion through those seen in older adults with a past history of concussions.

Aim 1: Effects of Concussion on Cognitive Measures

Recent research has focused on the potential for concussive symptoms lingering beyond the acute recovery phase. One subset of lingering symptoms that the scientific community has increasingly focused on is that of cognitive symptoms, specifically regarding their potential link to neurodegenerative disease (Lehman, Hein, Baron, & Gersic, 2012). Thus, many studies to date have examined the effect of concussions on cognitive outcomes in both younger and older adults. Some of these studies have found no effect of concussion history on cognitive functioning. However, relatively more studies have suggested some link between concussion history and deficits in one of five key domains of cognition: attention, working memory, inhibition, language, and memory.

No effects on cognitive tasks. Some researchers who have examined the persistent effects of concussion history on cognitive health in young adults have found no effect of concussion history or exposure to head impacts on cognitive measures (Bruce & Echemendia, 2009; Collie, McCrory, & Makdissi, 2006; Guskiewicz, 2002; Straume-Naesheim, Andersen, Dvorak, & Bahr, 2005). However, a crucial aspect of these studies is that none examined neural indices of cognitive health. In fact, several additional studies that found no effect of concussion history on cognitive status in young adults did document an effect of concussion history on neural health as measured through volumetric analysis of structural MRI (Meier, Bellgowan, Bergamino, Ling, & Mayer, 2015), as well as functional analysis of event-related potentials (Broglio, Pontifex, O'Connor, & Hillman, 2009; De Beaumont, Brisson, Lassonde, & Jolicoeur, 2007; Theriault, De Beaumont, Tremblay, Lassonde, & Jolicoeur, 2011). Thus, despite some studies in young adults indicating no lingering effects of concussions or head impacts on cognitive health, history of head impacts may have some long-term effects on neurocognitive functioning that may come to affect cognitive functioning later in life. Further, since no studies assessing the long-term cognitive effects of concussions in older adults found no cognitive deficits linked to concussion history, it could be the case that these persistent neural effects in the absence of cognitive deficits in younger adults are associated with risk for future cognitive impairment.

Effects on tasks of attention. One of the deficits associated with a history of concussions in young adults is in attentional processing. Attention is a domain of cognition critical towards the ability to direct cognitive processing resources towards specific, relevant aspects of the environment, while suppressing processing of irrelevant aspects of the environment. Past research on attentional processing in young adults with a history of multiple concussions found deficits in basic aspects of attention in this sample (Baillargeon, Lassonde, Leclerc, & Ellemberg, 2012; Terry et al., 2012). These deficits point to the fact that even at a young age, deficits in a core cognitive domain may arise as a function of past concussive injury. Additionally, in the only existing study specifically assessing neurocognitive functioning in middle-adulthood, former football players who had a higher genetic risk for accrued brain injury from head trauma (APOE-ε4 positive) showed deficits in attentional processing (Kutner, Erlanger, Tsai, Jordan, & Relkin, 2000). Despite these early-emerging persistent deficits in attentional processing in young adults, no studies examining cognitive functioning in older adults with a history of concussions have found deficits in attentional processing. Thus, these studies suggest that these deficits in attention that are linked to concussion history emerge early, but their absence in older adulthood suggests that over time they may be masked in the context of high variability in cognitive function during cognitive aging. Based on findings in young adults that concussion history is linked to deficits in attention, the present study utilized a flanker task as a measure of attentional processing to see whether these deficits persist in middle-adulthood.

Effects on tasks of working memory. Another deficit commonly seen in younger athletes with a history of concussion is that of working memory. Working memory draws heavily upon attentional resources in requiring attention to specific items in order to hold them in memory briefly and perform some degree of manipulation on them while doing so (Baddeley, 1992a, 1992b; Baddeley & Della Sala, 1996). Thus, it is not surprising that alongside deficits in attentional processing, younger individuals with a history of concussion may also show deficits in working memory (Baillargeon et al., 2012; Gardner, Shores, & Batchelor, 2010; Terry et al., 2012). Similar to the studies showing deficits in attention in younger adults but not older adults, there have been no studies in older adults suggesting that concussion history has a significant effect on working memory in the context of aging. Based on findings in young adults that concussion history is linked to deficits in working memory, the present study utilized a list sorting task as a measure of working memory abilities to see whether these deficits persist in middle-adulthood.

Effects on tasks of inhibition. Inhibition is one of the two domains of cognition that shows persistent deficits in both younger and older adults with a history of concussions. Tasks of inhibition primarily assess one’s ability to actively suppress response or attention to specific types of targets or stimuli. Two studies in young adults with a history of concussions have documented a persistent deficit in inhibitory function (Moore et al., 2015; Pontifex, O'Connor, Broglio, & Hillman, 2009), and inhibition was explicitly noted as a domain that shows deficits in a meta-analysis of the persistent effects of concussion on cognitive function (Belanger, Spiegel, & Vanderploeg, 2010). Additionally, inhibition is a domain that has been implicated in several studies examining the persistent effects of concussions on cognitive function in older adults. Three studies in older adults showed that older individuals with a history of concussions showed deficits in their ability to inhibit an inappropriate response (De Beaumont et al., 2009; Goswami et al., 2015; Stamm, Bourlas, et al., 2015). Thus, both older and younger adults may be equally at risk for deficits in inhibitory processing as a result of history of concussive injuries sustained earlier in life. Based on findings in both younger and older adults that concussion history is linked to deficits in inhibition, the present study utilized a color-word Stroop task as a measure of inhibitory processing to see whether these deficits can also be observed in middle-adulthood.

Effects on tasks of language. One deficit seen only in older adults with a history of concussion is that of language function and processing. Language is crucial towards the ability to communicate effectively and appropriately, using information one has learned in the past about words and word meaning to generate novel utterances and ideas. Studies in older adults with a history of concussions have found deficits in language production and comprehension alongside deficits in memory (Hart et al., 2013; Stamm, Bourlas, et al., 2015; Tremblay et al., 2013) and inhibitory processing (Stamm, Bourlas, et al., 2015). Thus, deficits in language may be observed in older adults with a history of past concussions, and may be likely to co-occur with deficits in other domains of cognition that also play a key role in successful language production and comprehension (i.e., memory and inhibition). Based on findings in older adults that concussion history is linked to deficits in language, the present study utilized the Controlled Oral Word Association Task (COWAT) task as a measure of language production fluency to see whether these deficits have already begun to arise in middle-adulthood.

Effects on tasks of memory. Lastly, and notably, one of the most common deficits reported in the context of cognitive deficits associated with concussion history is that of memory. Specifically, the deficits observed are primarily in the domain of long-term, explicit memory, or memory for specific stimuli and events after a delay. While this deficit is not very commonly observed in young adults with a history of concussion (Belanger et al., 2010; Iverson, Echemendia, Lamarre, Brooks, & Gaetz, 2012), it is very frequently documented in studies of older adults with a history of concussions (De Beaumont et al., 2009; De Beaumont et al., 2013; Ford, Giovanello, & Guskiewicz, 2013; Guskiewicz et al., 2005; Hart et al., 2013; Pearce et al., 2014; Randolph, Karantzoulis, & Guskiewicz, 2013; Stamm, Bourlas, et al., 2015; Strain et al., 2015; Thornton, Cox, Whitfield, & Fouladi, 2008; Tremblay et al., 2013). Further, in the study mentioned above assessing neurocognitive functioning in middle-adulthood, former football players who were older (in this case in their 30s) and had a higher genetic risk for accrued brain injury (APOE-ε4 positive) showed a deficit in memory (Kutner et al., 2000). Based on the above studies, it is clear that a deficit in memory is a common consequence in adults with a history of past concussions. Since memory function is known to decline in healthy aging (F. Craik & Jennings, 1992; F. I. Craik, 1990, 2008; Dennis & Cabeza, 2008; Grady & Craik, 2000; Luo & Craik, 2008), as well as in neurodegenerative disease (Albert et al., 2011; Greene, Hodges, & Baddeley, 1995; Hodges, Salmon, & Butters, 1990; McKhann et al., 2011; Morris & Baddeley, 1988; Perry & Hodges, 1996; Petersen et al., 1999; Sperling et al., 2011; Tromp et al., 2015), this pattern of deficits in memory in this population may reflect either accelerated patterns of aging, or early emergence of neurodegenerative disease. Thus, studying patterns of memory impairment associated with a history of past concussions is crucial towards gaining an understanding of the effects of concussions on the aging process. Based on findings in older adults that concussion history is linked to deficits in episodic memory, the present study utilized the Hopkins Verbal Learning Task (HVLT) task as a measure of episodic memory function to see whether these deficits have already begun to arise in middle-adulthood.

Concussions and neurodegenerative disease. Recent efforts to better characterize the neural underpinnings of the cluster of long-term symptoms associated with a history of multiple concussions have linked repetitive head trauma to a novel diagnosis of Chronic Traumatic

Encephalopathy (CTE; Baugh et al., 2012; Gavett, Stern, & McKee, 2011; McKee et al., 2009; Stern et al., 2013; Stern et al., 2011). CTE is characterized as a disorder marked by an extensive assortment of cognitive (i.e., memory, inhibition, attention) and psychiatric (i.e., depression, psychosis) problems (Omalu et al., 2006; Omalu et al., 2005). It is a neurodegenerative disease currently distinguished from existing diagnoses of MCI and AD by the distribution and extent of neuropathology present at autopsy. While tau tangles are a diagnostic neuropathological feature in MCI/AD and CTE, the tau tangles in MCI/AD show an initial affinity for medial temporal lobe and then spread to other limbic and neocortical regions (Braak & Braak, 1995, 1997). Tau tangles in CTE are more diffusely distributed throughout the cortex in superficial cortical layers, sulcal depths, and perivascular regions (McKee et al., 2009; Omalu et al., 2005; Small et al., 2013). However, there is a great degree of overlap in the cognitive profiles of MCI/AD and CTE, with primary cognitive deficits in explicit memory and inhibitory function (Albert et al., 2011; Baugh et al., 2012; Gavett et al., 2011; Greene et al., 1995; McKee et al., 2009; McKhann et al., 2011; B. I. Omalu et al., 2005; Perry & Hodges, 1996; Stern et al., 2011; Weiner et al., 2012).

In a recent study, Wagner et al. (2012) assessed biomarkers for predicting MCI to AD conversion and found that cerebrospinal fluid (CSF) tau levels were directly related to memory performance on a task of memory binding (Wagner et al., 2012). Specifically, after studying groups of members of a specific category (e.g., banana, grapes, apple, orange), individuals with MCI/AD performed similarly to age- and education-matched control participants for free recall of target objects, but showed less memorial benefit when provided with a relevant category cue (e.g., fruit). This reduction in the ability to benefit from the cue was directly related to tau levels (as measured via CSF). Given the high degree of memory impairment as a function of concussive injury, and since individuals with MCI/AD show a relationship between tau burden and memory binding performance, the present study will utilize a similar memory binding task in order to assess memory in another population known to have high levels of neural tau deposition: those with a history of concussive injuries.

Aim 2: Effects of Concussion on fMRI Measures

One tool gaining popularity as a tool for assessing the neurocognitive effects of concussion is fMRI collected in the context of a cognitive task. A benefit of task-based fMRI relative to structural MRI or resting state fMRI is its ability to measure online neural activation occurring in the context of cognitive challenge. In acute concussion fMRI has been shown to be predictive of recovery time (Lovell et al., 2007), and is considered a more sensitive measure for detecting lingering impairment after resolution of symptoms during the recovery period (Chen et al., 2004; Dettwiler et al., 2014; Keightley et al., 2014; Pardini et al., 2010; Ptito, Chen, & Johnston, 2007; Talavage et al., 2014). Thus, beyond the initial recovery period from concussion, fMRI has the potential for illuminating lingering neurocognitive differences that may go undetected by standard cognitive assessment.

Persistent effects of concussion on neural functioning during cognitive task. While fMRI has been utilized extensively as a measure of residual neural change following acute concussive episodes, few studies have utilized it as a measure of neural functioning in samples of individuals who sustained multiple concussive events in the past. One study using multiple cognitive tasks in the context of an fMRI scan found no neurological differences in activation related to history of concussions in a sample of young adults (Terry et al., 2012). However, two studies in older adults that utilized memory binding tasks in the context of an fMRI scan found functional neural inefficiencies[*] associated with a history of concussions either in the absence of behavioral differences in performance (Terry, Adams, Ferrara, & Miller, 2015), or alongside deficits in mnemonic performance (Ford et al., 2013). Thus, while fMRI differences may not be observed in young adults with a history of concussions, they may be more readily found in samples of older adults with a history of concussions. Additionally, since tasks differed drastically between the studies mentioned above in older and younger adults, it may also be the case that fMRI differences associated with concussion history may be more likely in the context of a memory task that taxes medial temporal lobe regions known to be affected by repeated concussive events. Since studies in older adults found functional neural differences as a function of concussion history during memory tasks, yet a study in younger adults found no differences between concussion groups during multiple shorter cognitive tasks, the present study utilized a task of memory binding in the context of an fMRI scan in order to assess differences in functional neural efficiency as a result of concussions sustained earlier in life.

Univariate vs. connectivity analysis. The three fMRI studies mentioned above utilized a univariate fMRI analysis which examines whole-brain or ROI-based differences in blood oxygen level dependent (BOLD) signal based on group and task condition. However, recent trends in neuroimaging research have begun utilizing functional connectivity analyses to measure network-scale differences in neural activation between groups. Unlike univariate analyses, these network-based approaches employ empirically-based network analyses to guide analysis of activation across functionally-defined neural networks. Of particular note is the emphasis on analysis of a neural network known as the default mode network (DMN), a network thought to

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[*] In Terry et al. (2015) these consisted of hypoactivation of task-relevant regions during a paired associates learning task. In Ford et al. (2013) these consisted of hypoactivation of task-relevant regions and hyperactivation of regions not associated with better performance on the memory task.

be engaged primarily during rest and mind-wandering thought (Dosenbach et al., 2007; Esposito et al., 2006; Greicius, Supekar, Menon, & Dougherty, 2009; Laird et al., 2009). While this network is traditionally studied during resting state fMRI scans, recent studies have examined how this network is engaged during a cognitive task, and have found that it “decouples” from task-related networks during performance of a task, such that correlated activity between task-relevant and task-irrelevant (DMN) networks ceases in the presence of a task (Fox et al., 2005; Grady et al., 2010; Prakash, Heo, Voss, Patterson, & Kramer, 2012).

Recently, this network-based approach to fMRI analysis has especially gained traction within special populations, such as older adults with and without neurodegenerative disease and individuals with a history of traumatic brain injury, due to its analysis of complex large-scale networks known to be structurally affected by brain aging and traumatic brain injury (Fujiyama et al., 2016; Jones et al., 2015; Xiao, Yang, Xi, & Chen, 2015). Importantly, unlike younger adults, older adults do not show the same degree of decoupling between the DMN and task-specific networks, and this lack of disconnect between networks negatively correlates with performance on the task (Miller et al., 2008; Prakash, Heo, Voss, Patterson, & Kramer, 2012). Since both older adult and former football player populations report deficits in memory, the lack of default mode and task-specific network decoupling may underlie this memory impairment, and thus is of particular interest to the present study as a sign of neural processing inefficiency.

While this type of connectivity research has specifically focused on the DMN and executive function-related task networks (Grady et al., 2010; Prakash et al., 2012; Uddin, Kelly, Biswal, Castellanos, & Milham, 2009), no studies have focused on the relationship between an episodic memory network and the DMN or another task-irrelevant network during an in-scanner memory task. Specifically, since the traditional definition of the DMN includes medial temporal lobe regions that may be task-relevant in the context of memory tasks (Greicius, Krasnow, Reiss, & Menon, 2003), the DMN may not be an appropriate task-irrelevant network in examining relationships between a task-relevant and task-irrelevant network in the context of a memory task. Recent studies by Stern, Habeck, and colleagues (2014 & 2016), however, utilized a set of 12 cognitive tasks to map out cognitive networks across the lifespan (Habeck et al., 2016; Y. Stern et al., 2014). These 12 tasks were comprised of 4 sets of 3 tasks corresponding to the different "reference abilities" or cognitive domains: Episodic Memory, Fluid Reasoning, Perceptual Processing Speed, and Vocabulary. The authors then examined regions showing relative increases and decreases in BOLD signal within each of the 12 tasks, as well as across tasks corresponding to each of the 4 reference abilities. These regions comprised task-related "networks" that were spatially and functionally distinct across participants of all ages (Habeck et al., 2016). Critically, these regions identified as significantly activated or deactivated were observed in the context of specific cognitive tasks. Since the regions were not identified based on identification of default or task-irrelevant networks from resting state and comparing this network to a task-based network identified in the context of a specific cognitive task, this suggests that these regions co-activate or co-deactivate during specific cognitive processes, and not only when comparing to rest. As such, these networks may represent regions that are necessary to engage during the cognitive process (activated regions), as well as the corresponding regions that are necessary to deactivate during the cognitive process (deactivated regions). Of primary interest to the current study is set of regions shown to be activated/deactivated in the context of the 3 memory tasks. While all memory tasks show similar trends in BOLD activation/deactivation patterns, the task that best mapped onto these patterns was the paired associate learning task (Habeck et al., 2016). Since the task in the present study assessed memory for word pairs, these memory-positive (regions showing increased BOLD signal during memory tasks) and memory-negative (regions showing decreased BOLD signal during memory tasks) networks may enable analyses assessing the behavioral outcomes of different patterns of connectivity. Additionally, to mirror previous studies examining relationships between networks and their effect on behavioral outcomes in older adults (Miller et al., 2008; Prakash, Heo, Voss, Patterson, & Kramer, 2012), the connectivity analyses presented here specifically focus on the correlation between memory-positive and memory-negative networks, and its effect on behavior during the in-scanner task.

Aim 3: Effects of Concussion on DTI Measures

DTI is another imaging modality becoming increasingly popular in the search for a neuroimaging biomarker of concussive injury. The primary metrics of DTI, Mean Diffusivity (MD), Fractional Anisotropy (FA), Axial Diffusivity (AxD), and Radial Diffusivity (RD) measure diffusion of water molecules along white matter tracts; white matter damage via traumatic brain injury, disease, aging, or other mechanisms results in these white matter tracts becoming “leaky” and showing less efficient diffusivity of water along these tracts (high MD and RD, low FA and AxD). As a diffuse axonal injury, repeat concussive events are known to cause some degree of axonal shearing and white matter damage as a function of brain movement inside the skull causing stretching and contracting of white matter fibers during this coup-contrecoup injury (Gennarelli, 1993; Hamberger, Viano, Säljö, & Bolouri, 2009). Research using DTI in acute concussion has pointed towards its utility in identifying white matter damage as a direct result of acute concussive injury, that may or may not be associated with symptom expression and severity (in acute concussion: Gardner et al., 2012; in post-concussion syndrome: Khong, Odenwald, Hashim, & Cusimano, 2016). Authors of these studies suggest that generally DTI may be a sensitive tool for detecting acute changes in white matter integrity as a function of concussive injuries. Additionally, and importantly, these studies also indicate that DTI metrics may be a useful tool for examining more persistent effects of concussions on neural health, even in the absence of behavioral indices of impairment.

Two previous studies have utilized DTI to assess long-term white matter abnormalities linked to concussion history in samples of younger adult athletes. These studies suggest that even months after resolution of concussive symptoms, young adults with a history of concussions, relative to those with just one concussion, show some abnormalities in their white matter integrity (Bazarian, Zhu, Blyth, Borrino, & Zhong, 2012; Henry et al., 2011). Since white matter integrity is crucial for efficient long-range neural communication, these early-emerging insults to white matter integrity may have consequences when considering white matter integrity also naturally declines with age, and is associated with accompanying detriments to neurocognitive functioning.

Additionally, a few studies have examined the long-term effect of concussions on white matter integrity in aging populations. All three studies have found some effect of concussions or onset of football/head impact exposure on DTI metrics of white matter integrity (Casson, Viano, Haacke, Kou, & LeStrange, 2014; Clark et al., In Press; Stamm, Koerte, et al., 2015). Thus, in addition to acute effects of concussions on white matter integrity, and more enduring effects of concussion history on white matter in younger adults, these abnormalities may persist throughout adulthood and interact with normal patterns of white matter integrity loss in aging.

Relevant to the current study, three previous studies have examined DTI metrics in active amateur soccer players (Lipton et al., 2013), current and former boxers (Wilde et al., 2016), and retired professional Canadian Football League athletes (Multani et al., 2016) in middle-adulthood. These studies found some effect of repeated head impacts, years of participation in boxing, and participation in contact sport (respectively) on white matter integrity in this age range. However, little is known about the exact risk factors for development of these white matter abnormalities. For example, these may be linked to unique concussive events, or they may arise as a function of repeated subconcussive head impacts. As such, the present study's focus on former athletes with a history of participation in either contact or non-contact sports in middle-adulthood helps illuminate how white matter integrity may be related to concussion history or exposure to subconcussive impacts a decade or more post-injury.

Whole-brain DTI statistics vs. tractography. There are many ways to analyze DTI data, but the two most commonly used analyses are tract-based spatial statistics (TBSS) analysis and tractography (probabilistic or deterministic). TBSS analyses first standardize DTI images to a normalized template, then mask each individual DTI image with a standard white matter skeleton to examine group differences in FA, MD, RD, and AxD within standard white matter tracts (Smith et al., 2006). This method allows for whole-brain analysis of white matter integrity, and enables easy comparison between subjects due to the strict normalization parameters used. Probabilistic tractography (i.e., TRActs Constrained by Underlying Anatomy, or TRACULA), on the other hand, estimates and reconstructs the location and direction of each major white matter tract (forceps major of the corpus callosum, forceps minor of the corpus callosum, unicinate fasciculus, inferior longitudinal fasciculus, superior longitudinal fasciculus temporal pathway, superior longitudinal fasciculus parietal pathway, thalamic radiation, corticospinal tract, and cingulum) within each subject's own DTI images based on each subject's segmented structural scans (Yendiki et al., 2011). Thus, unlike TBSS, there is no normalization to a standard template, which makes some parameters more difficult to compare between groups, however there is better overall estimation of the size and location of white matter pathways due to this lack of normalization. As such, this method allows for comparison of FA, MD, RD, and AxD in each major fiber tract, as defined by each subject's own anatomy, between groups without having to pull these metrics from regions specified in a standard white matter template.

Previous research in concussion (Chamard et al., 2013; Cubon, Putukian, Boyer, & Dettwiler, 2011; Fakhran, Yaeger, Collins, & Alhilali, 2014; Narayana et al., 2015; Sasaki et al., 2014; J. F. Strain et al., 2017) and neurodegenerative disease (Bosch et al., 2012; Damoiseaux et al., 2009; Liu et al., 2011; Mayo, Mazerolle, Ritchie, Fisk, & Gawryluk, 2017; van Bruggen et al., 2012) has used TBSS to study the effects of concussion or neuropathology on white matter integrity, and has found it useful in assessing differences between control and patient groups. However, some recent studies in other patient populations known to be affected by white matter damage (i.e., PTSD, epilepsy, ALS, bipolar disorder, etc.) have found TRACULA to also be useful in assessing differences in white matter integrity between patient and control groups, and have also found behavioral relationships between white matter integrity in specific tracts and symptom expression or severity (Ji et al., 2017; Kreilkamp, Weber, Richardson, & Keller, 2017; Olson et al., 2017; Sarica et al., 2014). Since concussion and neurodegenerative disease are similarly characterized by white matter damage, the present study utilized both TBSS and TRACULA to study the effect of repeat concussions or head impacts on white matter integrity across the whole brain via comparison to a normalized white matter skeleton (TBSS) and via estimation and reconstruction of specific white matter tracts in each participant's own DTI data (TRACULA). Further, based on past research using DTI data in concussion and neurodegenerative disease, the present study confined TRACULA analyses to specific tracts known to be affected by concussion or MCI/AD pathology: unicinate fasciculus (Chamard et al., 2013; Douaud et al., 2011; Fakhran et al., 2014; Goswami et al., 2015; Liu et al., 2011; Mayo et al., 2017; Niogi et al., 2008; J. Strain et al., 2013), inferior longitudinal fasciculus (Bazarian, Zhu, Blyth, Borrino, & Zhong, 2012; Chamard et al., 2013; Liu et al., 2011; Mayo et al., 2017; Murugavel et al., 2014; Narayana et al., 2015; Niogi et al., 2008), superior longitudinal fasciculus temporal pathway & superior longitudinal fasciculus parietal pathway (Chamard et al., 2013; Douaud et al., 2011; Liu et al., 2011; Mayo et al., 2017; Narayana et al., 2015; J. Strain et al., 2013), forceps major and minor of the corpus callosum (Chamard et al., 2013; Douaud et al., 2011; Hakun, Zhu, Brown, Johnson, & Gold, 2015; Henry et al., 2011; Khong et al., 2016; Liu et al., 2011; Mayo et al., 2017; Narayana et al., 2015; Niogi et al., 2008; Stamm, Koerte, et al., 2015; J. Strain et al., 2013; J. F. Strain et al., 2017; Tremblay et al., 2014; van Bruggen et al., 2012; Van Hecke et al., 2010; Zhang et al., 2010), and cingulum (Chamard et al., 2013; Douaud et al., 2011; Liu et al., 2011; Mayo et al., 2017; Niogi et al., 2008; Stebbins & Murphy, 2009; van Bruggen et al., 2012; Van Hecke et al., 2010). By utilizing both TBSS and TRACULA, the present study allowed for comparisons between the results produced by both types of DTI analyses in evaluating their utility in identifying white matter damage in this population.

II. THE PRESENT STUDY

Based on past studies on the effects of concussions on neurocognitive health in younger and older adults, the present study addressed questions about how young adult concussion-related cognitive deficits may develop into older adult deficits in a sample of former National Collegiate Athletic Association (NCAA) athletes between 30-45 years old. Participants included former NCAA football players with a history of 4 or more sport-related concussions (FC+), former NCAA football players with a history of 0 or 1 sport-related concussions (FC-), and former NCAA non-contact athletes with no history of concussion (C-). Using these three specific samples of former athletes enabled evaluation of the unique effect of concussion history (FC+ vs. FC- and C-) and the unique effect of football participation or exposure to repetitive head impacts on cognitive functioning (FC+ and FC- vs. C-). Examining cognitive functioning within these three groups of former athletes in middle-adulthood is central in capturing the timeframe of development of cognitive impairments linked to head impacts in former athletes.

Additionally, based on prior research in MCI patients directly linking tau burden to performance on a task of memory binding (Wagner et al., 2012), the present study also utilized a task of memory binding to assess memory performance within another population known to have high levels of neural tau deposition: those with a history of head impacts and/or concussive injuries. If such a task is truly sensitive to tau protein density, individuals with a history of concussions (therefore at higher risk for tau deposition) should show poorer performance on this task than individuals with no history of concussions (lower risk for concussion-related tau deposits).

Further, this measure of memory binding was collected in the context of a functional magnetic resonance imaging (fMRI) scan in order to examine how functional connectivity during encoding of these pairs of words may be associated with later cued recall, and with metrics of neural and cognitive health. We utilized fMRI data to measure the relationship between task-relevant (i.e., memory-positive) and task-irrelevant (i.e., memory-negative) networks in order to assess neural efficiency[†] during encoding of novel word pairs (Habeck et al., 2016; Y. Stern et al., 2014). Given previous studies showing neural inefficiency linked to concussion history in the context of a cognitive task (Dettwiler et al., 2014; Ford et al., 2013), individuals with a history of concussions may show a reduction in the ability to suppress the memory-negative network relative to the memory-positive network during encoding of word pairs of varying semantic relatedness. Further, based on studies in older adults indicating a relationship between lack of network decoupling and poorer task performance (Miller et al., 2008; Prakash et al., 2012), decoupling of networks should be positively correlated with task performance, such that those who are better able to segregate the networks show higher accuracy and fewer errors on the task.

In addition to examining the effect of past concussions on functional connectivity during the task, it is also critical to examine the effect of concussions on structural integrity and connectivity through DTI. Accordingly, white matter integrity was assessed through TBSS and TRACULA across the whole brain, and within specific white matter tracts known to be affected by concussions and neurodegenerative disease within each of the three groups of former athletes. Due to the white matter injury implicated in concussions, individuals with a history of concussions may show reduced white matter integrity, and this may contribute towards both the efficiency of their functional network connectivity, as well as their ability to successfully

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[†] Here conceptualized as appropriate suppression of the memory-negative network during the in-scanner task.

perform the in-scanner memory task. By evaluating the integrity of white matter structures and relating them to behavioral performance on a cognitive task, knowledge may be gained about how axonal injury affects neural functioning and cognitive performance in individuals who have ceased participation in contact sports.

Current research in cognitive neuroscience has focused on integrating results across multiple imaging modalities in order to gain a more comprehensive picture of how structure and function interact in influencing cognitive performance. Further, since functional connectivity analyses inform the study of both functional and structural neural connections, the combination of functional and structural neuroimaging analyses is crucial towards gaining a holistic view of dynamic and static neural connectivity. Past studies utilizing a combination of functional and structural neuroimaging have been inconsistent in finding direct relationships between white matter structure and function during a variety of tasks (Fujiyama et al., 2016; Greicius et al., 2009; Hirsiger et al., 2016; Xiao et al., 2015), and thus the current study furthers this line of research in an attempt to better understand that relationship. Additionally, this study represents the first study to utilize a combination of functional connectivity and structural neuroimaging analyses alongside traditional cognitive tasks to examine neurocognitive function in a sample of retired athletes, and as such represents an important application of cognitive neuroscientific techniques to the field of concussion research.

Specific aims. Using cognitive tasks along with two different imaging methodologies, the aims of the study are three-fold: (Aim 1) characterize cognitive impairment associated with a history of concussive and/or subconcussive injury, (Aim 2) identify functional connectivity biomarkers of relational memory performance in a sample of former collegiate football athletes, and (Aim 3) examine the relationship between measures of white matter integrity and measures of functional connectivity and relational memory performance. Aim 1 examined cognitive performance in a sample of retired collegiate athletes, and probed the effects of concussion history as well as experience playing football on cognitive function. Aim 2 assessed differences in functional connectivity based on concussion history in former collegiate football athletes, and its relationship to behavioral metrics of relational memory performance. Aim 3 measured white matter integrity in all former collegiate athletes, and tested the role of structural integrity as a mediator of the relationship between functional connectivity and task performance. Hypotheses for each of the three primary aims of the study are detailed below after a detailed description of the methods and procedures used in the present study.

III. METHODS

Participants

The present project was a component of an NCAA-funded funded Phase II prospective study of a cohort of collegiate athletes who completed prior baseline testing as college students between the years 1999-2001. Paper rosters of athletes who participated in the baseline testing conducted during that timeframe were consulted in order to query alumni organizations from the original participating schools for contact information for these former athletes. Phase I of the study was an online survey that asked questions regarding football experience and current health status; a total of n=163 participants completed Phase I (see Figure 1). This information was used to assess eligibility for participation in the in-person assessments comprising Phase II of the study; a total of n=75 participants who completed Phase I of the study were deemed eligible for participation based on their interest in further research, lack of MRI contraindications, and lack of endorsement of exclusionary criteria. For the parent Phase II study, former collegiate football athletes (n=54) were recruited from the database of eligible participants who completed the prior baseline and Phase I portions of the study. The former athletes were between the ages of 34-41 (M=37.728, SD=1.567) years old. Non-contact control participants (n=5) were matched with football athletes based on gender, relative age, and concussion exposure. Potential control participants were male and participated in collegiate (NCAA) non-contact sports (baseball, swimming & diving, fencing, track & field, golf, and cross country) between 1999-2001. Qualifying participants were contacted for interest and provided with the necessary consent forms. From the sample of 54 participants (n=49 football athletes, n=5 non-contact controls), 40 former NCAA athletes who completed their study procedures at UNC-Chapel Hill were recruited for participation in the neuroimaging portions of this study: 21 former football players who were identified as having 4 or more previous concussions (FC+), 14 matched football players who sustained 0 or 1 previous concussions (FC-), and 5 age-, education-, and sex-matched non-football athletes with no history of concussions (C-). Exclusion criteria for former football players included: history of brain surgery, non-English speaking, any contraindications for MRI (including claustrophobia, pacemaker, surgical clips, pins, plates, screws, metal sutures, or wire mesh), and participation in professional football lasting longer than 2 years. Exclusion criteria for non-contact athletes included participation in football, history of concussion, traumatic brain injury, or brain surgery, non-English speaking, and any contraindications to MRI as listed above. Of the 40 participants above who completed the neuroimaging components of this study, 7 were excluded from some of the analyses presented below based on quality of neuroimaging or behavioral data: 2 C- participants did not complete the finalized functional sequences, and 7 more participants (n=2 C- participants, and n=5 FC+ participants) completed these functional sequences but their BOLD data were not appropriate for the connectivity analyses presented here due to phase shifts present in their concatenated time series data (see Figure 1).

Measures and Procedures

Cognitive assessment (Aim 1). In order to assess cognitive functioning within this sample, the present study utilized measures representing each of the cognitive domains found to be persistently affected by concussion during specific age ranges: attention (young adults), working memory (primarily young adults), inhibition/executive function (younger and older adults), language (older adults), and memory (primarily older adults). Participants from all 3 groups completed all cognitive assessments in order to examine the effect of both concussion history (FC+ vs. FC- and C-) and exposure to football-related repetitive head impacts (FC+ and FC- vs. C-) in this sample. To measure each domain, the present study utilized a Flanker task as a measure of attention (Akshoomoff et al., 2014; Tulsky et al., 2014; Zelazo et al., 2014), a list sorting task as a measure of working memory (Akshoomoff et al., 2014; Tulsky et al., 2014; Weintraub et al., 2013), a color word Stroop task as a measure of inhibition/executive control (Comalli, Wapner, & Werner, 1962; MacLeod, 1991; Stroop, 1935), the Controlled Oral World Association Task (COWAT) as a measure of language production (Loonstra, Tarlow, & Sellers, 2001; Ruff, Light, Parker, & Levin, 1996), and the Hopkins Verbal Learning Test (HVLT) as a measure of memory function (Shapiro, Benedict, Schretlen, & Brandt, 1999). Additionally, to ensure that groups did not differ in premorbid intelligence (Holdnack, 2001), participants also completed the Wechsler Test of Adult Reading (WTAR). Participants completed these six tasks as part of a larger neuropsychological battery; however, the focus of the present study is on those domains known to be sensitive to the long-term effects of concussive injury.

In-scanner task (Aims 1-3). All participants completed an Associated Cued Recall (ACR) task developed in our laboratory that is based on an established task of free and cued recall known to be sensitive to neural tau burden (Wagner et al., 2012). The task was comprised of 4 lists of 20 word pairs that varied in associative strength (see Table 1): 40 low-association words (i.e., muscle-head), and 40 no association words (i.e., palace-lemon). Number of word pairs in similar studies of verbal paired associate learning included between 32-140 word or object pairs, and thus the present study's 80 pairs are considered a moderate number of paired associate stimuli (Cameron, Yashar, Wilson, & Fried, 2001; Duncan, Tompary, & Davachi, 2014; Ford et al., 2013; Han et al., 2007; Henson, Shallice, Josephs, & Dolan, 2002; Tompary, Duncan, & Davachi, 2015). Words were generated by the English Lexicon Project database

(Balota et al., 2007) and included frequent concrete nouns containing between 4 and 7 letters each. Word pairs were then created by cross-referencing words that were generated from the English Lexicon Project database with word associates in the University of South Florida Free Association Norms database (Nelson, McEvoy, & Schreiber, 2004). Low association pairs were represented by cues for which targets had been infrequently generated in response to the cue (average association strength = 0.007), and no association pairs were cues for which the target had never been generated in response to the cue (association strength = 0). Pairs of words were then counterbalanced such that each cue word (i.e., "diamond") was paired with a low ("stone" – List 1) and no ("ship" – List 2) association target across two different lists. Similarly, word pairs were also counterbalanced such that each target word (i.e., "gold") appeared as a low ("thread" – List 2), and no ("smoke" – List 1) associate with a cue word. As such, each participant in the current study saw the same 80 cue words and 80 target words, but the pairing depended upon the experimental condition. Within the task, word pairs were blocked by association type, such that each run contained only word pairs of the same association type (i.e., all 20 pairs in each block were either low or no association pairs). Additionally, run type alternated such that participants never had two association types back-to-back (i.e., Low-No-Low-No or No-Low-No-Low). As a result, based on these counterbalances, two lists of words and four possible task orders generated 8 different counterbalancing conditions, which were randomly assigned to the participants.

In addition to word pairs, participants also saw pairs of strings of consonants during the task. Consonant strings were generated using a random consonant string generator, and matched the word pairs in length. These pairs were generated in order to include a control condition in the scan session that was matched in stimulus appearance (4-7 letters per "word", 2 "words" per screen) and letter-based content (consonants instead of words). As such, this enabled later analyses to compare the word-based, mnemonic experimental conditions (Low and No Association word pairs) with an appropriate letter-based, non-mnemonic control condition (consonant string pairs).

Each block was constructed in the same order: 12-second fixation screen, 10 pairs of words presented on the screen one at a time (6 seconds per pair), 12-second fixation screen, 10 pairs of consonant strings presented on the screen one at a time (6 seconds per pair), 12-second fixation screen, 10 pairs of words (6 seconds per pair), 12-second fixation screen, 10 pairs of consonant strings (6 seconds per pair), 12-second fixation screen, 15-second test instructions, then a 2-minute cued recall test of all 20 word pairs presented on the screen one at a time (6 seconds per cue). Participants were instructed that they would view 4 blocks of 20 word pairs each, and to think of a sentence utilizing the two words. They were also informed that they would see pairs of strings of consonants, and were told to “read” the consonants from left to right. Participants were told that once all the word and consonant pairs have been shown, they would be tested on their memory for the second word in each word pair by being shown the first word in the pair and being asked to speak the second word in the pair aloud. Word and consonant string pairs appeared on the screen for 5.5 seconds each, followed by a 0.5 second fixation screen (scanned; see Figure 2). Once participants had seen all 20 word pairs and 20 consonant string pairs in Block 1, they were shown each of the 20 cue words from that run in random order separately on the screen (5.5 seconds each, 0.5 second fixation afterwards), and were asked to speak aloud the target word that appeared previously with that cue word (unscanned). The same procedure was used for runs 1 through 4. The task lasted approximately 28 minutes (7 minutes per run: 5 minutes scanned encoding, 2 minutes unscanned retrieval).

Task-based functional BOLD data (Aim 2). Magnetic resonance images were acquired using a Siemens Prisma 3T MRI scanner. Participants' heads were held in place using cushions and a headrest. The scan protocol began with a localizer scan, which was followed by two BIAS scans (body coil and head coil), a perfusion-weighted image, a susceptibility-weighted image, a high resolution T1-weighted scan (160 1mm slices, TR=1750ms, TE=4.38ms), a T2-weighted dark fluid scan, a T2-weighted scan, field mapping scans (AP and PA directions), two 7-minute resting state scans (PA and AP directions), DTI sequences, and finally the four 5-minute task-based BOLD functional runs. However, the analysis in the current paper focuses exclusively on the data from the task-based functional scans and the DTI scans. Functional scans were collected during all four BOLD runs. Whole brain, gradient-echo, echo planar images (fifty interleaved 3mm slices, TR=2000ms, TE=30ms, Flip angle=80º, 3 x 3 x 3 mm) were acquired at an angle parallel to the long axis of the hippocampus as identified during the T1 scan.

Structural diffusion imaging data (Aim 3). The diffusion weighted images were acquired with 96 interleaved axial slices by using an echo planar imaging (EPI) sequence that covered the whole brain. The acquisition parameters were as follows: TR = 4803 ms, TE = 69.60 ms, and spatial resolution = 1.5 × 1.5 × 1.5 mm3. A total volume of 83 directions were acquired, where one volume was without diffusion gradient ($b = 0$) and the remaining 83 volumes were with diffusion gradient of b=2,000 s/mm2. The acquisition time was approximately 7 minutes.

Data Analysis Procedures

Cognitive assessment data analysis (Aim 1). First, age-standardized scores on the cognitive assessments were used, such that scores represent performance relative to an age-standardized normal score. In order to assess the effects of concussion history and experience playing football on cognitive status within this sample, 6 (cognitive task domains: attention, working memory, inhibition/executive function, language, memory, premorbid IQ) separate one-way ANOVAS (group: FC+ vs. FC- vs. C-) were conducted to see whether there were any differences in cognitive performance or premorbid IQ based on concussion history or football participation history. ANOVAs were conducted independently since some tasks were standardized using different standardization criteria, making an omnibus 6 (cognitive domain) x 3 (group) omnibus ANOVA inappropriate for these data. As such, in order for a difference to be considered significant, the p-value threshold was Bonferrroni adjusted to be less than 0.0083. Further, in order to assess whether actual number of concussions were predictive of performance on the cognitive tasks of interest, correlational analyses were performed in order to test any linear relationship between concussion history and cognitive task performance ($p<0.0083$).

In-scanner task data analysis (Aims 1-3). Behavioral task data were first scored for accuracy on cued recall (number correct per condition divided by 40 total word pairs per condition). Since Wagner et al. (2012) found a specific deficit in benefit from the cue during cued recall, the primary analysis for this data was a 2 (Concussion History: FC+ vs. FC-) x 2 (word relatedness: low vs. no) ANOVA. Using this test enabled examination of the effects of concussion history on overall performance (main effect of concussion history), effects of word relatedness on overall performance (main effect of word relatedness), and any effects of concussion history on the ability to benefit from word relatedness (2-way interaction).

In addition to examining correct responses, errors were also analyzed to examine the potential effect of concussion history on number of errors and types of errors made. Specifically, any incorrect target words generated during retrieval were coded as either recombined (target or cue word from a different pair generated in response to the cue word) or new (non-list word generated in response to the cue word). Error types were analyzed using a 2 (Concussion

History: FC+ vs. FC-) x 2 (error type: recombined vs. novel) ANOVA. Using this test enabled examination of the effects of concussion history on overall performance (main effect of concussion history), differences in overall types of errors generated (main effect of error type), and any effects of concussion history on the difference in production of types of task errors (2-way interaction).

Lastly, correlational analyses were conducted to assess whether there is a linear relationship between actual number of concussions sustained and behavioral performance. Specifically, number of concussions sustained was correlated with task accuracy (p<.025 for statistical significance), and number of errors generated (p<.025 for statistical significance).

Functional connectivity data analysis (Aim 2). Images were preprocessed using SPM12 (Wellcome Department of Cognitive Neurology, London, UK) software implemented as a suite of commands in MATLAB (MathWorks, USA). Images were co-registered with each participant's anatomical scan, slice-time corrected, realigned, normalized and smoothed using a Gaussian 8mm kernel.

Time series data were then extracted using REX (Duff, Cunnington, & Egan, 2007) from regions that show increases or decreases in activity in the context of memory tasks (Habeck et al., 2016; Y. Stern et al., 2014). The areas identified by Habeck et al. (2016) showing increases in activity during memory tasks were considered the "task positive" network, while areas showing decreases in activity during the memory tasks were considered the "task negative" network. Prior studies validated that a paired associate learning task loads heavily and consistently upon this memory positive network, and found them to be largely unchanged with age and consistent across multiple samples (Habeck et al., 2016; Y. Stern et al., 2014). The coordinates from these two networks were used to generate 3mm-radius spheres in WFU

PickAtlas (Maldjian, Laurienti, Kraft, & Burdette, 2003) for each coordinate in each network, yielding 15 regions belonging to the memory-positive network and 19 regions belonging to the memory-negative network. Individual, preprocessed, BOLD time series data was then extracted from all 34 regions. In order to examine connectivity between these 2 networks, two methods were used and compared: (1) simple correlational analysis comparing average correlation coefficient among nodes within and between the two networks as a function of task condition, and (2) confirmatory factor analysis assessing the contemporaneous and lagged relationships between the two networks as a function of task condition. For all connectivity analyses, only 3 of the 4 conditions were analyzed: consonant pairs, low association pairs, and no association pairs[‡].

Correlational connectivity analyses. In order to perform the first connectivity analysis, time series data were concatenated by condition (fixation, consonants – 240 instances, low association – 120 instances, no association – 120 instances), then correlation matrices were generated for each of the 3 conditions of interest by correlating activity within each of the 34 ROIs with activity in each of the other ROIs. Cells within this matrix were then binned into 3 categories: within-task-positive-network correlation, within-task-negative-network correlations, and between-network correlations (see Figure 3). Cells within each category were then averaged in order to generate 3 metrics per condition: average within-task-positive-network correlation, average within-task-negative-network correlation, and average between-network correlation. These correlation coefficients were then Fisher transformed in order to ensure that they approximated a normal distribution. Then, a 2 (Concussion History: FC+ vs. FC-) x 3 (condition: consonants, low association, no association) x 3 (network: task-positive, task-negative, between-network) mixed ANOVA was conducted to test whether network correlation strength is

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[‡] The fixation condition was not included as a baseline in these analyses due to concerns that participants may have been actively rehearsing recently-learned word pairs during these 5 12-second rest periods of the task.

modulated by task condition (2-way interaction), and whether concussion history affects this modulation (3-way interaction). Additionally, correlational analyses were performed in order to assess the relationship between task accuracy (low accuracy and no accuracy; p<.025 for statistical significance), task error rates (recombined and new; p<.025 for statistical significance), and corresponding between-network connectivity (i.e., test correlation between low accuracy and between-network connectivity during low association blocks; between no accuracy and between-network connectivity during no association blocks; or between either type of error rate and between-network connectivity during no association blocks since errors are more likely to occur during difficult task conditions).

Dynamic factor analytic connectivity analyses. In order to perform the dynamic factor analytic connectivity analyses, time series data was concatenated by condition (fixation, consonants, low association, no association), then a lagged time series was generated for each condition representing activity within each ROI in each condition at time t-1. Next, a standard dynamic factor analytic design was employed for each condition, in which the latent variables being estimated were the “memory-positive” and “memory-negative” networks, and ROIs corresponding to each network were set to load only on their pre-specified corresponding latent network. Estimation of these models was conducted using Bollen’s automated model-implied instrumental variable selection algorithm (Bollen, 1996; Bollen, 2001; Bollen & Bauer, 2004), along with a two-stage least squares estimator. First, a baseline model with no lagged effects was estimated in order to examine contemporaneous between-network (latent variable) p-technique correlations (contemporaneous bidirectional network connectivity; see Figure 4), then a secondary model with directed lagged effects was estimated in order to examine directed relationships between networks over time (cross-lagged directed connectivity; see Figure 5;

Fisher, Bollen, Doyle, Lindquist, & Gates, 2016). For the first model, a 2 (group: FC+ vs. FC-) x 3 (condition: consonants, low association, no association) mixed ANOVA was conducted to test whether this correlation between networks is modulated by task condition, and whether concussion history affects this modulation (see Figure 4). For the cross-lagged effect model, a 2 (group: FC+ vs. FC-) x 3 (condition: consonants, low association, no association) x 2 (direction: negative-to-positive vs. positive-to-negative) mixed ANOVA was conducted to test whether the direction of the cross-lagged effect of one network on the other is modulated by task condition, and whether concussion history affects this modulation. Additionally, correlational analyses were performed in order to assess the relationship between task accuracy (low accuracy and no accuracy; $p<.025$ for statistical significance), task error rates (recombined and new; $p<.025$ for statistical significance), and corresponding between-network connectivity for models 1 and 2.

Structural integrity data analysis (Aim 3). In order to measure whole-brain differences in FA between groups, a tract-based spatial statistics (TBSS) analysis was performed. First, DTI data were converted from dicom to 4D nifti format, and b-vector and b-value files were generated for each participant. Next, the data were fed into a standard FSL DTI processing stream including eddy current and motion correction, brain extraction, and reconstruction of the diffusion tensor (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012; Smith et al., 2004; Woolrich et al., 2009). Each participant's FA images then completed TBSS preprocessing, regularization, post-regularization, and pre-stats (minimum FA value=0.2), before being compared between concussion (C- and FC-vs. FC+) and football participation (C- vs. FC- and FC+) groups (Smith et al., 2006).

Next, in order to measure differences in white matter integrity between groups within more specific individually spatially-defined, a probabilistic tractography analysis was performed using FreeSurfer's Tracts Contrastrained by Underlying Anatomy (TRACULA) DTI analysis toolbox (Dale, Fischl, & Sereno, 1999; Fischl et al., 2002; Fischl et al., 2004; Yendiki et al., 2011). First, each participant's T1 image was segmented in FreeSurfer in order to generate high-resolution segmented brain masks for each participant. Next, DTI data were preprocessed in a standard TRACULA preprocessing pipeline, including eddy-current compensation, computing head motion parameters, intra-subject registration (to individual T1 scan), inter-subject registration (to standard MNI template), creation of cortical and white-matter masks (based on FreeSurfer segmented T1), tensor fitting, and computation of anatomical priors for white-matter pathways.

Then preprocessed images were fed into FSL's bedpostX pipeline, which uses a ball-and-stick model of diffusion to estimate probability distributions of parameters of this model at every voxel in order to reconstruct the white matter pathways (Behrens, Berg, Jbabdi, Rushworth, & Woolrich, 2007). Finally, 18 white matter pathways were reconstructed based on these probability distributions in each participant, and FA, MD, AxD, and RD data was extracted from the 14 pathways corresponding to white matter tracts implicated in concussions and neurodegenerative disease (forceps major, forceps minor, L&R uncinate fasciculus, L&R inferior longitudinal fasciculus, L&R superior longitudinal fasciculus temporal pathway, L&R superior longitudinal fasciculus parietal pathway, and L&R cingulum). The extracted weighted FA, MD, RD, and AxD values were then clustered by tract (i.e., left uncinate fasciculus was combined with right uncinante fasciculus to generate one measure of integrity in the uncinate fasciculus), and compared in 4 separate (FA, MD, RD, AxD) mixed 5 (tract: corpus callosum, uncinate fasciculus, inferior longitudinal fasciculus, superior longitudinal fasciculus, and cingulum) x 3 (group: C-, FC-, FC+) ANOVA to test for an effect of group or an interaction between group and tract on each measure of white matter integrity.

Multi-modal analyses (Aim 3b). Additionally, in order to test the relationship between structural integrity, functional connectivity, and task performance, a partial correlation analysis was conducted. Aim 2 involves testing the correlation between functional connectivity between networks and task performance, while aim 3 includes testing the role of structural integrity in this relationship proposed in aim 2. To do so, a partial correlation analysis was conducted among between-network functional connectivity, task accuracy, and average weighted FA/MD/RD[§] across all tracts (mediator) for both task conditions (low and no relatedness). This analysis thereby tested whether the relationship between functional connectivity and task performance could be explained by differences in white matter integrity.

Additionally, to integrate all primary measures included in the present study, a regression analysis was performed, examining which of the primary variables might aid in predicting concussion history in a former athlete. As such, parameters in the following equation were tested to determine which measures might significantly predict lifetime number of concussions sustained:

$$\text{Number of concussions} = \beta_0 + \beta_1(\text{Flanker}) + \beta_2(\text{List Sort}) + \beta_3(\text{Stroop}) + \beta_4(\text{COWAT}) + \beta_5(\text{HVLT}) + \beta_6(\text{WTAR}) + \beta_7(\text{Low Accuracy}) + \beta_8(\text{No Accuracy}) + \beta_9(\text{ACR Errors}) + \beta_{10}(\text{lagged negative-to-positive network connectivity in low condition}) + \beta_{11}(\text{lagged negative-to-positive network connectivity in no condition}) + \beta_{11}(\text{average weighted FA}) + \beta_{11}(\text{average weighted MD}) + \beta_{11}(\text{average weighted RD}) + \varepsilon$$

Hypotheses

[§] Due to high overlap in the calculation of MD and AxD, analyses examining multiple metrics of DTI in parallel only examine FA, MD, and RD.

Cognitive Task Data (Aim 1). Based on previous studies showing deficits in attentional processing/inhibitory function and some onset of memory dysfunction within a sample of former football athletes in middle-adulthood (Kutner et al., 2000), I hypothesized to observe deficits in football players (FC+ and FC-) relative to non-contact controls on the Flanker task (attention), Stroop task (inhibition), list-sorting task (working memory), and HVLT (memory), but no differences between athletes and controls on the COWAT (language). Additionally, given the increased risk for cognitive dysfunction in the group who sustained multiple past concussions (FC+), I hypothesized that they would perform worse than former football players with no concussion history (FC-) and controls (C-) on each of the tasks mentioned above. Such results would support previous findings that older, former football players with a history of participation in football show generally worse cognitive functioning even in middle-adulthood (Kutner et al., 2000). Further, they would also suggest that such deficits may begin before the "normal" onset of the cognitive symptoms of neurodegenerative disease (Risacher et al., 2009; Weiner et al., 2012), and before onset of cognitive decline associated with normal healthy aging (F. Craik & Jennings, 1992; F. I. Craik, 1990, 2008; Grady & Craik, 2000).

In-Scanner Task Data (Aims 1-3). Based on previous use of a similar task in a sample of individuals with MCI (Wagner et al., 2012), I hypothesized that former collegiate athletes at higher risk for neural injury that mirrors that of neurodegenerative disorders such as MCI (FC+) to show poorer performance overall on this task than individuals with the same degree of experience playing football but no concussion history (FC-). Further, given the potentially disrupted language production/processing and ability to draw on semantic linguistic knowledge in individuals with a history of concussions (Hart et al., 2013; Stamm, Bourlas, et al., 2015; Tremblay et al., 2013), I hypothesized that individuals with a history of concussion (FC+) will specifically show a lessened benefit of the cue word, even when the cue and target are highly semantically related. Thus, individuals with a history of concussions may be less able to rely on contextually relevant semantic knowledge to aid in their completion of the cued recall task. Further, I hypothesized that former athletes with a history of concussions (FC+) will show higher error rates overall, specifically driven by relatively more recombined pair errors than new word errors in this group. Since these individuals are at greater risk for damage to medial temporal lobe structures given their history of repeated mTBI, they may show difficulty binding specific pairs of words together, and thus may be more likely than FC- to produce more recombined errors in which they generate a different word presented during the experiment (non-target list word) in response to a cue word.

Functional Connectivity (Aim 2). I hypothesized that, while participants are encoding word pairs, between-network connections would be significantly weaker than when participants are viewing pairs of strings of consonants, since distinction between these two networks during the memory task is critical for neural efficiency and task success (Grady et al., 2010; Uddin et al., 2009). More specifically, as word pairs became less semantically related (no vs. low), these networks would become increasingly distinct, since unrelated words are harder to bind together than related words and thus require greater segregation of task-relevant and task-irrelevant networks. I also hypothesized that FC+ participants (relative to FC-) will show less functional distinction between the 2 networks (higher correlation between networks) during encoding of word pairs due to early-onset of age-related decrements in neural efficiency within this group (Browndyke et al., 2013; Persson, Lustig, Nelson, & Reuter-Lorenz, 2007; Prakash et al., 2012).

For the correlational connectivity analyses, I hypothesized the two networks to show decreasing connectivity as the task moves from consonant pairs (non-word, non-mnemonic) to low relatedness pairs (low mnemonic burden) to no relatedness pairs (high mnemonic burden) in the FC- group, but no (or reduced) difference among the three conditions in the FC+ group. In the bidirectional dynamic factor analytic model, I hypothesized a similar trend as in the correlational connectivity analyses. However in the cross-lagged dynamic factor analytic model, I hypothesized this effect would be observed in the positive-to-negative direction if this effect were driven by compensatory activation of ancillary networks, or in the negative-to-positive direction if this effect were driven by intrusion of the task-irrelevant network on the task-relevant network. Specifically, in the absence of a relationship between network connectivity and behavior, I would expect greater positive-to-negative connectivity in the FC+ group, but if network connectivity is related to behavior, I would expect greater negative-to-positive connectivity in the FC+ group.

In relating behavioral task data to functional connectivity metrics, I hypothesized that cued recall accuracy on the task would be negatively correlated with the correlation between the two networks during the corresponding task condition, such that individuals who show lower correlations between the memory-positive and memory-negative networks during encoding would show higher accuracy on the task. Similarly, I hypothesized that error production would be positively correlated with the connectivity between networks during the no relatedness condition. This effect is consistently reported in other studies assessing the relationship between the DMN and task-specific networks (Eichele et al., 2008); specifically, research has shown that older adults show difficulty suppressing the DMN relative to the task-specific network and that this has direct effects on behavioral performance (Prakash et al., 2012; Uddin et al., 2009; Grady et al., 2010).

Additionally, employing a more simplistic correlational connectivity analysis method alongside a novel dynamic factor analytic connectivity analysis method affords the opportunity for comparisons between these two methods in how they explain trends in the data. Given the higher level of within-subject variability accounted for in the dynamic factor analytic connectivity analysis, and its ability to test directional connectivity effect, I hypothesized that it would perform better in identifying correlational patterns between connectivity and behavioral outcomes on the task. Further, I hypothesized that any correlations between directed network connectivity (cross-lagged directed connectivity analysis) and behavior to be stronger than correlations between bidirectional (correlational connectivity analysis and contemporaneous bidirectional network connectivity analysis) and behavior, since cross-lagged connectivity analyses are better able to capture the temporal contingency of connectivity between the two networks, thus potentially capturing aspects of dynamic cognitively-driven network flexibility.

Structural Integrity (Aim 3). Past studies investigating the long-term effects of concussions on neural integrity have found mixed results as to the effect of concussions on white matter integrity in younger (Bashir et al., 2012; Bazarian et al., 2012; Cubon et al., 2011; Niogi et al., 2008; Zhang et al., 2010) and older adults (Stamm, Koerte, et al., 2015). Based on these studies I hypothesized that I would find compromised structural integrity in individuals with a history of multiple past concussions (FC+), relative to former football players with no history of concussions (FC-) and participants with no history of participation in contact sports (C-).

Importantly, however, when relating this structural integrity to functional connectivity and behavioral task data, I hypothesized that structural integrity would mediate the relationship between functional connectivity and task performance. As such, there would be a relationship between functional connectivity between networks and performance on the task; however, it may also be the case that structural integrity accounts for a significant amount of this relationship (Fujiyama et al., 2016; Greicius et al., 2009; Hirsiger et al., 2016; Xiao et al., 2015).

IV. RESULTS

Cognitive Assessments (Aim 1)

After running parallel one-way (group: C-, FC-, FC+) ANOVAs for each cognitive task of interest, there was no significant difference between groups on any of the tasks of interest (see Table 2; Figures 6-11). One ANOVA revealed a marginally significant difference between groups on the COWAT (see Figure 10), such that FC- participants scored lower on this task than C- participants ($p=0.013$), but both groups were not significantly different from FC+ participants (C- $p=0.098$; FC- $p=0.440$). However, after correcting for multiple comparisons, this difference was no longer significant. Additionally, since age-standardized scores were analyzed, means could be compared to the population mean; all group means fell within the normal population mean (HVLT: M=50, SD=10; all others: M=100, SD=15) for all tasks (see Figures 6-11). Further, there was no correlation between performance on any of the tasks and number of concussions sustained (see Table 2).

In-Scanner Task (Aims 1-3)

A 2 (Concussion History: FC- vs. FC+) x 2 (Relatedness: Low vs. No) mixed ANOVA revealed a significant effect of relatedness on accuracy ($F_{1,33}=166.851$, $p<0.001$), but no effect of concussion history ($F_{1,33}=0.177$, $p=0.677$), and no interaction between relatedness and concussion history ($F_{1,33}=0.039$, $p=0.844$). The main effect of relatedness showed that all participants had significantly higher accuracy in the low relatedness condition (M=0.762; SD=0.132) than the no relatedness condition (M=0.445; SD=0.205; see Figure 12). Additionally, a 2 (Concussion History: FC- vs. FC+) x 2 (Error Type: Recombined vs. New) mixed ANOVA revealed a significant effect of error type on error rates ($F_{1,33}$=5.248, p=0.028), but no effect of concussion history ($F_{1,33}$=0.315, p=0.578), and no interaction between error type and concussion history ($F_{1,33}$=1.404, p=0.245). The main effect of error type showed that all participants produced significantly more recombined errors (M=3.857; SD=3.561) than new errors (M=2.821; SD=2.609; see Figure 13).

Additionally, neither accuracy (r_{low}=0.056, p=0.747; r_{no}=0.014, p=0.937) nor error type ($r_{recombined}$=0.281, p=0.101; r_{new}=0.199, p=0.251) was significantly correlated with number of concussions sustained.

Functional Connectivity (Aim 2)

Correlational connectivity analysis. A 2 (Concussion History: FC- vs. FC+) x 3 (Task condition: Consonants vs. Low Relatedness vs. No Relatedness) x 3 (Network: Memory Positive vs. Memory Negative vs. Between Network) mixed ANOVA revealed a significant effect of task condition ($F_{2,28}$=4.022, p=0.023) and network ($F_{2,28}$=44.469, p<0.001), but no main effect of concussion history ($F_{1,28}$=0.033, p=0.857), and no interactions between task condition and concussion history ($F_{2,28}$=1.590, p=0.213), network and concussion history ($F_{2,28}$=0.240, p=0.787), task condition and network ($F_{4,28}$=1.710, p=0.153), nor concussion history, task condition, and network ($F_{4,28}$=0.655, p=0.624). The main effect of task condition suggested that overall ROIs showed greater connectivity within and between networks during the no association condition (M=0.454, SD=0.137), than during the consonants condition (p=0.023; M=0.396, SD=0.142), but neither the consonants condition (p=1.000) nor the no association condition (p=0.201) was significantly different from the low association condition (M=0.400, SD=0.159). The main effect of network suggested that overall between-network connections (M=0.339, SD=0.137) were significantly weaker than both within-memory-positive (p<0.001; M=0.466, SD=0.120) and within-memory-negative ($p<0.001$; M=0.445, SD=0.148) connections, but within network connectivity was not significantly different between the two networks (p=0.730). Additionally, there was no significant correlation between number of concussions sustained and between-network connectivity during any of the three task conditions (r_{cons}=-0.005, p=0.977; r_{low}=-0.241, p=0.200; r_{no}=-0.072, p=0.707).

Correlational analyses conducted between task accuracy and corresponding between-network connectivity showed a relationship between connectivity between networks during the low relatedness condition and low relatedness accuracy (r=0.023, p=0.902), but not between connectivity between networks during the no relatedness condition and no relatedness accuracy (r=0.034, p=0.858). Further, there was no relationship between no relatedness between-network connectivity and recombined (r=0.054, p=0.777) or new errors (r=-0.105, p=0.582).

Dynamic factor analytic connectivity analysis.

Contemporaneous bidirectional network connectivity. A 3 (Task Condition: Consonants vs. Low Association vs. No Association) x 2 (Concussion History: FC- vs. FC+) mixed ANOVA revealed no effect of task condition ($F_{2,28}$=2.180, p=0.122) or concussion history ($F_{1,28}$=0.006, p=0.937), and no interaction between task condition and concussion history ($F_{2,28}$=1.180, p=0.315) on contemporaneous connectivity between latent networks. Correlational analyses conducted between task accuracy and corresponding contemporaneous between-network connectivity showed no relationship between connectivity between networks during the low relatedness condition and low relatedness accuracy (r=0.014, p=0.940), or between connectivity between networks during the no relatedness condition and no relatedness accuracy (r=0.166, p=0.380). Further, there was no relationship between no relatedness between-network connectivity and recombined (r=0.188, p=0.321) or new errors (r=-0.020, p=0.916).

Lagged directed connectivity. A 3 (Task Condition: Consonants vs. Low Association vs. No Association) x 2 (Concussion History: FC- vs. FC+) x 2 (Connection Direction: Positive-to-Negative vs. Negative-to-Positive) mixed ANOVA showed a significant interaction between connection direction and concussion history ($F_{1,28}$=13.267, p<0.001), but no main effect of connection direction ($F_{1,28}$=0.369, p=0.549), condition ($F_{2,28}$=2.401, p=0.100) or concussion history ($F_{1,28}$=0.317, p=0.578), and no interactions between task condition and concussion history ($F_{2,28}$=1.987, p=0.147), task condition and connection direction ($F_{2,28}$=1.340, p=0.270), or task condition, concussion history, and connection direction ($F_{2,28}$=0.462, p=0.633). The significant interaction between concussion history and connection direction demonstrates that across all conditions, FC- participants show greater positive-to-negative connectivity than negative-to-positive connectivity (t_{13}=-2.232, p=0.044), but FC+ participants show the reverse trend (t_{15}=2.945, p=0.010; see Figure 14). Specifically, the FC+ group showed a significantly positive average beta-weight in the negative-to-positive connection direction (95% confidence interval above 0), while all other beta-weights for the connection directions did not significantly differ from 0 (see Figure 14). Across all three task conditions, 19.61% of individual negative-to-positive connection beta estimates in the FC+ group were significantly positive, while in the FC- group only 10% of negative-to-positive connections were significantly positive. Correlational analyses conducted between task accuracy and corresponding cross-lagged negative-to-positive network connectivity showed a relationship between connectivity between networks during the low relatedness condition and low relatedness accuracy (r=-0.423, p=0.020), but there was no significant correlation in the no relatedness condition with no relatedness accuracy (r=-0.210, p=0.266). This suggests that greater connectivity from the memory negative network to the memory positive network during low relatedness pair encoding is associated with lower accuracy on the task. Additionally, there was a significant positive relationship between no relatedness negative-to-positive network connectivity and recombined ($r=0.434$, $p=0.016$) but not new errors ($r=0.280$, $p=0.135$). As such, higher levels of negative-to-positive network connectivity during the no relatedness condition were associated with higher rates of recombined error generation.

Structural Integrity (Aim 3)

Whole-brain TBSS on FA values for all participants revealed no significant difference in FA based on football participation or concussion history (all p-values>0.150). Further, there were no significant differences in mean ($F_{2,37}=1.062$, $p=0.356$) or max ($F_{2,37}=0.529$, $p=0.594$) global FA based on football participation or concussion history. Additionally, neither maximum ($r=0.050$, $p=0.757$) nor mean ($r=-0.041$, $p=0.804$) global FA were significantly correlated with number of concussions sustained.

In comparing white matter integrity in the 5 major tracts of interest (corpus callosum, uncinate fasciculus, inferior longitudinal fasciculus, superior longitudinal fasciculus, and cingulum) between groups, there were no differences between groups in FA ($F_{2,36}=2.373$, $p=0.108$), MD ($F_{2,36}=0.664$, $p=0.521$), RD ($F_{2,36}=1.638$, $p=0.209$), or AxD ($F_{2,36}=1.909$, $p=0.163$). Further, there was no significant interaction between group and tract for any of the metrics: FA ($F_{2,36}=0.589$, $p=0.785$), MD ($F_{2,36}=0.949$, $p=0.479$), RD ($F_{2,36}=0.536$, $p=0.828$), AxD ($F_{2,36}=0.701$, $p=0.690$).

Multi-modal imaging analysis. Partial correlation analyses revealed no substantive changes in the significance of the relationships between functional connectivity metrics and accuracy/error production on the in-scanner task (Table 3). Further, multi-modal regression analyses testing whether the primary variables in the present study (cognitive assessments, in-scanner task behavioral metrics, negative-to-positive network directed connectivity, and average weighted FA/MD/RD) predict number of lifetime concussions sustained showed that none of the predictors significantly predicted number of concussions sustained (model $R^2=0.460$).

V. DISCUSSION

Cognitive Assessments (Aim 1)

Results from the battery of standardized cognitive assessments showed no differences between groups based on any of the cognitive domains assessed (attention, working memory, inhibition, language, and episodic memory) or on premorbid IQ. Further, since the task scores were all standardized based on age, performance could also be compared to global population averages – all groups means fell within one standard deviation of the population mean on each domain assessed. As such, results from this study show that former athletes in middle-adulthood show no cognitive deficits based on concussion history when comparing to same-sport non-concussed former athletes, non-contact former athletes, as well as the overall population of same-age individuals.

These results suggest that, unlike some previous studies showing deficits in attention (Baillargeon, Lassonde, Leclerc, & Ellemberg, 2012; Kutner, Erlanger, Tsai, Jordan, & Relkin, 2000; Terry et al., 2012), working memory (Baillargeon et al., 2012; Gardner, Shores, & Batchelor, 2010; Terry et al., 2012), and inhibition (Belanger, Spiegel, & Vanderploeg, 2010; Moore et al., 2015; Pontifex, O'Connor, Broglio, & Hillman, 2009) in younger adults with a history of concussions, the present study supported the studies that found no differences between former athletes who had sustained concussions and those who had not (Bruce & Echemendia, 2009; Collie, McCrory, & Makdissi, 2006; Guskiewicz, 2002; Straume-Naesheim, Andersen, Dvorak, & Bahr, 2005). Thus, it may be the case that even in middle-adulthood, the cognitive deficits seen in older adults with a history of concussions have not yet emerged. This evidence would support the notion that these cognitive deficits tied to concussion history are not necessarily present and evolving throughout the lifespan, but instead may be deficits that emerge as a function of disordered patterns of cognitive aging exacerbated by lifetime accrual of neural damage from a history of mTBI.

In-Scanner Task (Aims 1-3)

Results from the in-scanner task overall showed that participants performed better in the low relatedness pair condition than the no relatedness pair condition. This validates the inherent semantic relationship between words in these pairs as established by the University of South Florida Free Association Norms database (Nelson, McEvoy, & Schreiber, 2004), and suggests that all participants are using this existing semantic relationship to bolster their memory for the target word in these pairs in response to the related cue word. The lack of interaction between this semantic relationship benefit and concussion history suggests that athletes in this age range do not show reduced ability to process and retain semantic information as a function of concussion history. While the lack of a control group hampers the ability to compare both football groups to an appropriately-matched control group, these data show no effect of concussion history on the ability to benefit from preexisting semantic knowledge during a cued recall task. Thus, it may be the case that the specific mechanism of tau deposition in those with a history of repeat concussions, unlike those with MCI/AD, does not affect cued recall performance and thus this deficit is specific to the mechanism of tau deposition in MCI/AD (Wagner et al., 2012), or it could suggest that any effect of tau deposition on cued recall performance has not yet emerged in these individuals in middle-adulthood.

Functional Connectivity (Aim 2)

Correlational Connectivity Analysis. Results from the correlational connectivity analyses showed that, contrary to the hypothesized pattern of results, participants showed greater connectivity within and between the memory positive and memory negative networks during the no relatedness condition relative to the consonants condition. While the direction of this trend was the opposite of what was hypothesized, it supports recent research examining connectivity during an episodic memory task, suggesting that more integrated/less segregated neural networks facilitate episodic memory encoding (Geib, Stanley, Dennis, Woldorff, & Cabeza, 2017; Westphal, Wang, & Rissman, 2017). However, given that these connectivity metrics showed no relationship with task performance, it is unclear whether increased connectivity during the most difficult condition of this task actually benefitted memory encoding.

Results from these analyses also showed greater within- than between-network connectivity. This suggests that, regardless of task condition, participants showed clear network distinction. This functional distinction between networks corroborates general connectivity research patterns that show overall segmentation of connectivity data into functional networks that clear functional distinction from other networks even at rest (review: van den Heuvel & Hulshoff Pol, 2010). Since the networks used here were not "traditional" network delineations using standard functional atlases, this result validates the functional distinctiveness between these empirically-derived cognitive networks, and suggests that they may represent distinct neural networks for use in these and other similar connectivity analyses (Habeck et al., 2016; Y. Stern et al., 2014).

Dynamic Factor Analytic Connectivity Analysis. The preliminary model investigating bi-directional contemporaneous connectivity between the memory-positive and memory-negative networks showed no modulation of within- or between-network connectivity based on either concussion history or task condition. These results do not mirror results from the correlational connectivity analyses in that they do not show overall increases in connectivity during the most difficult task condition. Since this dynamic factor analytic technique better accounts for within-subject variance in estimating network-based factor loadings, this calls into question the significance and interpretability of the effect seen in the correlational analyses.

However, the model examining directed lagged connectivity provided novel findings regarding the directionality of between-network connectivity. Results from this analysis showed an interaction between connection direction and concussion history, such that FC+ participants showed greater negative-to-positive network connectivity than positive-to-negative network connectivity, while FC- participants showed the opposite effect. Critically, however, correlational analyses showed a negative relationship between negative-to-positive network connectivity during the low relatedness condition and low relatedness pair accuracy, and a positive relationship between negative-to-positive network connectivity during the no relatedness condition and production of recombined errors. Thus, unlike in the correlational connectivity analyses, these between-group differences carry cognitive significance in that this negative-to-positive network connectivity is associated with lower accuracy (in the low relatedness condition) and production of more recombined errors (in the no relatedness condition). While these two groups did not differ in task accuracy or error production, one group showing a pattern of connectivity that may be associated with poorer performance on the task could suggest inefficient network functioning in this group, and the potential for behavioral differences between groups later in life. As such, we can interpret this greater negative-to-positive network connectivity in the FC+ group as inefficient network functioning, since it is independently associated with poorer performance on the task. As in past studies showing poorer behavioral outcomes as a result of intrusion of the task-irrelevant network on the task-relevant network (Bonnelle et al., 2012; Eichele et al., 2008; Hoekzema et al., 2014; Weissman, Roberts, Visscher, & Woldorff, 2006), this pattern could be reflective of disrupted task-relevant network processing, resulting in less efficient processing of task stimuli. Further, the relationships between these metrics of connectivity and behavioral measures collected during the task may suggest greater utility of this connectivity approach over a more simplistic correlational connectivity approach in enabling analysis of directed patterns of functional connectivity between cognitively-defined networks that map onto key behavioral outcomes.

This finding also mirrors recent research showing that individuals with a history of mTBI show reduced ability to segregate task-positive and default mode networks during a working memory task (Bonnelle et al., 2012; Sours, Kinnison, Padmala, Gullapalli, & Pessoa, 2017), but builds upon these findings by examining the link between this reduced ability to segregate two cognitively-defined networks during a memory task and behavioral performance on that memory task. Further, this set of results also suggests that the effect observed in prior studies showing that connectivity between task-relevant and task-irrelevant networks is associated with poorer performance on tasks of executive function (Grady et al., 2010; Prakash et al., 2012; Sours et al., 2017; Uddin et al., 2009) may not be unique to these executive function tasks.

Structural Integrity (Aim 3)

Results from analyses of DTI white matter integrity showed no differences in FA, MD, RD, or AxD based on either concussion history or football participation history in both TBSS (whole-brain) and TRACULA (tract-based) analyses. This finding calls into question previous studies in younger adults and former/current athletes in middle-adulthood showing differences in white matter integrity based on concussion history or exposure to subconcussive impacts, since no differences between groups were observed in this sample of participants in middle-adulthood (Bazarian, Zhu, Blyth, Borrino, & Zhong, 2012; Henry et al., 2011; Lipton et al., 2013; Multani et al., 2016; Wilde et al., 2016). Key distinctions between the present study and previous studies in athletes in middle-adulthood include its inclusion of participants who are no longer active athletes (Lipton et al., 2013), its focus on former football players as the contact sport group (Lipton et al., 2013; Wilde et al., 2016), and its inclusion of athletes who did not participate in professional football (Multani et al., 2016). As such, while this study's finding of no differences in white matter integrity based on concussion history or participation in contact sport could also reflect the fact that these athletes are no longer actively participating in contact sport, and that their highest level of athletic participation was collegiate athletics. The lack of difference also suggests that it could be the case that white matter damage doesn't necessarily accrue incrementally as a function of each football-related concussion or head impact, but instead may be subtle, and may interact with white matter loss in aging to produce the effects on concussions on white matter integrity seen in older, retired athletes (Casson, Viano, Haacke, Kou, & LeStrange, 2014; Clark et al., In Press; Stamm, Koerte, et al., 2015).

Multi-Modal Imaging Analysis. Further, white matter integrity did not account for the relationship between functional connectivity and behavioral performance. While this was an exploratory aim, it suggests that the relationship between negative-to-positive connectivity and accuracy/error production is not simply a product of structural connectivity integrity. As such, it is not necessarily the case that functional connectivity and behavioral performance are both detrimentally impacted by the integrity of white matter connections, and that the integrity of these connections is the true, independent, predictor of neurocognitive functioning in this sample.

Additionally, none of the primary variables in the present study significantly predicted lifetime number of concussions sustained. Given the few group differences based on concussion history, as well as the lack of significant correlation between number of concussions sustained and the many metrics in the current study, this was not necessarily a surprising finding, but does suggest that the variability in these primary metrics is not explained by concussion history. It could be the case that such variability might be better explained by history of exposure to subconcussive impacts (McAllister & McCrea, 2017; Montenigro et al., 2017; Stamm, Bourlas, et al., 2015; Stamm, Koerte, et al., 2015), genotype (Casson, Viano, Haacke, Kou, & LeStrange, 2014; Kutner et al., 2000; Tremblay et al., 2013), expression of depressive symptomology (Guskiewicz et al., 2007; Montenigro et al., 2017; Multani et al., 2016; R. A. Stern et al., 2011; J. Strain et al., 2013), etc., however these questions are outside of the scope and hypotheses of the present study.

Summary

Overall, the results from the present study showed no differences between former contact and non-contact athletes or athletes with a history of concussions and athletes with no history of concussions on cognitive assessments or DTI measures of white matter integrity. However, former football athletes with a history of 4+ concussions showed more inefficient functional connectivity during encoding of word pairs than former football athletes with no history of concussions. While these results do not show strong effects of concussion history in these former collegiate athletes in middle-adulthood, they show some subtle differences in neural functioning tied to concussion history that could indicate potential for cognitive impairment later in life. Thus, these athletes with a history of multiple concussions may not show marked cognitive or structural neural deficits, but instead may show more subtle signs of cognitive processing inefficiency that have the potential to illuminate mechanisms of cognitive impairment in the context of cognitive aging.

These findings bring to mind the distinction between the concepts of brain or neural reserve (Bartres-Faz & Arenaza-Urquijo, 2011; Satz, 1993) and cognitive reserve (Bartres-Faz & Arenaza-Urquijo, 2011; Barulli & Stern, 2013; Y. Stern, 2002, 2006, 2012). Brain reserve is conceptualized as the amount of neural damage or integrity loss necessary to produce cognitive impairment, whereas cognitive reserve suggests that variables such as education level/participation in leisure activity/IQ may affect the ability to effectively recruit neural networks and cognitive resources, which in turn affects cognitive performance. The results presented here suggest that directed functional connectivity between a task-relevant and task-irrelevant network may better predict cued recall task performance than metrics of white matter integrity, suggesting that this measure of network efficiency may play a greater role in cognitive functioning than white matter damage alone. This supports the notion expressed by some in the field of concussion research that cognitive reserve may play a significant role in symptom expression in former contact sport athletes (Broglio, Eckner, Paulson, & Kutcher, 2012). While the present study is limited in only analyzing DTI data as a measure of structural integrity/health, concussions are thought to affect white matter integrity through axonal shearing, and as such should show long-term effects on DTI measures of white matter health. Thus the lack of difference in white matter integrity as a function of concussion history in this sample fails to support the hypothesis that brain or neural reserve are impacted by concussive injury (Randolph, Karantzoulis, & Guskiewicz, 2013), however this difference in network connectivity in the absence of differences in underlying structural connectivity suggests that concussions may be impacting the ability to flexibly modulate network function in response to cognitive demands.

This relatively early emergence of functional network inefficiency could be seen as a sign of diminished cognitive reserve, and thus potentially lower ability to resist age-/neurodegeneration-related cognitive decline later in life (Barulli & Stern, 2013; Y. Stern, 2012). Thus, individuals who presently show this inefficient pattern of neural recruitment may be at higher risk for development of cognitive impairment earlier than those who do not show this pattern. Since this pattern of functional recruitment is independently tied to lower accuracy and higher rates of error production, it could indicate that over time these individuals may begin to show cognitive impairments as a function of this network inefficiency. Future studies assessing this network connectivity over time may aid in clarifying whether these functional inefficiencies observed earlier in life affect cognitive function later in life. Additionally, while the participants in the present study were matched on years of education, and showed no differences in premorbid IQ (WTAR), conclusions about the direct effect of standard metrics of cognitive reserve are limited. However, future studies might be able to assess the effect of social/cognitive/physical activity on this functional connectivity metric in order to assess the direct effect of metrics of cognitive reserve on functional connectivity, and in turn on cognitive functioning.

Limitations

One key limitation of the present study is the lack of an appropriate control group; given the restrictive criteria to be included in the present study (participated in original study between 1999-2001, able to travel to participate, no MRI contraindications, etc.), it was difficult to recruit participants who met study criteria, and even more difficult to recruit non-contact control participants who likely had less personal investment in concussion research as opposed to those who had participated in college football. While this is a limitation in interpreting the fMRI findings, all cognitive task data were age-standardized and thus represent deviation from an age-appropriate "normal" score, and cognitive and DTI data did include 5 additional control participants who were able to complete all non-fMRI study procedures. As such, given that there were no cognitive or DTI differences between former football athletes and control athletes, it may be the case that, as of this period of middle-adulthood, this football sample does not significantly differ in many ways from a normal control sample.

Another limitation of the present study is the unequal sample sizes between low concussion (n=14) and high concussion (n=21) football athletes. Again, considering that in most cases participants had to travel to the study sites for a full day of participation, it could simply be the case that low concussion athletes were less personally invested in concussion research, and thus less likely to be willing to participate in the current study. Alternatively, given the recent media attention surrounding the potential neurodegenerative effects of repetitive concussive injury, it could be the case that former athletes who sustained multiple concussion were more personally invested in concussion research, and thus were more likely to be willing to participate in the current study. While the present study employed some correlational analyses in order to probe the additive effects of concussions independent of this dichotomous concussion history grouping, given the non-normal distribution of concussions in this sample[**] it could be the case that correlational relationships between concussion history and some of the outcome measures here may be difficult to observe.

[**] The "low concussion" group (n=14) consisted of people with 0 or 1 concussions, this group is fairly evenly distributed between those with 1 concussion (n=8), and those with 0 concussions (n=6), while the "high concussion" group (n=21) includes individuals with a range of number of concussions sustained from 4 concussions (n=5) to 24 concussions (n=1). As such, the number of concussions sustained is more heavily weighted at 1, or between 4-10, and is entirely missing those who have sustained 2 or 3 concussions.

A third limitation of the present study is the duration of the scanned ACR task. Due to scan time restrictions, only 20 minutes of encoding data (5 minutes per encoding run; 4 minutes total per encoding condition) were able to be collected for each participant in this study. Since the study design was blocked in order to maximize the potential to observe effects related to word pair association strength (low vs. no), this strengthens the ability to study these effects given the task time constraints; however, the low number of trials in each condition (120 TRs per condition) may have affected the ability to observe functional differences related to task condition. Finally, a limitation of this blocked design is the inability to look at subsequent memory effects, and thus model differences in functional activity based on later ability to recall the target word in response to the cue word. However, since the primary outcome measures for the fMRI data collected in the present study were network-based connectivity metrics, the block design was better suited for modeling of connectivity data.

Implications

In spite of these limitations, the present data illuminate ways in which neural efficiency may differ as a function of concussion history, in the absence of behavioral differences in cognitive performance. The finding that FC+ participants show overall greater connectivity directed from a memory-negative network to a memory-positive network, and that greater strength of this connection is associated with poor behavioral outcomes (lower accuracy and higher recombined error rate) suggests that in middle-adulthood former football players with a history of concussion may be starting to show signs of inefficient neural recruitment patterns that could be suggestive of cognitive declines to come. This would indicate lower levels of cognitive reserve in these participants, suggesting a reduced ability to resist cognitive decline in aging or neurodegenerative disease onset.

Further, the lack of behavioral differences between concussion groups on most metrics used in the present study suggests that it may not be the case that individuals with a history of concussions are universally impaired relative to those with no history of concussions throughout the lifespan. While there were some key differences between those with 4+ or 0-1 concussions, the lack of differences on neurocognitive testing, the in-scanner task, and DTI metrics suggest that it is not always the case that those with a history of concussions show reduced neurocognitive health relative to those with no history of concussions. Based on these findings, the present study does not provide considerable evidence for concussion-related deficits in middle-adulthood, but does show potential for reduced neural processing efficiency that could result in cognitive deficits in high concussion athletes later in life. Unlike many studies in older and younger adults that have documented persistent long-term effects of multiple concussions, the present study provides limited evidence supporting the presence of neurocognitive deficits in middle-adulthood associated with a history of multiple concussions.

Future Directions

Based on the results from the present study, future studies should examine neurocognitive functioning using similar metrics in former athletes in older age brackets to test whether this inefficient neural processing observed in middle-adulthood persists into older adulthood, and whether or when it begins to result in behavioral impairment for these former athletes with a history of concussions. Additionally, it would strengthen conclusions about potential development of cognitive impairment over time linked to functional inefficiency observed at the present time point to follow participants from the present study longitudinally. In order to fully explore the development of cognitive deficits or neural damage linked to concussion history, it is necessary to have cognitive assessment and neuroimaging data at multiple time points throughout the lifespan. Further, future studies should include a more robust control group in order to make comparisons between former football players and former non-contact athletes in neurocognitive and DTI data, and also to enable comparisons between football players and former non-contact athletes in fMRI functional connectivity metrics.

APPENDIX 1: TABLES AND FIGURES OF RESULTS

Table 1

ACR Task Cue-Target Word Lists by Association Strength and List.

Cue	Target - Low	List - Low	Association - Low	Target - No	List - No
angel	hair	1	0.007	wallet	2
ankle	calf	2	0.007	stars	1
apple	teacher	1	0.007	hockey	2
barrel	cheese	2	0.006	robe	1
beast	bull	1	0.006	coral	2
berry	farm	2	0.007	arrow	1
blade	hockey	1	0.008	book	2
blanket	robe	2	0.008	police	1
brain	coral	1	0.006	sailor	2
brick	sand	2	0.006	juice	1
bridge	stream	2	0.008	kitchen	1
bubble	baby	1	0.007	house	2
butter	cake	1	0.006	hair	2
button	sleeve	2	0.007	horse	1
cabinet	cookies	2	0.007	tire	1
canoe	ship	1	0.008	jewelry	2
chain	truck	2	0.006	sand	1
costume	parade	1	0.006	woods	2
diamond	stone	1	0.005	ship	2
dough	roll	1	0.005	shot	2
earth	stars	2	0.006	lock	1
elbow	finger	2	0.007	cottage	1
essay	novel	2	0.007	cheese	1
fairy	queen	1	0.007	church	2
feast	table	1	0.006	beach	2
fiddle	barn	2	0.007	spring	1
frame	house	1	0.007	wave	2
glove	shoe	2	0.006	plane	1
grape	soda	1	0.007	bull	2
gravy	syrup	1	0.008	message	2
ground	shovel	1	0.006	theater	2
heaven	gate	2	0.007	novel	1
highway	police	2	0.007	reef	1
hotel	beach	1	0.007	soda	2

human	pets	2	0.007	gate	1
island	reef	2	0.007	sleeve	1
letter	message	1	0.007	frog	2
liquid	juice	2	0.007	guitar	1
lobby	door	1	0.007	bowl	2
market	jewelry	1	0.007	jeans	2
mermaid	scales	2	0.007	barn	1
motor	plane	2	0.007	cookies	1
mouse	chicken	1	0.007	skin	2
muscle	head	2	0.007	oven	1
napkin	lunch	2	0.007	truck	1
needle	shot	1	0.006	stairs	2
night	gown	1	0.006	door	2
onion	skin	1	0.007	teacher	2
orange	seed	1	0.01	park	2
peach	orchard	2	0.01	calf	1
picture	wallet	1	0.01	seed	2
pigeon	bench	2	0.01	weapon	1
planet	wave	1	0.006	table	2
pocket	comb	2	0.007	orchard	1
potato	oven	2	0.007	scales	1
prairie	woods	1	0.007	parade	2
rabbit	bird	1	0.006	syrup	2
rifle	weapon	2	0.007	shoe	1
robin	spring	2	0.007	comb	1
shield	wall	1	0.007	baby	2
singer	guitar	2	0.008	turkey	1
skirt	jeans	1	0.006	stone	2
smoke	cigar	2	0.008	gold	1
snake	frog	1	0.006	wall	2
spoon	bowl	1	0.008	gown	2
square	book	1	0.007	queen	2
steeple	stairs	1	0.007	roll	2
stool	kitchen	2	0.007	ghost	1
supper	turkey	2	0.007	pets	1
sword	arrow	2	0.006	lunch	1
thread	gold	2	0.006	stream	1
ticket	theater	1	0.007	bird	2
track	tire	2	0.006	head	1
trail	park	1	0.006	cake	2
trunk	lock	2	0.007	farm	1

valley	horse	2	0.007	finger	1
village	cottage	2	0.007	cigar	1
wedding	church	1	0.007	shovel	2
witch	ghost	2	0.007	bench	1
yacht	sailor	1	0.008	chicken	2

Table 2

Task means, ANOVA F- and p-values, and correlation coefficient with number of concussions sustained for neurocognitive tasks (standard deviations in parentheses). All F-tests had 2 between-group degrees of freedom, and 51 within groups degrees of freedom.

Domain	Task	ANOVA		Means			Correlation	
		F	P-Value	C-	FC-	FC+	R	P-value
Attention	Flanker	0.077	0.926	94.000 (6.856)	96.250 (13.392)	95.240 (12.685)	0.032	0.820
Working Memory	List Sort	1.463	0.241	112.400 (6.348)	110.600 (10.117)	106.210 (11.030)	-0.008	0.957
Inhibition	Stroop	1.350	0.268	100.400 (14.258)	94.950 (12.484)	91.310 (12.160)	-0.241	0.079
Language	COWAT	4.568	0.015	123.800 (4.919)	102.700 (17.918)	108.760 (11.948)	-0.184	0.183
Memory	HVLT	1.049	0.358	50.600 (6.229)	65.450 (27.719)	58.310 (21.017)	-0.032	0.816
Premorbid IQ	WTAR	2.633	0.079	119.000 (2.449)	113.550 (6.716)	111.280 (7.819)	-0.280	0.041

Table 3

Partial correlation results examining correlations between behavioral task performance (low accuracy, no accuracy, recombined error production, new error production) and functional connectivity (correlational between-network connectivity - CorrCon, bidirectional between-network dynamic factor analytic connectivity - FAConnBid, and directed negative-to-positive network dynamic factor analytic connectivity – FAConnN2P), after controlling for 3 measures of white matter integrity (average weighted FA/MD/RD from the 6 tracts of interest).

Behavioral Variable	Connectivity Variable	Partial Correlation		Original Correlation	
		R-value	p-value	R-value	p-value
Low Accuracy	CorrConn - Low	-0.080	0.697	0.023	0.902
	FAConnBid – Low	0.005	0.981	0.014	0.940
	FAConnN2P - Low	**-0.428**	**0.029**	**-0.423**	**0.020**
No Accuracy	CorrConn – No	-0.031	0.879	0.034	0.858
	FAConnBid – No	0.119	0.564	0.166	0.380
	FAConnN2P - No	-0.058	0.779	-0.210	0.266
Recombined Errors	CorrConn – No	0.134	0.515	0.054	0.777
	FAConnBid – No	0.193	0.345	0.188	0.321
	FAConnN2P - No	**0.410**	**0.037**	**0.434**	**0.016**
New Errors	CorrConn – No	-0.037	0.858	-0.105	0.582
	FAConnBid – No	0.039	0.848	-0.020	0.916
	FAConnN2P - No	0.216	0.290	0.280	0.135

Table 4

Regression parameters from multi-modal imaging analysis.

Predictor	B-value	SD	T-value	p-value
Constant	235.622	1503.033	0.859	0.404
Flanker	0.262	0.882	1.633	0.123
List Sort	0.092	0.707	0.718	0.484
Stroop	-0.178	0.745	-1.309	0.210
COWAT	-0.052	0.641	-0.442	0.665
HVLT	-0.076	1.024	-0.408	0.689
WTAR	-0.082	1.068	-0.421	0.680
Low Accuracy	-5.559	92.686	-0.329	0.747
No Accuracy	8.755	61.049	0.785	0.444
Total Errors	0.167	1.402	0.653	0.524
Negative-to-Positive Low Condition	-6.630	37.985	-0.956	0.354
Negative-to-Positive No Condition	6.718	50.308	0.731	0.476
Average Weighted FA	-359.481	2930.562	-0.672	0.512
Average Weighted MD	273523.395	3785757.668	0.396	0.698
Average Weighted RD	-516573.095	5422938.793	-0.522	0.609

Figure 1

Study flowchart.

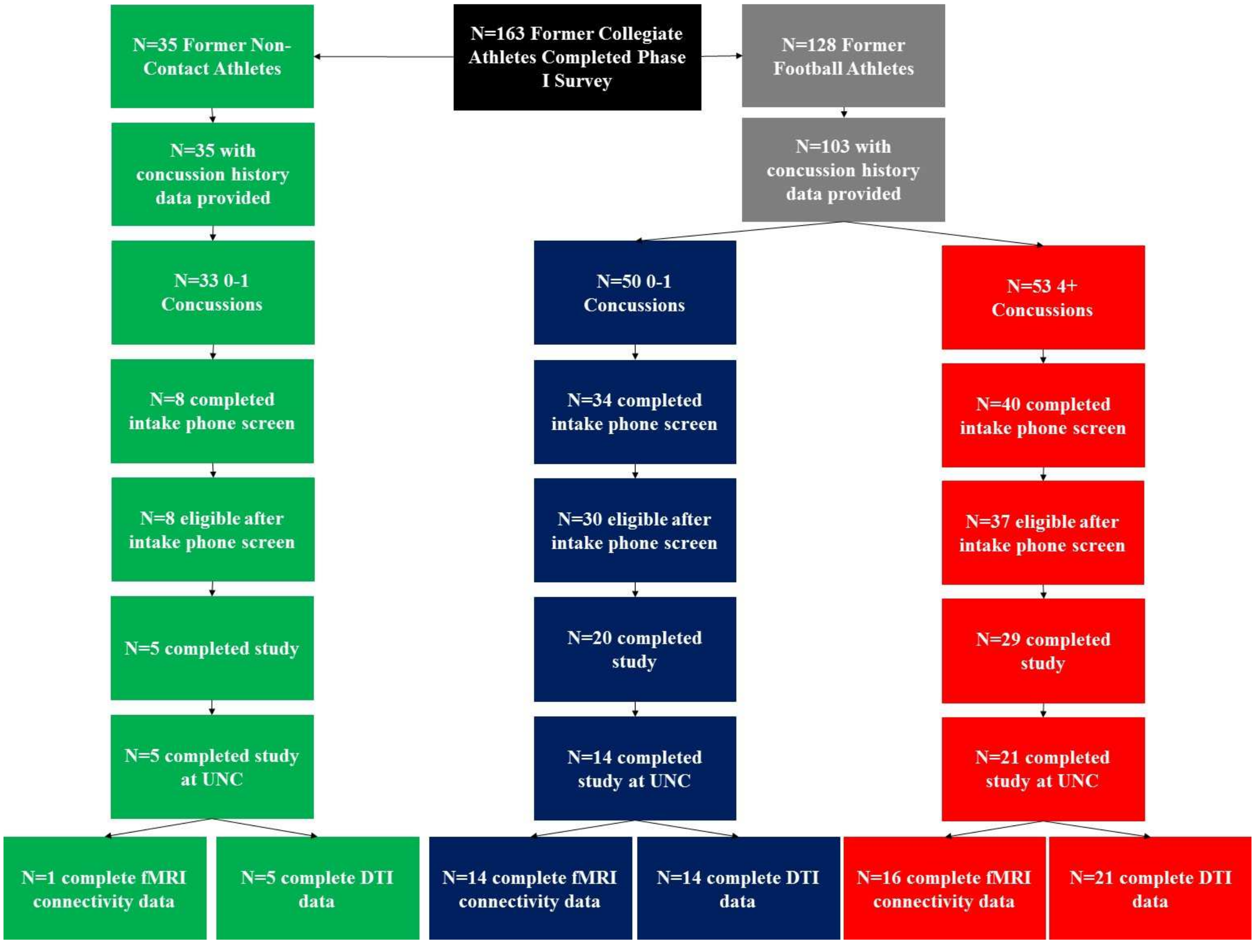


Figure 2

ACR task illustration.

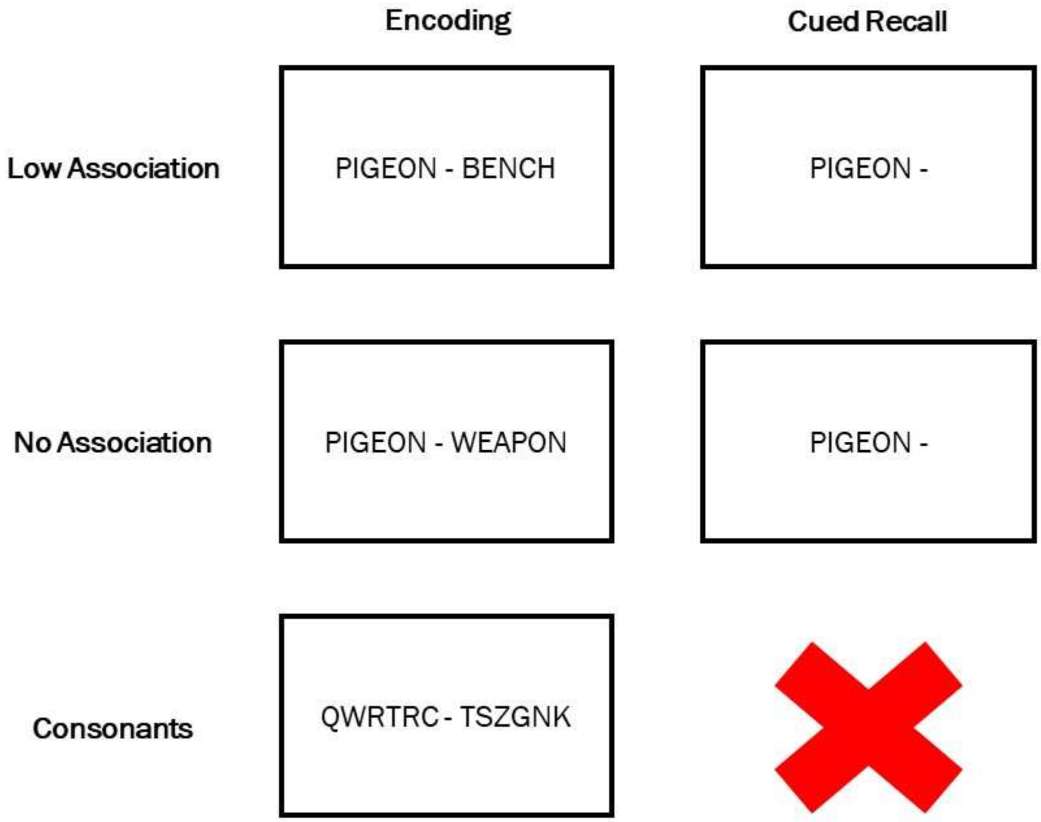


Figure 3

Illustration of simple correlational connectivity design. Matrix represents correlation matrix among all 34 ROIs (first 15: memory positive network; last 19: memory negative network), and coloring represents cells that were averaged to generate average correlation within (memory positive: yellow; and memory negative: turquoise) and between (green) networks for each task condition for each participant. Cells filled in black are self-correlations equal to 1 that were not included in these metrics.

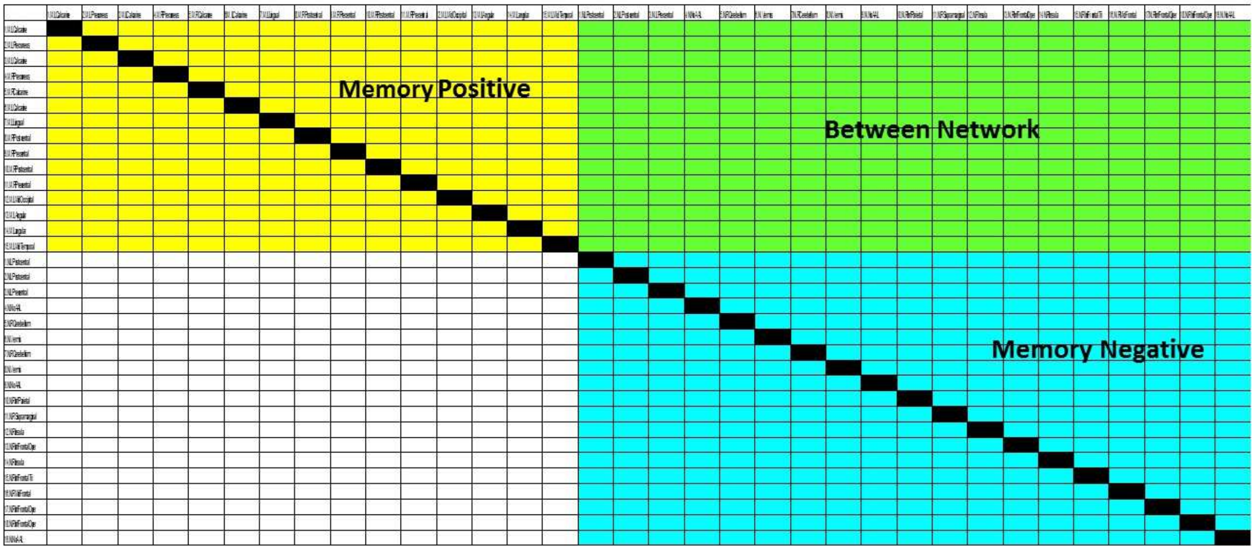


Figure 4

Illustration of contemporaneous bidirectional network connectivity design. ROIs are numbered based on their position in the table of coordinates in Habeck et al. (2016).

Figure 5

Illustration of cross-lagged directed network connectivity design.

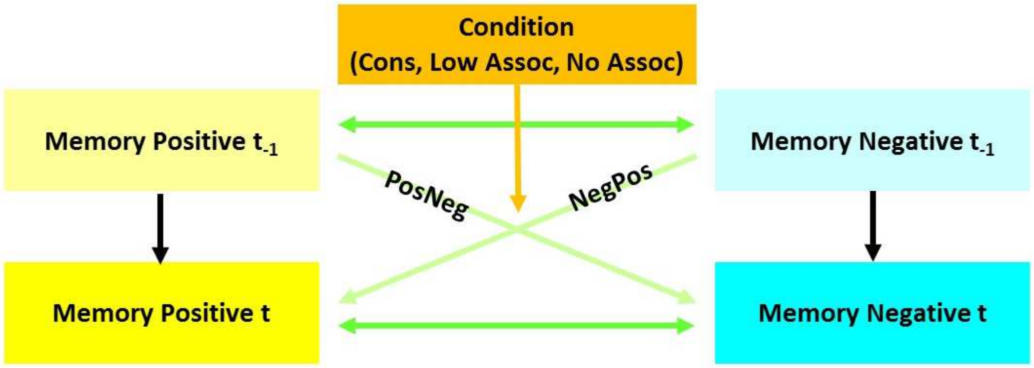


Figure 6

Group means for age-corrected standard scores on the flanker task. Dashed line represents standardized population mean (SD=15).

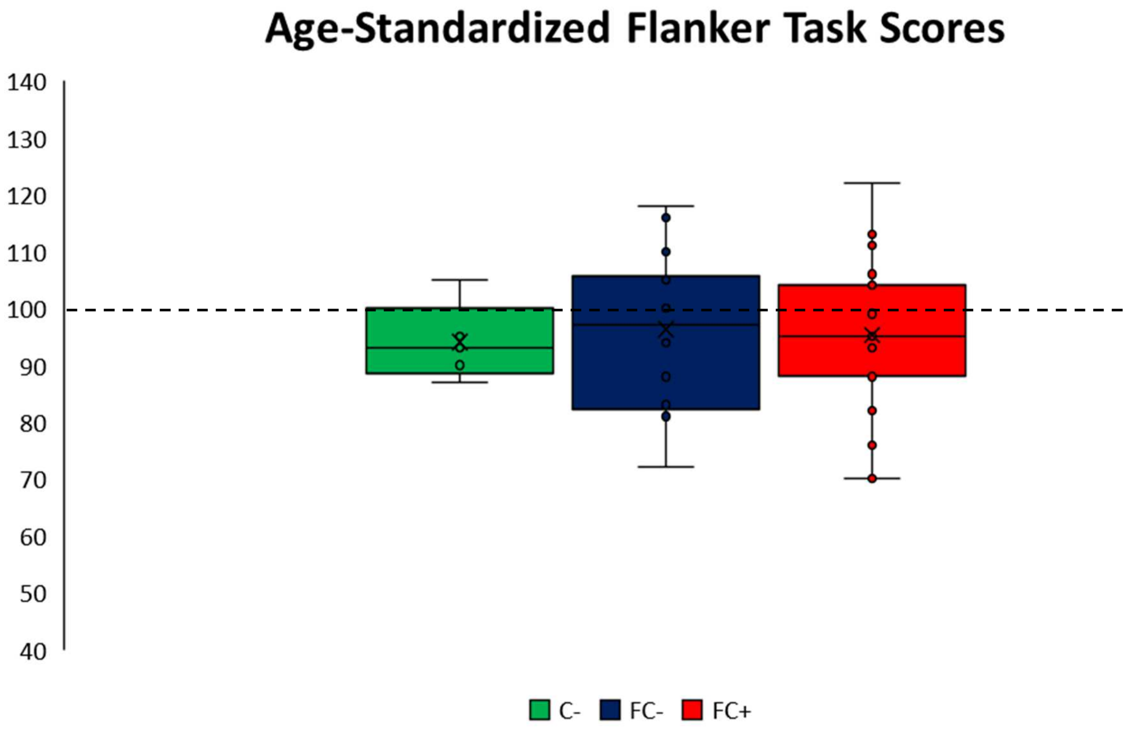


Figure 7

Group means for age-corrected standard correct reaction time scores on the Stroop task. Dashed line represents standardized population mean (SD=15).

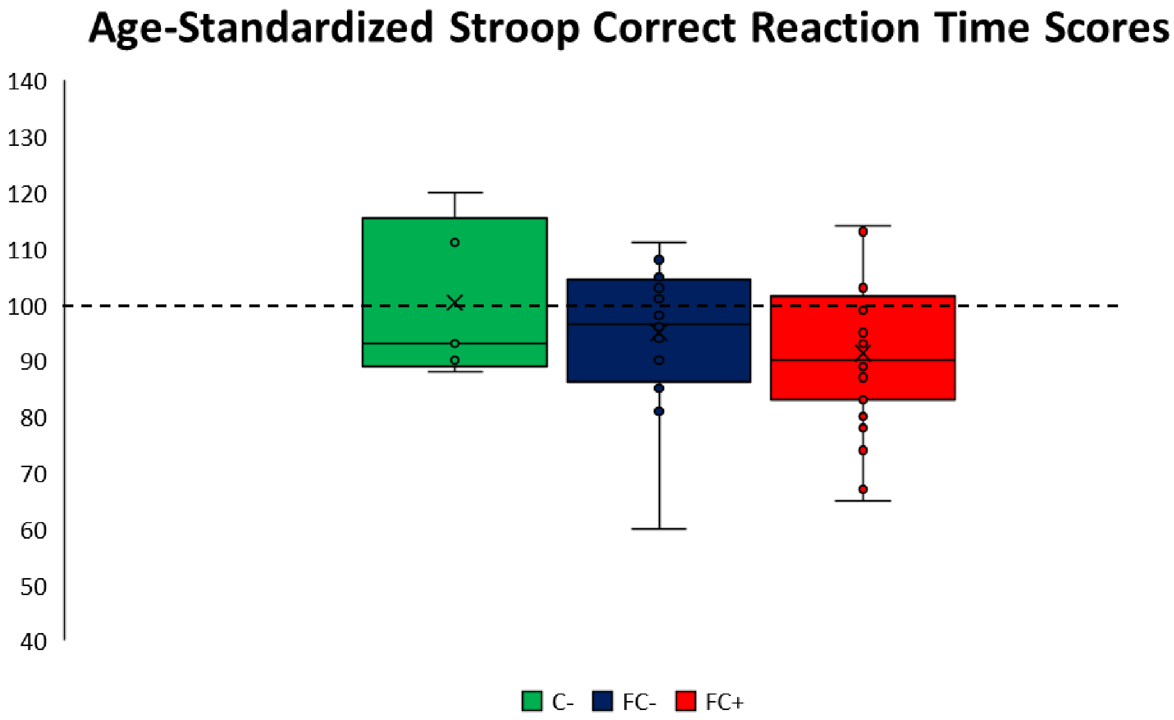


Figure 8

Group means for age-corrected standard scores on the list sorting task. Dashed line represents standardized population mean (SD=15).

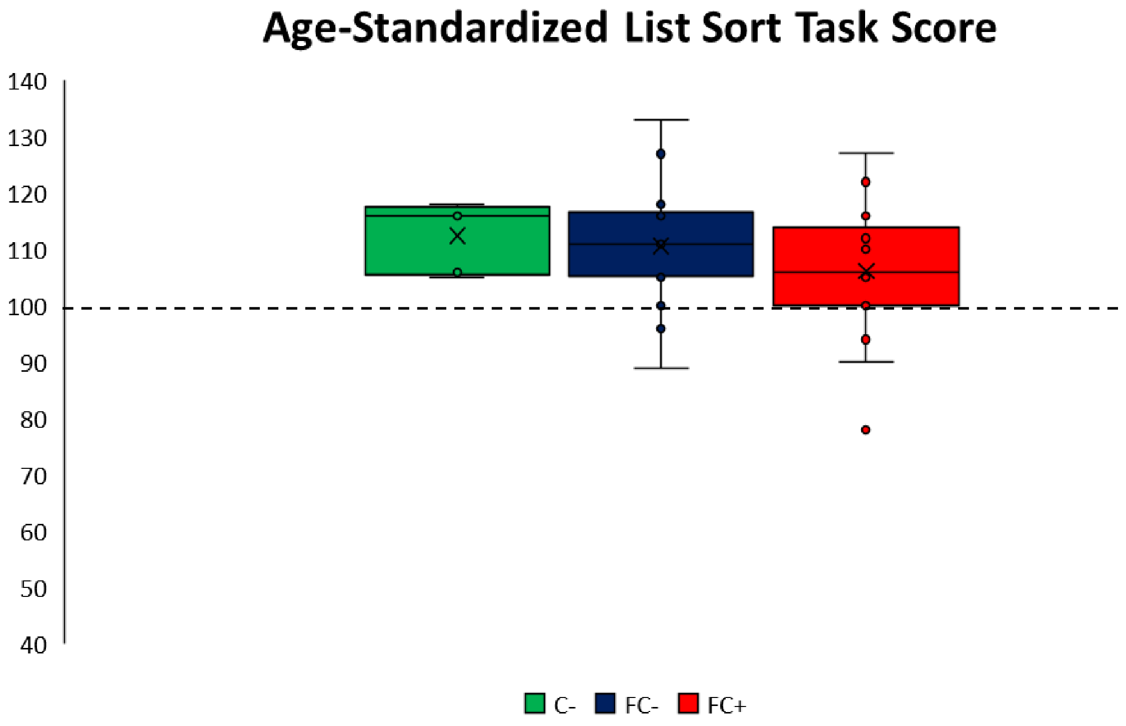


Figure 9

Group means for total t-scores on the Hopkins Verbal Learning Task (HVLT). Dashed line represents standardized population mean of 50 (SD=10).

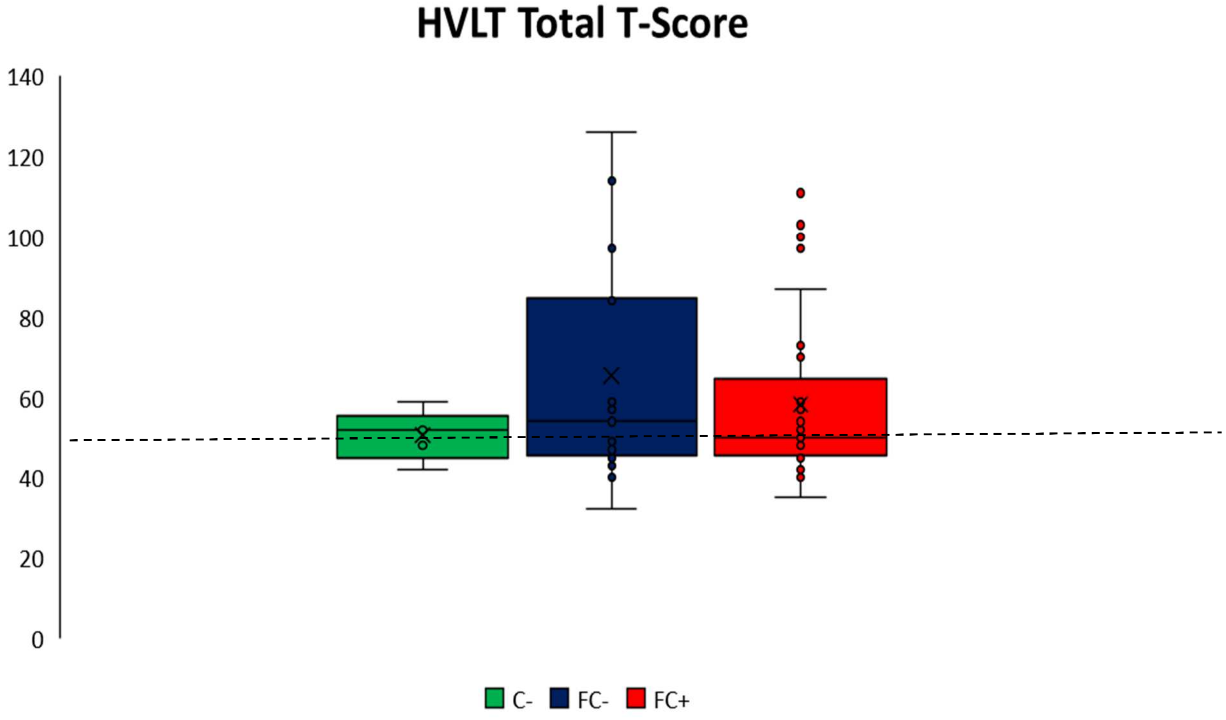


Figure 10

Group means for age-corrected standard scores on the Controlled Oral Word Association Task (COWAT). Dashed line represents standardized population mean (SD=15).

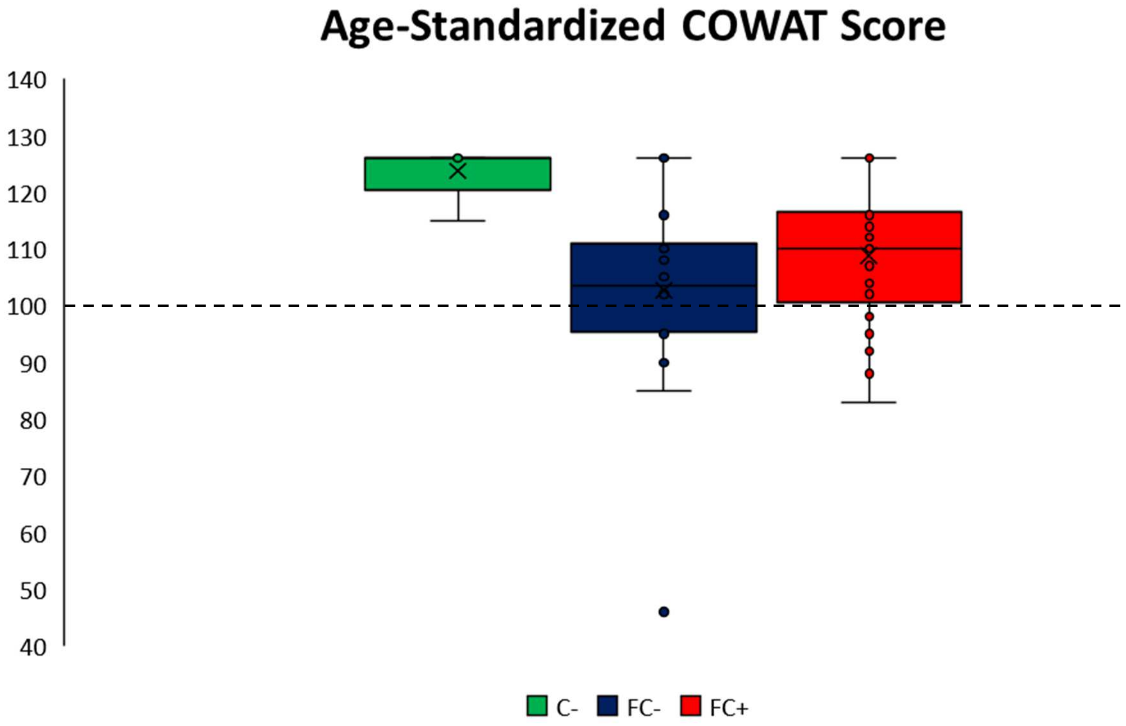


Figure 11

Group means for age-corrected standard scores on the Wechsler Test of Adult Reading (WTAR). Dashed line represents standardized population mean (SD=15).

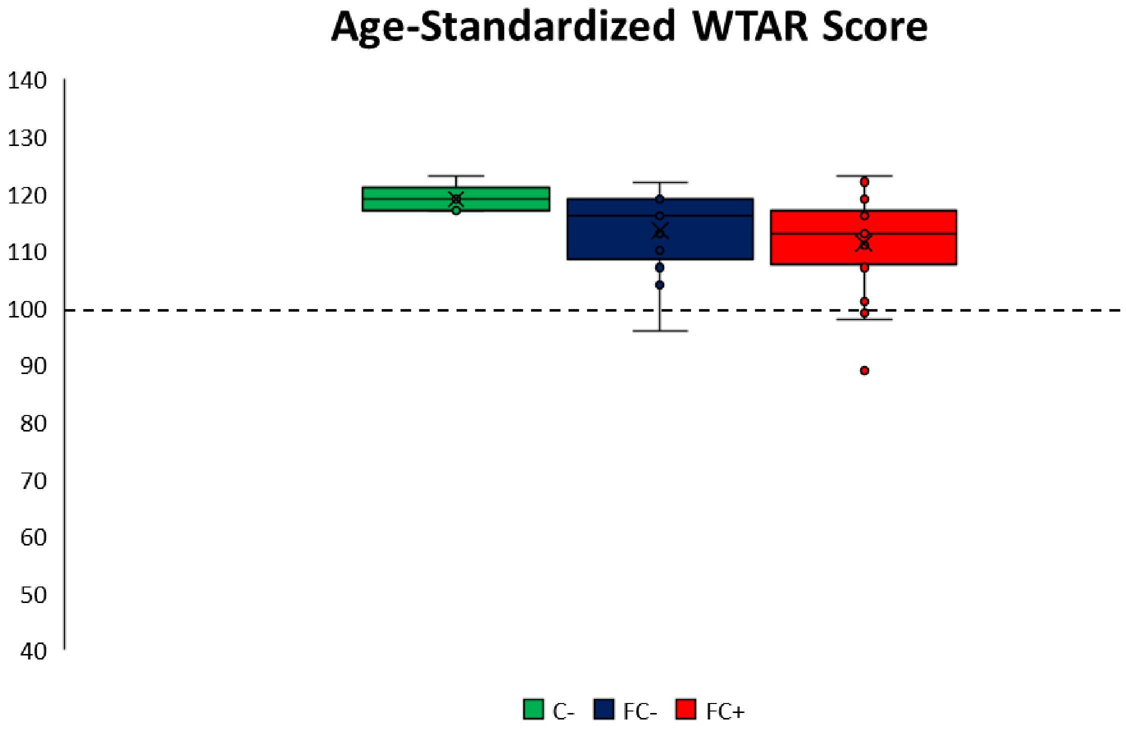


Figure 12

ACR Task Accuracy (error bars represent 95% confidence intervals of the mean).

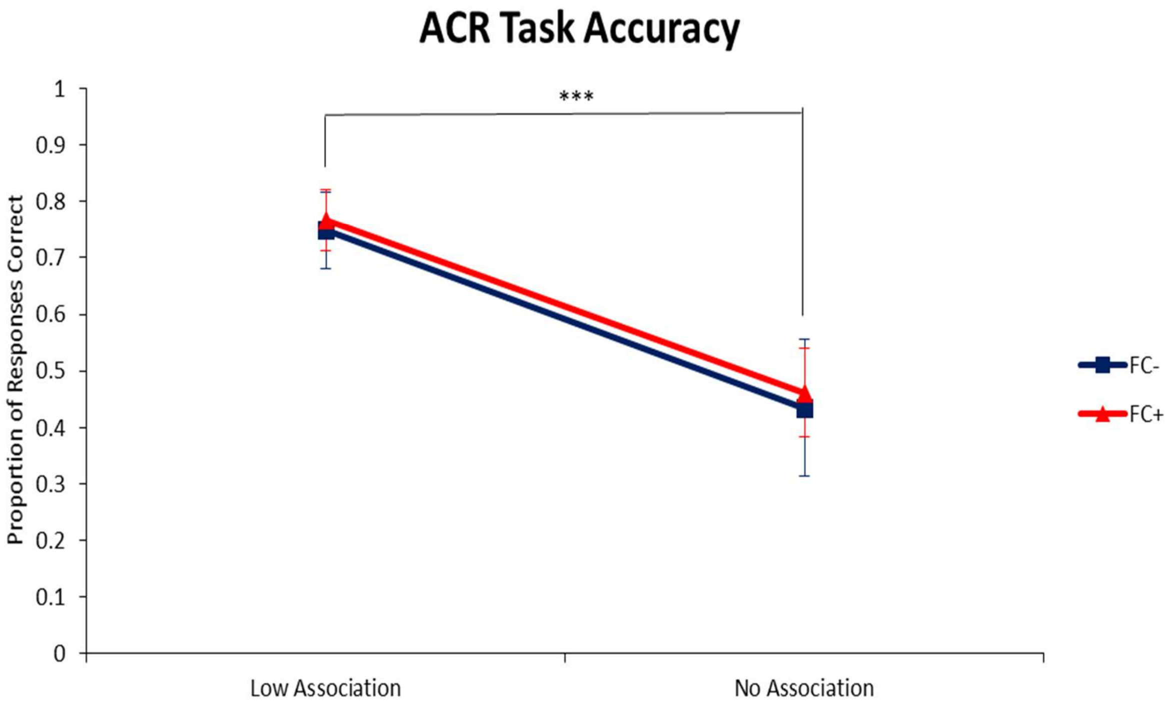


Figure 13

ACR Task Errors (error bars represent 95% confidence intervals of the mean).

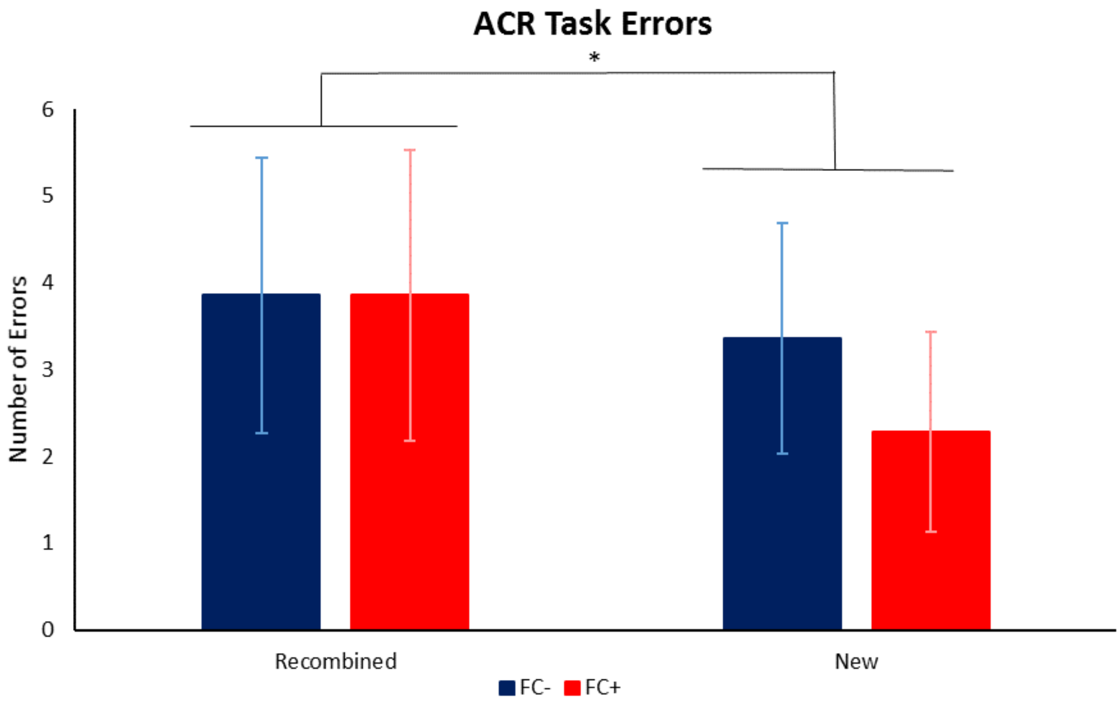
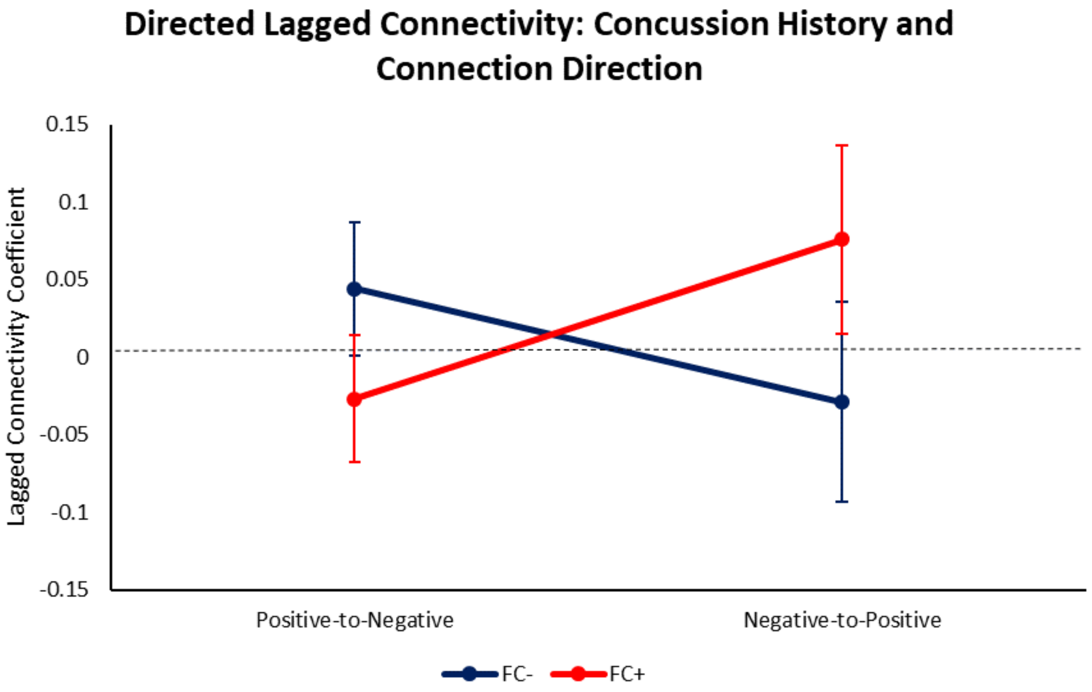


Figure 14

Dynamic factor analytic directed lagged connectivity analysis significant interaction between connection direction and concussion history (error bars represent 95% confidence intervals of the mean).



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