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by

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Abstract

Oxidative stress is a key mechanism of the aging process that can cause damage to brain white matter and cognitive functions. Allele variations of two polymorphisms (*SOD2*, *CAT -262*) have been associated with abnormalities in antioxidant enzyme activity, suggesting a risk for enhanced oxidative damage to brain white matter and cognition among older individuals with these genetic mutations. The present study utilized diffusion tensor imaging (DTI) and neuropsychological assessment to compare differences in microstructural white matter integrity and cognitive performance among 96 older adults (age 50-85) with and without genetic risk factors of *SOD2* (rs4880) and *CAT -262* (rs1001179). Results revealed significantly higher radial diffusivity (RD) in the anterior thalamic radiation (ATR) among CC genotypes of *SOD2* compared to CT/TT genotypes. Further, the CC genotype significantly moderated the relationship between the hippocampal segment of the cingulum (CHC) and processing speed. Neither *CAT-262,* nor the combined effect of *SOD2* and *CAT-262* risk alleles were significantly associated with brain outcomes in this cohort. Collectively these results suggest that the CC genotype of *SOD2* is an important genetic marker of suboptimal brain aging in this cohort of otherwise healthy older adults.

Keywords: Brain aging, oxidative stress, *SOD2*, *CAT-262*, white matter, cognition

Genetic risk for increased oxidative stress in the aging brain: Implications for white matter integrity and cognition

Aging is associated with a systemic decline in cellular processes that leads to structural brain changes and cognitive difficulties (Grigsby et al., 1994; Gunning-Dixon, & Raz, 2000; Holtzer et al., 2004; Mitrushina & Satz, 1991; Raz, Gunning-Dixon, Head, Dupuis, & Acker, 1998; Raz, 2004; Zelinski & Burnight, 1997). Reductions in total brain volume occur around 40-50 years of age (Ge et al., 2002; Miller, Alston, & Corsellis, 1980; Pfefferbaum et al., 1994). Although total brain volume remains relatively preserved until the fifth decade, a steady decline in gray matter begins in early adulthood and continues throughout the lifespan (Ge et al., 2002; Pfefferbaum et al., 1994). By contrast, white matter aging follows a quadratic pattern of change that peaks around the fourth decade and declines thereafter (Ge et al., 2002; Giorgio et al., 2010; Sowell et al., 2003). The inverse relationship between gray matter and white matter in early adulthood likely contributes to the relative stability of total brain volume (defined strictly by gray and white matter tissue) until middle age, and also suggests that decline in total brain volume is heavily dependent on the transition from white matter maturation to degeneration in middle adulthood (Ge et al., 2002; Salminen & Paul, 2014). This theory is consistent with evidence that white matter is a stronger predictor of intraindividual variability in cognitive performance in advanced age compared to gray matter (Lovden et al., 2013; Moy et al., 2011). As a result, there is increased interest in the importance of white matter decline as it relates to overall brain integrity in older adulthood (Bartzokis, 2004; Head et al., 2004; Salat et al., 2009).

Histological studies have revealed significant age-related changes in myelin integrity including decreased pallor, splitting of myelin lamellae, and formation of myelin balloons (Peters, 2002). Over time these changes result in myelin rarefaction, decreased fiber length, and a decrease in the total number of myelinated axons (Marner et al., 2003). Collectively these microstructural white matter changes negatively impact cognition (Bartzokis, 2004; Kövari et al., 2004; Peters & Kemper, 2012). The evolution of age-related white matter decline is partly a result of chronic oxidative damage (Bartzokis, 2004), and it is possible that individual differences in oxidative damage contribute to variability in cognitive aging.

Neurobiology of oxidative stress and oligodendrocyte vulnerability

Under normal physiological conditions human brain cells consume 20% of total oxygen intake, despite accounting for less than 2% of body weight (Aoyama et al., 2008). More than 95% of cellular oxygen is used for ATP synthesis during oxidative phosphorylation (OXPHOS; Boveris & Navarro, 2008; Cannizzo, Clement, & Sahu, Follo, & Santambrogio, 2011; Reiter, 1995), reducing the remaining oxygen (< 5%) to harmful reactive oxygen species (ROS) such as superoxide anion (O_2^-) and hydrogen peroxide (H_2O_2; Hensley et al., 2000). Production of these highly toxic ROS can cause protein modification and DNA strand breaks (Dringen et al., 2000), particularly in the mitochondrial electron transport chain (Hensley et al., 2000). Because mitochondria are a major source of ROS production, alterations in organelle structure reduce detoxification capacity resulting in a net increase of ROS (Lin and Beal, 2006). Mitochondria become further impaired as ROS are replicated, causing damage to other organelles and mutations to mitochondrial DNA (mtDNA; Mecocci et al., 1993). Point mutations and deletions

begin around the third decade and accumulate with age (Wei & Lee, 2002). The repair capacity of mtDNA is tissue specific, with oligodendrocytes (OLs) demonstrating less efficient repair mechanisms compared to other brain cells (Hollensworth et al., 2000; LeDoux, Druzhyna, Hollensworth, Harrison, & Wilson, 2007; Salminen & Paul, 2014).

OLs are particularly susceptible to oxidative damage due to the high metabolic rate of myelin maintenance and production (Connor & Menzies, 1996). In order to synthesize large quantities of myelin, OLs require high concentrations of ATP and iron that increase aerobic metabolism (Conner & Menzies, 1996; McTigue & Tripathi, 2008). H_2O_2 is a toxic byproduct of ATP synthesis that reacts with iron to produce ROS when it is not fully metabolized (Rouault & Cooperman, 2006), including the production of the highly toxic hydroxyl radical (Smith, Kapoor, & Felts, 1999). Accordingly, studies have shown that *in vitro* exposure of OLs to H_2O_2 is a direct cause of DNA damage and OL apoptosis (Ladiwala et al., 1999; Mouzannar et al., 2001; Salminen & Paul, 2014; Uberti et al., 1999).

In addition to high iron content, OLs contain low levels of antioxidants, thereby increasing their vulnerability to free-radical reactions (Bartzokis, 2004). One antioxidant found in remarkably low concentrations is the tripeptide, glutathione (GSH); comprised of glutamate, cysteine, and glyceine (Meister & Anderson, 1983). GSH is a critical neutralizer of free radical toxicity in OLs, and it is highly sensitive to intracellular shifts in oxidative state (Droge, 2005). ROS accumulation can trigger the reduction of GSH to oxidized glutathione disulfide (GSSG), thereby depleting intracellular GSH and leaving OLs increasingly vulnerable to oxidative damage (Droge, 2005). Although GSH redox can be reversed, the intracellular ratio of reduced GSH to oxidized GSH is heavily

influenced by oxidative alterations in signaling pathways and surrounding GSH concentrations (Jozefczak et al., 2012; Salminen & Paul, 2014).

Oxidative stress in the aging brain and implications for white matter damage

Age-related increases in ROS promote immunoscenescence in the central nervous system (CNS) through activation of inflammasomes (Cannizo et al., 2011; Salminen, Kaarniranta, & Kauppinen, 2012). Inflammasome complexes facilitate cytokine maturation and pyroptosis (an apoptosis analogue specific to inflammation), and are highly expressed in OLs (Kummer et al., 2007). The cytokine, interleukin-1β (IL-1β), is a specific target of inflammasomes that has been implicated in the development of Alzheimer's disease (AD) (Rothwell & Luheshi, 2000). Specifically, IL-1β induces tau phosphorylation and Aβ neurotoxicity (Friedman et al., 2005), causing direct damage to myelin sheaths (de Chaves & Narayanaswami, 2008). Aβ interactions with neuronal membranes also induce inflammasome activation when there is a potassium efflux in Aβ ion channels (Salminen & Kaariniranta, 2009). These pathological interactions result in a chronic state of low-grade inflammation that reduces cellular antioxidant capacity and causes aggregated damage to macromolecules (Lopez-Armada et al., 2013). Because antioxidant concentrations are normally low in OLs, age-related decline in antioxidant capacity further leads to mitochondrial dysfunction and neural cell death (Farooqi and Farooqi, 2009; Salminen & Paul, 2014).

Iron concentrations also increase with advanced age to maintain OL differentiation, thereby increasing OXPHOS and intracellular oxidation in brain regions with an abundance of late-differentiating OLs (Bartzokis, 2004; Bartzokis et al., 2001). In contrast to early-differentiating OLs that myelinate large diameter axons, late-

differentiating OLs have a "weaker" lipid profile that produces thinner myelin sheaths for many small diameter axon segments (Wood & Bunge, 1984). These small diameter axon fibers myelinate later in life and are believed to be the first to decline in older age (Pakkenberg et al., 2003; Tang, Nyengard, Pakkenberg, & Gunderson, 1997). This "last in first out" pattern of white matter aging is commonly referred to as retrogenesis, which describes the breakdown of white matter that follows the reverse sequence of myelogenesis (Reisberg et al., 1999). Late-differentiating OLs have reduced capacity for myelin turnover and repair, and therefore the resultant thin myelin sheaths are highly susceptible to age-related oxidative damage and destruction. Thinner myelin sheaths are predominantly located in intracortical association areas involved in higher-order cognitive integration (Bartzokis, 2004; Bartzokis et al., 2001; Kemper, 1994). As will be discussed, white matter fiber tracts traversing these brain regions are at increased risk for oxidative damage, which may result in cognitive difficulties (Bartzokis, 2003; Bartzokis, 2004; Hof, Morrison, & Cox, 1990).

Relationships between oxidative stress and cognitive processes

Modest concentrations of ROS are necessary for learning and memory consolidation (Serrano & Klann, 2004). In fact, long-term potentiation (LTP) can be attenuated from an imbalance of low ROS and high antioxidant levels (Knapp & Klann, 2002; Thiels et al., 2000). ROS molecules such as O_2^- and H_2O_2 are critical for LTP and synaptic plasticity in the hippocampus. Activation of the N-methyl-D-aspartate (NMDA) receptor is also critical for LTP and synaptic plasticity, and is a direct source of ROS generation in the glutamatergic pathway. ROS produced from NMDA receptor activation

causes oxidation of the protein kinase C substrate, neurogranin, which has shown to initiate LTP (Kishida & Klann, 2007; Salminen & Paul, 2014).

A homeostatic imbalance of ROS and antioxidants, however, is believed to be a major determinant of cognitive dysfunction. Animal studies have demonstrated positive associations between age-related increases in ROS and impaired LTP (Auerbach & Segal, 1997; Watson et al., 2002), which is supported by observed relationships between hippocampal protein oxidation and learning deficiencies in aged rats (Nicolle et al., 2001). Research by Urano and colleagues (1997; Fukui & Urano, 2007) has provided insight into microcellular changes of oxygen-exposed rats and non-manipulated aged rats through synaptosome stimulation by potassium chloride (KCl). Both oxygen-exposed and normal aged rats demonstrated decreased acetylcholine release from the synaptosome terminal following KCl administration (Urano et al., 1997; Urano et al., 1998). Because acetylcholine release is crucial for executive processes such as decision-making and attention, these results offer evidence that oxidative stress has a direct impact on cognitive networks (Salminen & Paul, 2014).

Previous research has identified several other biological mechanisms by which oxidative stress contributes to impaired learning and memory consolidation. First, ROS-induced lipid peroxidation has been shown to alter the activity of LTP signaling pathways and enhance membrane impermeability, resulting in reduced LTP capacity (Lynch, 1998; Watson. Arnold, Ho, & O'dell, 2006). Second, aging is associated with increased inflammasome activation in hippocampal neurons, causing upregulation of IL-1β and impaired modulation of synaptic plasticity (Mawhinney et al., 2011). Animal studies have demonstrated negative associations between activation of the hippocampal nucleotide-

binding domain leucine-rich repeat (NLRP) inflammasome and spatial learning in aged rats (Mawhinney et al., 2011). Third, age-related decline in glutamate release and NMDA receptor signaling causes a shift in intracellular redox status and subsequent inhibition of LTP (Knapp & Klann, 2002). Reduced NMDA receptor involvement also results in altered intracellular calcium (Ca^{2+}) levels that decrease synaptic strength, reduce cellular excitability, and ultimately lead to long-term depression (Foster, 2007; Salminen & Paul, 2014).

In addition to learning and memory, oxidative damage to the myelin sheath results in dysfunctional saltatory conduction, causing slower signal transmission and a longer refractory period of an axon potential. As a result, information processing speed is reduced and the ability to integrate information across highly distributed brain networks is compromised (Bartzokis 2004). Conduction delays are a signature of normal aging, and have been shown to explain the majority of cognitive difficulties in healthy older adults (Spaan, 2015; Verhaeghen & Salthouse, 1997).

Antioxidant defense mechanisms in the aging brain

Superoxide dismutase (SOD) and catalase (CAT) are two of the most critical first-line antioxidant defense mechanisms in the human brain. SOD and CAT work in conjunction with other metalloproteins to reduce ROS toxicity via enzyme-catalyzed dismutation of O_2^- to H_2O_2, which is further reduced to oxygen and water (Masella et al., 2005). While SOD and CAT activity cannot fully prevent the production of reactive compounds, these redox reactions are essential for limiting oxidative damage (Salminen & Paul, 2014).

Despite high demand for ROS detoxification, the brain contains significantly lower antioxidant concentrations compared to other organs in the body (Reiter, 1995). Suboptimal antioxidant levels in the brain make it difficult to combat the large quantities of highly reactive polyunsaturated fatty acids, iron, and ROS that accumulate with age (Reiter, 1995), particularly in the cortex, hippocampus, striatum, and hypothalamus (Favreliere et al., 1998; Mythri et al., 2011; Ulmann, Mimouni, Roux, Porsolt, & Poisson, 2001; Yehuda, Rabinovitz, Carasso, & Mostofsky, 2002). Accordingly, analysis of postmortem brain tissue has revealed significant decreases in antioxidant activity in the hippocampus and frontal cortex with advanced age, specifically in the enzymatic activity of SOD and CAT (Venkateshappa, Harish, Mahadevan, Bharath, & Shankar, 2012a). Similar reductions in the activity of these antioxidants have been observed in conjunction with increased protein oxidation in the substantia nigra of aging individuals (Salminen & Paul, 2014; Venkateshappa et al., 2012b).

Although aging has been associated with a decline in cerebral antioxidant activity, several studies have reported elevated antioxidant levels in postmortem brain tissue of individuals with Parkinson's disease (PD) and Lewy body disease (Mythri et al., 2012; Power & Blumbergs, 2009). This is consistent with recent findings from a magnetic resonance spectroscopy (MRS) study that revealed a significant negative relationship between GSH and poor neuropsychological performance among individuals with mild cognitive impairment (MCI; Duffy et al., 2014). While these results seem contradictory to antioxidant changes during normal aging, antioxidant activity may increase under pathological conditions to compensate for the increased load of oxidative stress associated with neurodegenerative disease. It is difficult to determine the cause of

increased antioxidant activity, however, as oxidative stress is a component of both normal aging and pathological processes (Albers & Beal, 2000). There is additional evidence that previous reports of antioxidant markers obtained from postmortem tissue may not accurately reflect antemortem antioxidant activity due to inconsistencies in tissue storage time and agonal state of the donor (Harish et al., 2013; Salminen & Paul, 2014).

Given the methodological limitations of neurochemical studies, investigation of genetic predispositions for antioxidant deficiencies may be a more valuable method for evaluating age-related changes in antioxidant activity. Genetic risk factors for low antioxidant levels may explain a degree of variability in brain aging, and individuals with these risk factors might be susceptible to an accelerated risk for oxidative damage (Salminen & Paul, 2014). In support of this hypothesis, genetic polymorphisms that encode antioxidant enzymes for SOD and CAT have been associated with numerous disorders involving oxidative stress (Abu-Amero et al., 2015; Babusikova, Jesenak, Evinova, Banovcin, & Dobrota, 2013; Bairova et al., 2014; Chistiakov et al., 2006; Eskafi et al., 2014; Fukai, Folz, Landmesser, & Harrison, 2002; Gromadzka et al., 2015; Khodayari et al., 2013; Liu et al., 2015; Rajaraman et al., 2008; Rosen et al., 1993; Shen et al., 2015; Shimoda-Matsubayashi et al., 1996; Landeghem, Tabatabaie, Beckman, Beckman, & Andersen, 1999; Vats, Sagar, Singh, & Banerjee, 2015; Wiener, Perry, Chen, Harrell, & Go, 2007; Zotova et al., 2004).

SOD

Three forms of SOD have been identified in the human brain, differing by their metal cofactor. Copper (Cu) and zinc (Zn) make up SOD1 and SOD3, and are located in the cytosol and extracellular space, respectively (Crawford et al., 2012). Although

abnormalities in SOD1 and SOD3 have been variably implicated in neuromuscular and cardiovascular conditions (Fukai et al., 2002; Rosen et al., 1993), manganese SOD (also referred to as SOD2) is likely most relevant to brain integrity due to localization within the mitochondrial matrix (Holley, Dhar, & St. Clair, 2010). SOD2 is an important enzyme for controlling ROS production because it is the only known antioxidant located within the mitochondria (Crawford et al., 2012; Salminen & Paul, 2014). Animal studies of transgenic AD mice have demonstrated that a partial reduction in SOD2 causes an increase in Aβ plaque formation and accelerates behavioral changes (Esposito et al., 2006; Li et al., 2004). Similarly, deficient SOD2 expression in model organisms has shown to cause mitochondrial dysfunction, neuronal atrophy, and accelerated CNS senescence (Paul et al., 2007). By contrast, evidence from cortical cultured cell lines has shown that SOD2 overexpression is protective against NMDA and nitric oxide neurotoxicity (Gonzalez-Zulueta et al., 1998); a common consequence of age-related decreases in intracellular energy (Calabrese et al., 2004; Salminen & Paul, 2014).

Previous studies have investigated the impact of genetic polymorphisms encoding SOD2 in the human genome, particularly as it relates to disease risk. The *SOD2* gene contains a c.47T>C single nucleotide polymorphism (SNP; rs4880) that results in a missense mutation (valine > alanine) at position 16 of the mitochondrial targeting sequence (Soerensen, Christensen, Stevnsner, & Christiansen, 2009). The C allele of *SOD2* has been associated with neurodegenerative diseases including AD (Wiener et al., 2007), PD (Shimoda-Matsubayashi et al., 1996), and sporadic motor neuron disease (Landegham et al., 1999), and psychiatric conditions such as schizophrenia (Akyol et al.,

2004). In addition, the CC genotype has been associated with increased immunosenescence and DNA damage (Salminen & Paul, 2014; Taufer et al., 2005).

CAT

CAT is a critical antioxidant for monitoring H_2O_2 concentrations in the intracellular space, by reducing peroxisomal H_2O_2 to oxygen and water (Babusikova, Evinova, Hatok, Dobrota, & Jurecekova, 2013). Although no studies have examined the impact of human CAT deficiency on the brain integrity *in vivo*, animal studies have shown that CAT knockout mice demonstrate a slower rate of ATP synthesis in brain mitochondria compared to transgenic mice with CAT overexpression (Schriner et al., 2005). Similarly, transgenic mice with overexpressed mitochondrial CAT are associated with decreased oxidative damage, longer life span, and neuroprotection against cerebral ischemia (Armogida et al., 2011; Salminen & Paul, 2014; Schriner et al., 2005).

The promoter region of the human *CAT* gene contains a common SNP (rs1001179) that involves a cytosine to thymine substitution at amino acid -262 of the 5' region (*CAT*-262C>T; Crawford et al., 2012). Evidence suggests that enzymatic expression of the *CAT*-262 C and T alleles may differ between organ tissues (Forsberg, Lyrenas, Morgenstern, & de Faire, 2001), and as a result, a clear risk allele for neurodegeneration has not been defined. However, there is literature to suggest that the common C allele poses a greater risk for oxidative damage in the CNS than the minor T allele. Specifically, the T allele has shown to protect against the development of diabetic neuropathy (Chistiakov et al., 2006; Zotova et al., 2004), acoustic neuroma (Rajaraman et al., 2008), and neurological manifestations of Wilson's disease (Gromodzka et al., 2014) compared to the C allele. Research specifically regarding *CAT*-262C>T and brain

integrity is limited, however, and the extent to which allele variation imposes enhanced risk for neurodegenerative disease is unclear (Salminen & Paul, 2014).

Antioxidant enzyme expression in the aging brain

Oxidative stress is responsible for regulating gene expression of antioxidant enzymes and is highly variable between individuals (Franco et al., 1999). This may explain why previous studies of antioxidant enzyme expression have been somewhat contradictory. Some studies have reported decreased antioxidant activity in erythrocytes with age (Anderson, Nielsen, Nielsen, & Grandjean, 1997; Artur et al., 1992; Guemouri et al., 1991; Perrin et al., 1990), while others have reported no change in antioxidant activity in plasma and erythrocytes of healthy aging individuals (Barnett & King, 1995; Loguercio, Taranto, Vitale, Beneduce, & Blanco, 1996; Wang &Walsh, 1996). Contrary to both of these findings, Rizvi and Maurya (2007) reported increased antioxidant activity in response to age-related increases in ROS production.

Genetic expression of antioxidant enzymes in the brain is even less understood and appears to vary with age (Lu et al., 2004). Previous research has identified relatively homogenous expression levels in the brain among individuals ≤ 42 and individuals ≥ 73, and heterogeneous enzyme expression between ages 43-72. There is additional evidence that extensive oxidative DNA damage is associated with lower levels of gene expression in the aging brain, and that this effect is most robust in genes that are down-regulated with advanced age (Lu et al., 2004). Collectively these findings suggest that early changes in genomic expression, particularly those related to oxidative processes, may impact age-related neurodegeneration and subsequent cognitive decline (Salminen & Paul, 2014).

Antioxidant defense genes and neuropsychological performance

Despite biological evidence of an oxidative impact on brain integrity and cognitive processes, only one large scale genetic association study has explored relationships between antioxidant defense SNPs and cognitive aging (Harris et al., 2007). In a study by Harris et al. (2007), longitudinal data were obtained from non-demented individuals in the Lothian Birth Cohort of 1921 (LBC1921; $n = 437$) and the Aberdeen Birth Cohort of 1936 (ABC1936; $n = 485$) to examine cognitive change across the lifespan. Individuals in the LBC1921 were evaluated at ages 11 and 79 on a test of non-verbal reasoning (Raven's Standard Progressive Matrices; Raven. Raven & Court, 1990), and individuals in the ABC1936 were evaluated at ages 11 and 64 on the same cognitive test. Of the 325 SNPs examined, joint analysis of both cohorts revealed a significant relationship between a SNP in the amyloid precursor protein gene (*APP*; rs2830102) and later life cognitive performance (Harris et al., 2007). Specifically, GG genotypes (risk) demonstrated significantly lower cognitive scores on later life performance on the Raven's test compared to AG and AA genotypes, with a dose response trend effect of the G allele on cognitive function. Because *APP* encodes the precursor protein for Aβ, these results provide modest evidence for a relationship between genetic risk for oxidative stress and cognitive aging. It is likely that more robust associations were not found due to the genome-wide assumption that SNPs contribute to only a small portion of variance in any given population (Frazer, Murray, Schork, & Topol, & 2009), making it difficult to identify SNPs associated with heterogeneous "conditions" such as cognitive aging (Salminen & Paul, 2014).

Only one candidate polymorphism study has been conducted on a phase I antioxidant defense SNP (*CAT*-262) and aging phenotypes in healthy older adults (Christiansen et al., 2004). In this study cognitive function was evaluated using the total score on the Mini Mental State Examination (MMSE; a screening measure designed to detect severe cognitive impairment; Folstein & Folstein, 1975), and a composite score of cognitive tests of executive function, attention, and memory. The authors reported a slight positive association between TT genotypes (no risk) of *CAT*-262 and cognition using both the MMSE and composite scores, yet these associations were not statistically significant. It is important to note, however, that the lack of significant relationships between *CAT*-262 and cognition may be due to the methodological design. Specifically, the MMSE is insensitive to minor cognitive difficulties associated with aging, and the use of a composite score for executive function, attention, and memory may have masked significant relationships between genetic risks and cognitive domains with greater sensitivity (executive function) than others (attention). Thus, the relationship between genetic risk for decreased antioxidant defense and brain aging remains largely unknown (Salminen & Paul, 2014).

This gap in the literature represents an important area for future research. Although the relationship between aging and oxidative stress has been well established, few studies have examined the impact of genetic risk for increased oxidative damage as a mechanism of age-related cognitive decline, and no studies have combined neuroimaging and neuropsychological indices to examine the impact of these risk factors in older individuals.

Evaluating the impact of oxidative stress on white matter integrity and cognition

Diffusion tensor imaging (DTI) is a non-invasive neuroimaging technique used to measure directional properties of water diffusion in white matter tracts (Basser & Pierpaoli, 2011; Conuro et al., 1999; Pierpaoli & Basser, 1996). Because diffusion of water molecules in brain white matter is directionally restricted (referred to as anisotropy), DTI can detect changes in underlying microstructure when there is a directional change in water movement. Fractional anisotropy (FA) and mean diffusivity (MD) are commonly used scalar metrics of white matter integrity, which measure directional properties of water molecules within an image voxel (Assaf & Pasternak, 2008; Burzynska et al., 2010). Specifically, FA measures the degree of directional water restriction that is indicated by axonal fiber density and coherence (Beaulieu, 2002). FA values range from 0-1, with 1 indicating perfectly anisotropic diffusion and 0 indicating perfectly isotropic diffusion. Conversely, MD measures the average rate of water diffusion within a voxel that is determined by the density of anatomical barriers (e.g., myelin sheaths) and the exchange of water molecules between cellular compartments (Beaulieu, 2002; Sen & Basser, 2005). Axial diffusivity (AD) and radial diffusivity (RD) are two vector metrics that characterize the directionally dependent rate of water diffusion that occurs parallel and perpendicular to axon fibers, respectively (Alexander, Lee, Lazar, & Field, 2007). Although multiple patterns of white matter diffusion have been reported in advanced age (Burzynska et al., 2010; Madden et al., 2012), the majority of studies using DTI scalar and vector metrics report decreased FA and increased MD, AD and RD (Bennett, Madden, Vaidya, Howard, & Howard, 2010; Burzynska et al., 2010; Lebel et al., 2012; Madden et al., 2012; Sexton et al., 2014; Westlye et al., 2009). This pattern of change typically occurs along an anterior to posterior gradient (Head et

al., 2004; Madden et al., 2004; O'Sullivan et al., 2001; Pfefferbaum et al., 2000; Pfefferbaum, Adalsteinsson, & Sullivan, 2005; Salat et al., 2005) and is believed to result from predominant demyelination and myelin loss. Disruption to both myelin and axons has also been associated with this pattern of diffusion in commissural white matter fibers (Madden et al., 2012).

To date no studies have used DTI to examine relationships between markers of oxidative stress and white matter integrity in normal aging, yet numerous studies acknowledge that oxidative stress is a likely driver of age-related changes in late-myelinating white matter pathways (i.e., retrogenesis). Studies of brain aging demonstrate early age-related decline in white matter fiber bundles that traverse association brain regions, otherwise known as "association tracts" (Brickman et al., 2012; Davis et al., 2009; de Groot et al., 2015; Kennedy & Raz, 2009; Stadlbauer, Salomonowitz, Strunk, Hammen, & Ganslandt, 2008). White matter association tracts are the latest myelinating fiber tracts in the brain and connect cortical areas within each hemisphere (Jellison et al., 2004; Kinney, Kloman, & Gilles, 1988; Yakovlev & Lecours, 1967). Association tracts include the superior longitudinal fasciculus (SLF), inferior longitudinal fasciculus (ILF), inferior fronto-occipital fasciculus (IFOF), uncinate fasciculus (UF), and cingulum bundle (CB) (Jellison et al., 2004).

The theory of retrogenesis has also been applied to cognitive aging, which postulates that damage to late-myelinating white matter tracts mediates age-related changes in cognitive performance. Accordingly, Brickman et al. (2012) revealed that FA in the ILF mediated age differences in executive function among healthy individuals. Other studies have found partial support for the retrogenesis model of cognitive aging.

The following relationships have been identified between DTI scalar metrics in association tracts and age-related cognitive decline: lower FA and higher MD, AD, and RD in the IFOF and executive function, processing speed (Bender, Prindle, Brandmaier, & Raz, 2015; Bendlin et al., 2010; Cremers et al., 2016; Laukka et al., 2013; Mella, de Ribaupierre, Eagleson, & de Ribaupierre, 2013; Perry et al., 2009; Sasson, Doniger, Pasternak, Tarrasch, & Assaf, 2012), visuospatial construction (Voineskos et al., 2012), and delayed memory (Charlton, Barrick, Markus, & Morris, 2013); lower FA and higher AD and MD in the ILF and psychomotor speed (Voineskos et al., 2012), information processing speed (Sasson et al., 2012), executive function (Borghesani et al., 2013; Perry et al., 2009) and memory (Davis et al., 2009; Mella et al., 2013; Schmahmann et al., 2007); lower FA and higher MD, AD, and RD in the CB and executive function (Bender et al., 2015; Borghesani et al., 2013; Mella et al., 2013; Metzler-Baddeley et al., 2012; Sasson et al., 2012), information processing speed (Bendlin et al. 2010; Laukka et al., 2013; Sasson et al., 2012), and cognitive control (Metzler-Baddeley et al., 2012); lower FA and higher MD, RD, and AD in the SLF and executive function and information processing speed (Bendlin et al., 2010; Borghesani et al., 2013; Laukka et al., 2013; Mella et al., 2013; Perry et al., 2009; Salami et al., 2012; Sasson et al., 2012); lower FA and higher MD, AD and RD in the UF and memory (Bender et al., 2015; Charlton et al., 2013; Mella et al., 2013; Metzler-Baddeley et al., 2011) and executive function (Bender et al., 2015; Borghesani et al., 2013; Perry et al., 2009), and psychomotor performance (Zahr, Rohlfing, Pfefferbaum, & Sullivan, 2009). Across these studies the most consistent relationships between DTI and cognition were related to information processing speed,

executive function, and memory, suggesting that white matter damage in association tracts may explain age-related decline in these cognitive domains.

Although the relationships noted above provide support for the retrogenesis model of cognitive aging, age-related decline in white matter projection tracts contributed to cognitive decline in some of these studies (Bendlin et al., 2010; Cremers et al., 2016; Laukka et al., 2013; Sasson et al., 2012). Projection tracts are located within distinct subregions of the internal capsule of the brain and connect areas of the cortex with the thalamus, brainstem and spinal cord (Jellison et al., 2004). The projection tracts are hypothesized to underlie various brain functions and can be categorized into specific fiber systems based on their projection sites (Parent, 1996; Mori et al., 2008; Wassermann et al., 2016). Pertinent to this study, the anterior thalamic radiation (ATR) is the major fiber bundle within the anterior limb of the internal capsule that connects the prefrontal cortex to the anterior and medial nuclei of the thalamus (Behrens et al., 2003; Mori et al., 2002; Mori et al., 2008; Wakana, Jiang, Nagae-Poetscher, Van Zijl, & Mori, 2004). Early decline in the ATR has been reported with advanced age using DTI (Baker et al., 2014; Cremers et al., 2016; Mella et al., 2013), and these alterations have been associated with poorer performance on executive function and information processing speed in healthy older adults (Borghesani et al., 2013; Cremers et al., 2016; Mella et al., 2013). Further, Mella et al. (2013) reported a significant association between DTI alterations in the bilateral ATR and increased intraindividual variability in simple and complex processing speed over a period of one week. The anterior thalamic nuclei are also associated with encoding and retrieval of information, and therefore disruptions to the ATR may negatively impact learning and memory (Dalrymple-Alford et al., 2015; Fama &

Sullivan, 2015; Nishio et al., 2014). In contrast to other projection fiber bundles in the internal capsule, the ATR traverses association brain regions that are vulnerable to oxidative damage (Mori et al., 2002; Wakana et al., 2004), which may explain previous observations of ATR abnormalities in DTI studies of brain aging.

Collectively the abovementioned findings suggest that cognitive performance is partially driven by white matter tract alterations with age, but the pattern of these changes and their relationship to cognition is not well understood. Oxidative stress is likely a driver of white matter alterations in small diameter white matter tracts and projection tracts that innervate association brain regions, which may underlie cognitive variability among older individuals. However, it is currently unclear if aging individuals with genetic risk for increased oxidative stress demonstrate enhanced white matter damage and cognitive difficulties compared to their non-risk counterparts. Examination of white matter integrity among individuals with genetic risk factors for *SOD2* and *CAT-262* will be an important next step for determining if oxidative stress manifests differently in individuals who may have lower levels of SOD2 and CAT in the brain. This is particularly important to investigate among a healthy sample of older individuals, as oxidative load increases across the lifespan (Cannizzo et al., 2011; Wei & Lee, 2002).

Public Health Relevance

The neurobiological variables that underlie the variability in brain aging have not been defined, yet this represents a major public health concern given the increasing population of older individuals. Oxidative stress is considered a risk factor for brain deterioration among older individuals, and it is possible that genetic risk for enhanced oxidative damage is a key factor associated with variability in cognitive function among

older adults. Because life expectancies are continuously increasing, it is critical to determine genetic markers of brain abnormalities to improve the quality of life in a growing elderly population. Understanding the relationship between antioxidant defense genes and brain integrity will allow for the development of preventative mechanisms and behavioral intervention strategies to reduce negative outcomes associated with oxidative stress. Importantly, identifying genetic risk factors for suboptimal brain health will further our knowledge of variability associated with the aging brain.

Summary

Normal aging involves a gradual breakdown of physiological processes that leads to a decline in brain integrity and cognition, yet the onset and progression of decline is variable among older individuals. Oxidative stress is a key mechanism of the aging process that can cause direct damage to cellular architecture within the brain. OLs are at a high risk for oxidative damage due to their role in myelin maintenance and production and limited repair mechanisms, suggesting that white matter may be particularly vulnerable to oxidative activity. Reduced antioxidant defense mechanisms in the brain contribute to accumulation of toxic ROS and progressive neurodegeneration during normal aging, yet it is unclear if certain genetic risk factors contribute to premature neurodegeneration as a result of deficient protection against age-related increases in highly reactive compounds. Allele variations in *SOD2* and *CAT* -262 have been associated with abnormal antioxidant concentrations in human brain tissue and have been identified as risk factors for disease development. Individuals with a genetic predisposition towards cerebral deficiencies in SOD2 and CAT might be susceptible to an

accelerated risk for neuronal decline and cognitive difficulties as a reflection of oxidative-induced structural brain impairment.

The primary purpose of this study was to identify the link between genetic risk factors of oxidative damage and white matter integrity in healthy older adults using DTI metrics of FA, MD, AD, and RD. I hypothesized that individuals with genetic risk variants of *SOD2* and *CAT-262* would exhibit lower FA and higher MD, AD, and RD in white matter association tracts and the ATR compared to individuals without these risk factors. Since the association tracts and ATR are vulnerable to demyelination from oxidative stress, I predicted that white matter in these pathways would be more sensitive to genetic risk for oxidative damage than other white matter tracts. Additionally, I hypothesized that individuals with genetic risk variants of *SOD2* and *CAT -262* would perform more poorly on tests of processing speed, executive function, and memory compared to individuals without these risk factors. I predicted that genetic risk would correspond to poorer performance in these cognitive domains due to the oxidative mechanisms that influence these functions. Further, white matter association tracts and the ATR tap processing speed, executive function, and memory processes, and damage to these tracts would likely result in poor performance in these domains. As such, I hypothesized that alterations in white matter tracts would be associated with poor performance in processing speed, executive function and memory, and that these relationships would be moderated by *SOD2* and *CAT-262* status. I further hypothesized that abnormalities in white matter tracts and cognitive function would be more pronounced among individuals with genetic risk factors for both *SOD2* and *CAT-262.*

Approach

The present study utilized DTI and neuropsychological indices to examine the impact of genetic risk for increased oxidative stress on brain integrity among healthy older adults. Genomic DNA was extracted from preserved saliva samples of 96 healthy individuals participating in a larger study focused on vascular health and brain integrity among older individuals (R01-NS052470; PI: Dr. Paul). This study extends the scope of the parent grant by examining brain integrity among individuals with genetic markers of oxidative stress; an area of study not investigated in the parent R01.

Research Design Considerations

A number of important methodological design issues were considered related to the proposed science. Below were three potential areas of concern along with the rationale for the decisions applied to the final design.

The first design consideration centered on whether to examine RNA expression from tissue samples versus genetic variants from DNA samples. While the aim of the proposed study is to determine the influence of antioxidant defense genes on brain integrity, this inherently assumes that certain genetic risk variants negatively influence the expression of antioxidant enzyme activity. Previous studies have indicated that genetic expression varies between different kinds of cells and also across individual phenotypes, making it difficult to ascribe direct mechanisms of histopathology. Further, work by Spielman et al. (2007) indicated that genetic variation between populations significantly influences gene expression phenotypes and may contribute to population differences in disease susceptibility. As such, the decision was made to examine genetic variants from DNA samples to identify a functional profile of brain integrity that is independent of individual phenotypes. Obtaining plasma markers of protein oxidation to

supplement the genetic data was considered, yet the association between central and peripheral nervous system levels is not consistent (Reiter, 1995; Harish et al., 2013).

The second important consideration focused on sample size and power due to the base rate frequencies of the polymorphisms of interest. The Single Nucleotide Polymorphism Database (dbSNP; Sherry et al., 2001) revealed that the frequencies of the risk allele (C allele) for *SOD2* is high among Caucasians (47%) and African Americans (35%), which are the two dominant races of individuals included in the parent R01. While a clear risk allele has not been defined for *CAT-262*, the weight of literature suggests that the C allele poses greater risk for neural damage than the minor T allele (Chistiakov et al., 2006; Christiansen et al., 2004; Rajaraman et al., 2008; Zotova et al., 2004). Prevalence for the *CAT-262* C allele is very high among Caucasians (77%) and African Americans (98%). These numbers provide confidence that risk can be adequately assessed in the present study. As described in the power analysis section, different genetic models were tested for *SOD2* and *CAT-262* to account for differences in allelic frequency distributions between the two SNPs and optimize power.

The final design consideration involved the determination of the white matter tracts for the outcome measures of the primary aims. Given the extant literature on late-differentiating OLs and demyelination, the decision was made to focus on white matter association tracts previously linked to cognitive aging. These include the SLF, ILF, IFOF, UF, and CB. The CB was sectioned into cingulate gyrus (CGC) and parahippocampal (CHC) segments to allow for comparisons with previous studies that have reported a relationship between distinct subregions of the CB and cognition (Bendlin et al., 2010; Laukka et al., 2013; Metzler-Baddeley et al., 2012). In addition to the association tracts,

the ATR was included as a tract of interest (TOI). Although the ATR is not classically defined as an association tract, this tract innervates association areas and has been previously associated with brain aging and decline in executive function, processing speed, and memory (Baker et al., 2014; Cremers et al., 2016; Nishio et al., 2014). Of note, projection tracts have been categorized as association tracts in previous work (de Groot et al., 2012; Mori et al., 2002), as they connect brain regions within the same hemisphere. Additional projection tracts such as the CST and PTR were not examined, as these tracts are less likely to be influenced by genetic risk for increased oxidative damage due to their anatomical location in posterior brain regions (Cremers et al., 2016; Westlye et al., 2009). Similarly, it was difficult to determine which subregions of the corpus callosum (CC) might impact cognition as a result of increased oxidative load. While the genu of the CC has been implicated in brain aging and connects prefrontal association areas (Hofer & Frahm, 2006), the splenium of the CC has been more closely associated with memory and executive function (Voineskos et al., 2012). The variability in CC segmentations across studies further complicated the delineation of structure and function. Given these issues, the CC was excluded from the analyses to facilitate data reduction.

Method

Participants

Data from 96 English-speaking older adults were extracted from an existing database associated with the parent study. Cognitive data, participant demographics and relevant health histories were obtained at the University of Missouri, St. Louis (UMSL) during the neuropsychological evaluation. Neuroimaging procedures were completed in a

subset of these individuals (n = 71) at Washington University within one month of the neuropsychological visit for the majority of participants. The Institutional Review Board (IRB) of UMSL and Washington University approved all study protocol. All participants provided informed consent and received financial compensation for their involvement in the study.

Inclusion/Exclusion Criteria

Individuals were excluded from the study based on a self-reported history of a substance use disorder, psychiatric diagnosis (i.e., all Axis I and II disorders with the exception of managed depression), learning disability, a medical or neurological condition capable of impacting cognition (e.g., thyroid disease, multiple sclerosis, etc.), history of head injury (defined by a loss of consciousness greater than 30 minutes), history of treatment-dependent diabetes, and contraindications for MRI (e.g., claustrophobia). All individuals were required to independently complete basic and instrumental daily functions according to the Lawton and Brody Activities of Daily Living (ADLs; Lawton & Brody, 1969), and receive a score ≥ 24 on the MMSE to exclude individuals with probable dementia. A physician visually inspected all MRI scans to screen for possible anatomical abnormalities unbeknown to the participant. Individuals demonstrating clinically significant abnormalities were excluded from the study and instructed to contact their primary care physician.

DNA extraction

Genetic isolation and processing was completed at Genetics Repositories Australia. Genomic DNA was extracted from saliva samples using the Oragene DNA collection kit (DNA Genotek, Ottawa, Canada) and the Autopure LS nucleic acid

purification system (QIAgen). Genotypes for *SOD2* and *CAT-262* was ascertained using predesigned Taqman SNP assays. The QIAGEN Multiplex PCR Kit (QIAGEN Pty Ltd., Victoria, Australia) was used for DNA amplification using the following primers: (*SOD2*; rs4880) forward: 5'- GGCTGTGCTTTCTCGTCTTCA-3', reverse: 5'-TCTGCCTGGAGCCCAGATAC -3'; (*CAT-262*; rs1001179) forward: 5'-TAAGAGCTGAGAAAGCATAGCT-3', reverse: 5' AGAGCCTCGCCCCGCCGGACCG -3'. Amplicons were digested with HpaII, and products were separated by agarose gel electrophoresis and visualized using ethidium bromide.

Imaging Acquisition and Analysis

All imaging acquisition was performed using a head-only Magnetom Allegra 3T MRI scanner (Siemens Medical Solutions, Erlangen, Germany) located at Washington University. This high performance scanner has gradients with a maximum strength of 40 m/T/m in a 100 μs rise time and a slew rate of 400/T/m/s, with 100% duty cycle. Acquisition parameters were designed for whole-brain coverage, high signal-to-noise ratio (SNR), and minimal artifact. Subject head movement was restrained using specialized foam pads and the application of surgical tape across the forehead. An initial scout scan consisting of three orthogonal planes was obtained at the beginning of each scanning session to confirm head position. Daily quality assurance tests were performed to ensure consistent scanner performance across subjects. The same scanner, operating system and processing software were used throughout the duration of the study. Total scan time was < 1 hour. Structural whole-brain scans were collected using a T1-weighted magnetization-prepared rapid-acquisition gradient echo (MPRAGE) sequence (Mugler &

Brookeman, 1990), a double-echo proton-density (PD)/T2-weighted turbo spin echo (TSE) sequence, and a T2-weighted fluid-attenuated inversion-recovery (FLAIR) TSE sequence (Hajnal et al., 1992). Standard shimming was applied.

Axial diffusion-weighted images (DWIs) were obtained with a custom single-shot multislice echo-planar tensor encoded pulse sequence with diffusion-encoding gradients applied in 31 non-collinear directions and 24 main directions ($b = 996$ s/mm^2). To maximize SNR and directional coverage we used a "core" of tetrahedral-perpendicular directions ($b = 1412$ and 680 s/mm^2) with 5 I_0 acquisitions ($b \sim 0$) (Conturo et al., 1996). The following pulse sequence parameters were also implemented: TE= 86.2 ms; TR= 7.82 s; 64 contiguous 2.0-mm slices; and an acquisition matrix of 128 x 128 with a FOV of 256 x 256 mm (isotropic 2.0x2.0x2.0 mm voxels). A total of 72 acquisitions were averaged over 2 scan repeats.

Brain tissue was extracted using the FSL Brain Extraction Tool and diffusion-weighted volume was corrected for subject motion and artifacts by affine registration using FSL FLIRT (Jenkinson, Bannister, Brady, & Smith, 2012). Linear least squares and trilinear interpolation was used to reconstruct the diffusion tensors of the DWI signal (Zhukov & Barr, 2002). Individual tracts were identified using deterministic whole-brain streamline tractography with one randomly placed seed per voxel, second-order Runge-Kutta integration, a 35° flip angle, FA of 0.15, and minimum fiber length of 10mm. Each participant's FA image was registered to the Johns Hopkins University (JHU) white matter atlas using FSL FLIRT with mutual information. TOIs included the SLF, ILF, IFOF, UF, CGC, CHC, and ATR. Each tract was modeled separately by hemisphere for a total of 12 distinct tracts. As described in the statistical analysis section below, tracts

were collapsed across hemispheres to provide an average measure of FA, MD, AD, and RD for each fiber bundle. The JHU atlas was used to determine which streamlines would be included in a specific bundle. Streamlines were retained in the bundle if at least 80% of fiber arc length was included in the bundle mask. Streamlines that came within .8 mm of an existing tract were removed from the analysis (Zhang, Demiralp, & Laidlaw, 2003). Numerical integration was used to compute average scalar and vector values along each streamline, and average FA, MD, AD, and RD for each bundle was computed for the streamline measures.

Neuropsychological Assessment

All participants completed a comprehensive neuropsychological evaluation at UMSL. Demographic information and health history were obtained via self-report questionnaires. Blood pressure was measured at three time points during the cognitive visit to account for the potential influence of hypertension on cognitive performance. The neuropsychological tests were chosen based on established sensitivity to age-related cognitive decline (Amodio et al., 2002; Clark et al., 2012; Gontkovsky et al., 2004; Myerson, Emery, White, & Hale, 2003). This study focused on cognitive domains of processing speed, executive function, and memory, as previous research suggests that these functions may be influenced by age-related increases in oxidative stress. Cognitive difficulties in these domains have also been linked to alterations in white matter association tracts and the ATR. Composite scores for each cognitive domain were used as the primary outcome measures for the neuropsychological variables to facilitate data reduction. In order to determine composite scores, raw scores from each cognitive test

were converted to z scores and averaged for each domain. Scores measured in completion time were multiplied by -1 to result in all positive integers.

Processing Speed

The following tests were used to measure processing speed: 1) Trails A from the Trail Making Test (Army Individual Test Battery, 1944), 2) Trial 1 from the Color-Word Interference Task (CWIT) of the Delis-Kaplan Executive Function System (Delis, Kaplan, & Kramer, 2001), and 3) Coding from the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph, 1998). Trails A requires participants to connect a series of letters in alphabetical order such that a line is drawn from A to B to C, etc. Time to completion was the primary outcome measure. During Trial 1 of the CWIT, participants are presented with four rows of color blocks. Participants are required to correctly identify the color of each block, in order, as quickly as possible. Time to completion was the primary outcome measure. Coding requires participants to match numeric digits to their corresponding symbols as identified in the key. The primary outcome measure was the total number of correctly matched digits and symbols at the end of 90 seconds.

Executive Function

The following tests were used to measure executive function: 1) Trails B from the Trail Making Test, 2) Trial 4 from the CWIT, and 3) Letter Number Sequencing (LNS) from the Wechsler Adult Intelligence Scale-III (Wechsler, 1991). Trails B requires participants to connect numbers in ascending order and letters in alphabetical order in an alternating sequence. Numbers and letters are connected by drawing a line from 1 to A, A to 2, 2 to B, etc. Time to completion was the primary outcome measure. In normal

populations, the recommended time limit is 300 seconds before the test is discontinued (Heaton, Miller, Taylor & Grant, 2004). Thus, scores ≥ 300 were excluded from the analyses. During Trial 4 of the CWIT, participants are presented with four rows of color-words (i.e., the word red) that are printed in a contrasting color-word combination (i.e. the word red printed in blue ink). Participants are required to identify the ink color of each color-word unless the color word is presented inside a box. Participants are required to read the name of the color-word when it is presented inside a box. Time to completion was the primary outcome measure. LNS requires participants to arrange a series of number and letters within a string by placing numbers in order first, followed by letters in alphabetical order. Each letter-number string has a distinct number of characters (begins with 2 and ends at 9) and there are three strings within a block. The task is discontinued once a participant fails to complete any strings within a block. The number of successfully completed strings was the primary outcome measure.

Memory

Memory included subtests of list learning, story memory, list recall, and story recall from the RBANS. List learning requires participants to listen to a list of 10 unrelated words and repeat back as many words as they can remember across 4 trials. The primary outcome measure was the total number of recalled words. Story memory requires participants to listen to a short story and repeat back as much of the story as they can remember across 2 trials. The total number of accurately recalled key words and phrases in the story across 2 trials was the primary outcome measure. List recall and story recall require participants to freely remember as many items from the initial memory tasks as possible. The primary outcome measures were the total number of accurately recalled

items within each task. Scores for list learning and story memory were used to create a subdomain of immediate memory, and scores for list recall and story recall were used to create a subdomain of delayed memory. Subdomain scores were computed separately as the underlying cognitive processes tap different neural systems. As indicated in the statistical analysis section, correlations were computed between subdomain scores and a composite score of memory was also computed.

Genetic Approach

In genetic association studies involving candidate polymorphisms, models of disease penetrance are used to define genetic risk in individuals with a given genotype. The following models are standard approaches to quantifying genetic risk by the penetrance parameter (*y*) with alleles *a* (no risk) and *A* (risk), and possible genotypes *a/a, a/A, AA* (Clark et al., 2011): 1) Multiplicative: risk increases *y*-fold with each *A* allele, 2) Addititve: risk increases *y*-fold with one *A* allele (*a/A*) and 2*y*-fold with two *A* alleles (i.e., *A/A*), 3) Recessive: two *A* alleles are required to increase risk *y*-fold (i.e., only the *AA* genotype confers risk), and 4) Dominant: one or two *A* alleles are required to increase risk *y*-fold (i.e., *a/A + AA* genotypes confers risk). Selection of the appropriate model is necessary for optimizing power, yet these models are rarely known *a priori* (Balding, 2006). Various statistical procedures can be used to determine the appropriate model of risk for case-control studies (e.g., chi square, odds ratios, Cochran-Armitage trend test) (Clark et al., 2011), yet these methods cannot be applied in the absence of a clinical cohort. Thus, genetic model testing in healthy participants involves running the same set of analyses for each genetic model. This approach requires large cell sizes per genotype to test the fit of the abovementioned models, and therefore some models may not be

testable in small-scale studies. Thus, it was necessary to determine the prospective genotypic frequency distributions of *SOD2* and *CAT-262* for the proposed study.

SOD2 and *CAT-262* were initially selected based on established frequency distributions of risk alleles among Caucasians and African Americans, who comprise 90.4% of the participant sample in the parent R01 (racial distribution is consistent with regional census data). Because allele frequencies are not expected to change within a given population (Jankowska, Milewski, Gorska, & Milewsk, 2011), we were able to calculate a reliable estimate of individuals with each genotype to be included in the proposed study using dbSNP (N = 96; estimates calculated according to race). Estimates were as follows: *SOD2*: CC n = 19, CT n = 49, TT n = 27; *CAT-262*: CC n = 63, CT n = 30, TT n = 2. These estimates were approximate to the following observed frequencies *SOD2*: CC n = 26, CT n = 43, TT n = 27; *CAT-262*: CC n = 61, CT n = 32, TT n = 3. As such, a dominant grouping system was selected for *CAT-262* (CC vs. CT/TT) for the primary analysis. While these genotypes are arranged according to a recessive grouping system, this model is functionally dominant as the C allele is far more common than the minor T allele and thus is meant to have the dominant effect. Homozygous genotypes of *SOD2* (CC vs. TT) were examined for the primary analysis, in order to isolate genetic risk and reduce the possibility of grouping error. As noted in the power analysis section, these grouping systems provided adequate power to test the study hypotheses. Secondary analyses examine group differences in the imaging and cognitive variables using alternative genetic models.

Statistical Analyses

Data were examined for violations of normality prior to statistical computation. The shape of the distribution was visually inspected using Q-Q plots and boxplots. Skewness and kurtosis were also examined. Variables that were non-normally distributed were log transformed and re-examined for normality.

Preliminary analyses involved examination of key demographic variables including age, gender, race, and years of education. Chi square analyses were used to examine group differences in gender and race, and independent samples t-tests were used to examine group differences in age and years of education. Group differences in descriptive variables such as hypertension (systolic blood pressure $\geq$ 140 mmHg or diastolic $\geq$ 90 mmHg), intracranial volume (ICV), or *CAT-262* genotypic status were also analyzed using chi square analyses and t-tests. To determine the need for covariance in the main analyses, demographic and descriptive variables (collectively referenced as descriptive variables herein) that differed significantly ($p < .05$) between groups were examined in conjunction with the dependent variables using the appropriate statistical test (e.g., bivariate correlations versus independent samples t-tests or ANOVA). Descriptive variables that were significantly correlated with the dependent variables were included as covariates in the main analyses to control for any intervening effects on the outcome measures.

To facilitate data reduction, bivariate correlations were completed between white matter tracts of the left and right hemispheres to determine if tracts could be aggregated across both hemispheres. While some studies of brain aging examine tracts bilaterally, the majority of studies examining tract-specific relationships with cognition have used an aggregate measure of tract integrity. Statistical significance was initially determined

using an alpha level of .05. False Discovery Rate (FDR) corrections were implemented to control for type 1 error.

Primary Aim 1: Determine the impact of *SOD2* and *CAT-262* on the microstructural integrity of white matter tracts using DTI metrics. Aim 1 was tested using separate multivariate analysis of variance (MANOVA) models (or MANCOVAs where appropriate) for *SOD2* and *CAT-262*. Genetic status served as the independent variable and white matter tracts served as the dependent variables in each MANOVA. DTI outcomes were analyzed in separate MANOVAs to minimize metric-specific variance. Intercorrelations between tracts were examined prior to each analysis to ensure the dependent variables in each MANOVA were moderately correlated ($r > .4$).

Primary Aim 2: Determine the impact of *SOD2* and *CAT-262* on cognitive performance in domains of processing speed, executive function, and memory. Aim 2 was tested using separate ANOVA models (or ANCOVAs where appropriate) for *SOD2* and *CAT-262*. Genetic status served as the independent variable and cognitive domain scores served as the dependent variable in each analysis.

Secondary Aim 1: Determine if genetic risk for increased oxidative stress moderates relationships between white matter tracts and cognitive performance on tests of processing speed, executive function, and memory. Multiple regression models were computed to determine the relationship between tract-specific DTI metrics and cognitive domain scores (main effects), and whether these relationships were moderated by genetic status (interactions). To reduce multicollinearity, DTI metrics and genetic status (e.g., *SOD2*) were mean-centered prior to calculation of the interaction terms (Aiken & West, 1991). Cognitive domain scores were then regressed onto mean-centered DTI metrics, the

mean-centered genetic variable, and the interaction term (mean-centered DTI variables * mean-centered genetic variable). Mean centered DTI variables were entered into block 1 of the regression model. Mean-centered *SOD2* was entered into block 2, and the interaction term was entered into block 3.

Secondary Aim 2: Investigate white matter integrity and cognitive performance among individuals with multiple genetic risk variants of *SOD2* and *CAT-262*. The same statistical analyses employed for primary aims 1 and 2 were used to assess the impact of multiple genetic risk variants on white matter and cognition. Genetic risk was dichotomized into "low risk" and "high risk" groups according to genotypic combinations of *SOD2* and *CAT-262*.

Power Analysis

To determine the appropriate sample size needed for adequate power (.80), effect sizes (Cohen's d) were calculated for the DTI and neuropsychological variables using preliminary data from 21 participants extracted from the parent database. G*Power (Faul, Erdfelder, Buchner, & Lang, 2009) was used to calculate the necessary sample size from input parameters for an independent samples t-test. Power analyses were based on the independent samples t-test versus MANOVA because the key input parameters for MANOVA were initially unknown (e.g., number of variables in each MANOVA and number of MANOVAs). Thus, power analyses were calculated for bilateral white matter tracts and individual neuropsychological tests. Effect sizes ranged from 1.17 to 3.40 for the majority of white matter tracts, indicating that a total sample size of 26 was required to detect significant differences in DTI metrics between groups (Aim 1). Effect sizes ranged from .62 to 1.30 for the majority of neuropsychological tests, indicating that a

sample size of 84 was required to detect significant differences in cognitive performance between groups (Aim 2). Collectively these numbers indicate that the sample of 96 individuals, 71 of whom have imaging data, should be sufficiently powered to detect significant effects that are present in the study.

Results

Data Screening and Preliminary Analyses

Data screening of the cognitive variables indicated that < 5% of scores were missing and therefore mean imputation was not completed. Two individuals received scores of 300 on Trails B (indicating test discontinuation) and as such were removed from the analyses in pairwise fashion. Initial examination of domain scores indicated that assumptions of skewness and kurtosis were violated (> +/- 2; West, Finch, & Curran, 1995) for processing speed. Executive function was leptokurtic (.611) and negatively skewed (-.814), but within normal limits. Q-Q plots and boxplots indicated that abnormal performance scores from one subject were driving the abnormal shape of the distribution and this subject was removed from the analyses. Removal of this subject reduced skewness and kurtosis for both domains (< +/- 2) and Q-Q plots revealed a normal distribution. Domain scores for memory were normally distributed and did not require data cleaning. Data screening for the imaging measures revealed slightly different cell sizes across DTI metrics due to Freesurfer processing errors in the CB, ILF and IFOF across three subjects. Tests of normality indicated that RD and AD variables were leptokurtic and positively skewed beyond the acceptable range. A log10 transformation was applied to all RD and AD variables and re-examined for normality. While skewness and kurtosis improved, Q-Q plots and boxplots revealed extreme scores (> 3x

interquartile range) for one subject across multiple tracts. This subject was removed from the analyses and the shape of the distribution was normalized.

A total of five domain scores were calculated: processing speed, executive function, immediate memory, delayed memory, and global memory (composite of immediate and delayed memory). Bivariate correlations indicated that the immediate and delayed memory domain scores were highly correlated (r =.7), resulting in strong correlations with the global memory domain score (r's >.8). Given the strength of these correlations, immediate and delayed memory domains were dropped from the analyses and the global memory domain score was utilized as the measure of memory. Domain scores were analyzed in three separate univariate ANOVAs (processing speed, executive function, and global memory) due to potential differences in the sensitivity of each domain to discriminate between groups.

Bilateral white matter tract correlations revealed moderately large correlations between hemispheres for the majority of tracts on all DTI metrics (r's range from .4- .9). As such, white matter tracts were averaged across both hemispheres to create a composite measure of tract integrity. Correlations between DTI metrics revealed very strong correlations (r's > .8) between MD and RD for nearly all tracts. As such, MD was dropped from the analysis to reduce redundancy in the outcomes. RD was retained in the analyses (versus MD) due to its enhanced sensitivity to demyelination and observations that MD changes are often driven by changes in RD (Lentz et al., 2014; Song et al., 2002). Correlations between FA, RD, and AD ranged from .1 to .7 across each of the tracts, and intercorrelations between tracts were moderately strong for each metric. As such, tracts were examined in three separate MANOVAs according to DTI metric.

Pillai's Trace was used for MANOVAs that violated statistical assumptions (Box's M < .001, Bartlett's test > .001, Levene's test < .05; Meyers, Gamst, & Guarino, 2006). Univariate differences were not examined for non-significant MANOVAs.

Primary Aims 1 and 2: Genetic differences in white matter and cognition

Descriptive variables did not differ between the CC (n = 26) and TT (n = 26) genotypes of *SOD2,* and the CC/CT (n = 60) and TT (n = 34) genotypes of *CAT-262* (Table 1). As such, covariates were not utilized in the main analyses.

For *SOD2*, a multivariate trend effect was observed for RD (Pillai's Trace = 0.318, $F(7,33) = 2.20$, $p = 0.060$, $f^2 = 0.47$) between CC and TT genotypes. Specifically, the CC group demonstrated higher RD in the ATR (p = .003) and CGC (p = .027) compared to the TT group. Significant multivariate main effects were not observed for FA (Wilks' $\Lambda = 0.720$, $F(7,33) = 1.84$, $p = 0.113$, $f^2 = 0.39$) or AD (Pillai's Trace = 0.174, $F(7,33) = .993$, $p = 0.454$, $f^2 = 0.21$). Groups did not differ significantly on processing speed ($F(1,49) = .10$, $p = 0.756$, $f = .04$), executive function ($F(1,49) = .07$, $p = 0.788$, $f = .14$), or memory ($F(1,50) = .18$, $p = 0.674$, $f = .08$). Group differences in the ATR and CGC did not remain significant after applying FDR corrections to the univariate outcomes across the three MANOVAs (adjusted cutoff p < .002).

For *CAT-262,* no significant multivariate effects were observed for FA (Wilks' $\Lambda = 0.926$, $F(7,58) = .66$, $p = 0.701$, $f^2 = 0.08$), RD (Wilks' $\Lambda = 0.904$, $F(7,58) = .88$, $p = 0.527$, $f^2 = 0.12$), or AD (Wilks' $\Lambda = 0.822$, $F(7,58) = 1.79$, $p = 0.107$, $f^2 = 0.22$). Groups did not differ significantly on processing speed ($F(1,88) = .00$, $p = 0.981$, $f < .001$), executive function ($F(1,86) = .02$, $p = 0.903$, $f < .001$), and memory ($F(1,92) = .00$, $p = 0.953$, $f < .001$).

Outcomes for alternative genetic models of *SOD2*

Preliminary analyses indicated that groups did not differ significantly on descriptive variables for recessive and dominant genetic models. Thus, covariates were not used in these analyses. Cell sizes varied slightly across the imaging analyses.

For the recessive model, individuals with the CC genotype (n = 26) of *SOD2* were compared against individuals with the CT/TT genotypes (n = 68). A significant multivariate main effect was observed for RD (Pillai's Trace = 0.243, $F(7,58) = 2.67$, $p = 0.018$, $f^2 = 0.32$), with the CC group demonstrating significantly higher RD (p = .001) in the ATR compared to the CT/TT group (Figure 1A). Groups did not differ significantly for AD (Pillai's Trace = 0.172, $F(7,58) = 1.72$, $p = 0.122$, $f^2 = 0.21$) or FA (Wilks' $\Lambda = 0.870$, $F(7,58) = 1.24$, $p = 0.295$, $f^2 = 0.15$). No significant differences were observed for processing speed ($F(1,88) = .07$, $p = 0.791$, $f = .03$), executive function ($F(1,86) = .30$, $p = 0.588$, $f = .05$), or memory ($F(1,92) = .67$, $p = 0.415$, $f = .08$). RD in the ATR remained statistically significant (p < .002) after applying FDR corrections to the univariate outcomes.

For the dominant model, individuals with the TT genotype (n = 26) were compared against individuals with the CC/CT genotypes (n = 68). Statistical assumptions were satisfied with the exception of Levene's test in all analyses. Groups did not differ significantly for FA (Pillai's Trace = 0.168, $F(7,58) = 1.68$, $p = 0.133$, $f^2 = 0.20$), RD (Pillai's Trace = 0.159, $F(7,58) = 1.57$, $p = 0.164$, $f^2 = 0.19$), and AD (Pillai's Trace = 0.071, $F(7,58) = .63$, $p = 0.727$, $f^2 = 0.08$). Groups did not differ significantly on processing speed ($F(1,88) = .09$, $p = 0.766$, $f = .03$), executive function ($F(1,86) = 1.26$, $p = 0.265$, $f = .12$), or memory ($F(1,92) = .01$, $p = 0.914$, $f = .01$).

For the additive model, genotypes were compared using a 3-group design: CC (n = 26) vs. CT (n = 42) vs. TT (n = 26). Preliminary analyses revealed significant group differences in years of education between the CC and CT groups (p = .042). Bivariate correlations between education and white matter tracts revealed modest but significant associations in the ATR, IFOF, ILF, and both segments of the CB (r's between .2 and .4). Thus, education was used as a covariate in the tract-based analyses. Interestingly, significant correlations were not observed between education and the cognitive measures, and as such education was not used as a covariate in the cognitive analyses.

A significant multivariate effect was observed in RD between groups (Pillai's Trace = 0.390, $F(14,114) = 1.97$, $p = 0.026$, $f^2 = 0.24$) (Figure 1B). Specifically, Tukey's HSD revealed higher RD in the ATR among CC genotypes versus CT genotypes (p = .020) and TT genotypes (p = .003). Significant differences were not observed between CT and TT genotypes (p = .477). Univariate differences in the CGC were trending towards significance between CC and TT groups (p = .059). Pairwise comparisons in the CGC revealed higher RD in CT genotypes compared to TT genotypes (p = .033), and a trend for higher RD in CC genotypes compared to TT genotypes (p = .058). Groups did not differ significantly on FA (Wilks' $\Lambda = 0.763$, $F(14,112) = 1.16$, $p = 0.319$, $f^2 = 0.14$) or AD (Pillai's Trace = 0.322, $F(14,114) = 1.56$, $p = 0.100$, $f^2 = 0.19$). No significant differences were observed for processing speed ($F(2,87) = .06$, $p = 0.944$, $f = .03$), executive function ($F(2,85) = .63$, $p = 0.535$, $f = .12$), or memory ($F(2,91) = .36$, $p = 0.701$, $f = .09$). Results did not remain significant after applying the FDR correction to the univariate outcomes (p > .002).

Secondary Aim 1: Relationships between white matter tracts and cognition by *SOD2*

To address whether genetic status moderated relationships between white matter tract alterations and cognition, the *SOD2* recessive model (CC vs. CT/TT) was used as the moderating grouping variable since univariate outcomes did not survive the FDR correction in the homozygous analyses. Regression models were not run for *CAT-262* due to the lack of significant relationships with white matter and cognition. Collinearity assumptions were satisfied for all analyses (Tolerance > .4, VIF < 2.5; Allison, 1999). Model 2 in the regression (mean centered DTI variable and mean centered *SOD2* on cognition) did not offer meaningful information beyond model 1 (mean centered DTI variable on cognition) and model 3 (mean centered DTI variable, mean centered SOD2, and interaction term on cognition), and therefore model 2 was not interpreted. Results were considered significant at the .05 alpha level if both the ANOVA model and Sig. ΔF were < .05. FDR corrections were applied separately to each cognitive domain (42 comparisons).

For processing speed, significant main effects were observed with FA in the ILF and IFOF; AD in the SLF, IFOF, CGC, ATR, and UF; and RD in the ILF, IFOF, SLF, CGC, ATR, and UF (Table 3). Lower FA and higher AD and RD in these tracts was associated with slower processing speed. The addition of *SOD2* and the interaction term did not improve model fit for any significant main effect. However, a significant interaction effect was observed between RD in the CHC and *SOD2* on processing speed (F (3,60) = 3.30, p = 0.026), with the interaction term (RD in the CHC**SOD2*) uniquely explaining 12% of the variance in processing speed. Simple slope analyses indicated that individuals with the CC genotypes demonstrated a strong negative relationship between RD in the CHC and processing speed (t = -3.12, p = .003). Significant relationships were

not observed between RD in the CHC and processing speed in individuals with the CT/TT genotypes (t = .32, p = .747). This suggests that slower processing speed is related to higher RD in the CHC among individuals with the CC genotype. By contrast, higher RD in the CHC of individuals with the CT/TT genotypes is not related to slower processing speed (Figure 2A). A significant interaction was also observed between FA in the CGC and *SOD2* (F (3,63) = 2.91, p = 0.041), with the interaction term (FA in the CHC**SOD2*) uniquely explaining 6% of the variance in processing speed.). Simple slopes also revealed a strong positive relationship between FA in the CGC and processing speed among CC genotypes (t = 2.87, p = .006), whereas no significant relationship was observed in CT/TT genotypes (t = .69, p = .492). This suggests that slower processing speed is related to lower FA in the CGC among individuals with the CC genotype, but lower FA in the CGC is not related to processing speed in CT/TT genotypes (Figure 2B). After applying FDR corrections, all main effects and interactions remained significant with the exception of the interaction effect in the CGC.

For executive function, significant main effects were observed for FA in the ILF and IFOF; AD in the SLF, ATR, and UF; and RD in the ILF, IFOF, and CGC (Table 4A). Lower FA and higher AD and RD in these tracts was significantly associated with poorer performance on executive function tasks. The addition of *SOD2* and the interaction term did not improve model fit for any significant main effect. Interaction effects were not observed. After applying FDR corrections, only FA in the ILF and IFOF remained significant.

For memory, only one significant main effect was observed for FA in the ILF (Table 4B). Lower FA in the ILF was associated with poorer memory performance,

though this effect did not survive the FDR correction. The addition of *SOD2* and the interaction term did not improve model fit and interaction effects were not observed.

Secondary Aim 2: Impact of combined risk alleles of *SOD2* and *CAT-262*

Low risk groups were defined by a *SOD2* genotype of CT or TT, and a *CAT-262* genotype of CT or TT. The results of the primary analyses and genetic model testing indicated that two C alleles are required to increase risk for *SOD2*, and as such, CT and TT genotypes were considered low risk. Consistent with primary aims, low risk for *CAT-262* was also defined by the CT and TT genotypes. High risk was strictly defined by possession of the CC genotype for both *SOD2* and *CAT-262*. Participants with one high risk genotype and one low risk genotype were excluded from the analyses. Twenty-three individuals were identified as low risk (*SOD2* CT + *CAT-262* CT or TT, *SOD2* TT + *CAT-262* CT or TT), and 15 individuals were identified as high risk (*SOD2* CC + *CAT-262* CC). Imaging data were available for 15 individuals in the low risk group and 11 individuals in the high risk group. Groups did not differ significantly on descriptive variables.

Groups did not differ significantly for FA (Wilks' $\Lambda = 0.838$, $F(7,18) = .50$, $p = 0.824$, partial $eta^2 = 0.162$), RD (Wilks' $\Lambda = 0.676$, $F(7,18) = 1.23$, $p = 0.337$, partial $eta^2 = 0.324$), and AD (Pillai's Trace = 0.284, $F(7,18) = 1.02$, $p = 0.450$, partial $eta^2 = 0.284$). Groups did not differ significantly on processing speed ($F(1,34) = .07$, $p = 0.801$, partial $eta^2 = 0.002$), executive function ($F(1,34) = .03$, $p = 0.856$, partial $eta^2 = .001$), or memory ($F(1,36) = .32$, $p = 0.577$, partial $eta^2 = .009$).

Discussion

The present study is the first to examine the influence of antioxidant defense genes on brain white matter and cognition in a healthy sample of older individuals. Results revealed higher RD in the ATR of individuals with the CC genotype of *SOD2* compared to those with the CT and TT genotypes. Group differences in RD were also evident in the CGC, though this finding did not survive the FDR correction. With regard to cognition, the CC genotype moderated the relationship between higher RD in the CHC and slower processing speed. By contrast, *CAT-262* did not significantly influence white matter or cognition, and possession of high risk genotypes from both *SOD2* and *CAT-262* was not associated with poorer brain outcomes. Collectively these results suggest that the CC genotype of *SOD2* is a significant risk factor for microstructural white matter damage and associated reductions in processing speed in otherwise healthy older adults.

Research examining the impact of the *SOD2* polymorphism on the brain is limited, and existing work in humans has been conducted almost exclusively in clinical cohorts using case-control designs. Nevertheless, the observation that the C allele of *SOD2* was associated with a greater risk for brain abnormalities is consistent with evidence that the C allele of *SOD2* is overrepresented in neurodegenerative conditions such as AD (Wiener et al., 2007), PD (Shimoda-Matsubayashi et al., 1996), motor neuron disease (Landegham et al., 1999), and psychiatric conditions such as schizophrenia (Akyol et al., 2004). The recessive model (CC vs. CT/TT genotypes) was the most robust genetic model to brain alterations, suggesting that two C alleles are required to influence brain integrity in a sample of cognitively normal individuals. This observation is in agreement with work by Bastaki et al. (2005), who revealed 33% higher SOD2 enzyme activity in CT/TT genotypes compared to CC genotypes.

In the present study, CC genotypes of *SOD2* demonstrated localized alterations in the ATR, and to a lesser extent the CB. The ATR and CB are prominent white matter tracts that include connection sites with the prefrontal cortex (PFC), cingulate cortex, and thalamic nuclei (Chiu et al., 2011; Mori et al., 2008). Studies utilizing fiber dissection techniques and DTI tractography have shown that the ATR and CB are fiber bundles within the Papez circuit (Jang & Yeo, 2013; Shah, Jhawar, & Goel, 2012), which is a limbic system pathway involved in emotional expression and memory (Papez, 1937). Signaling pathways within the Papez circuit are primarily excitatory (Morgane, Galler, & Mokler, 2004), resulting in ROS production via NMDA receptor activation (Bindokas, Jordán, Lee, & Miller, 1996; Urano et al., 1998). Excess ROS production can deplete the already limited stores of cellular antioxidants, ultimately leading to perpetuated mitochondrial dysfunction, glutamate neurotoxicity, and cell death (Atlante et al., 2001).

Alterations in the Papez circuit, specifically the ATR and CB, have been reported in previous studies of brain aging (Baker et al., 2014; Cremers et al., 2016; Gunbey et al., 2014; Mella et al., 2013), AD (Aggleton, Pralus, Nelson, & Hornberger, 2016; Hornberger et al., 2012; Torso et al., 2015), PD (Kamagata et al., 2012; Vercruysse et al., 2015), and schizophrenia (Ellison-Wright et al., 2014; Whitford et al., 2014), among others. Oxidative stress has been implicated in the pathogenesis of these conditions and is consistent with studies reporting an increase risk for AD, PD, and schizophrenia among CC genotypes of *SOD2*. NMDA receptors are located in OLs and myelin sheaths and have shown to become activated in response to neuronal injury (Butt, Fern, & Matute, 2014; Salter & Fern, 2005). In addition, overexpression of SOD2 in cultured cell lines has been shown to protect against NMDA neurotoxicity (Gonzalez-Zulueta et al., 1998).

It is possible that reduced integrity of the ATR and CB among older individuals with the CC genotype is due to lower levels of SOD2 in the Papez circuit, and a resultant decrease in the detoxification capacity of ROS. Although this remains conjecture at this point, imaging modalities such as positron emission tomography (PET) would be useful for identifying relationships between *SOD2* genetic status and *in vivo* glutamate and NMDA receptor binding within regions of the Papez circuit.

RD was the most robust DTI metric to genetic differences in *SOD2*, which is consistent with the hypothesis that oxidative stress is detrimental to myelin integrity. RD is believed to be preferentially sensitive to changes in the myelin sheath compared to other DTI metrics. Work by Song et al. (2002, 2005) demonstrated that RD could distinguish demyelination from axonal damage in mouse models of retinal ischemia and multiple sclerosis. Additional work from Nair et al. (2005) revealed increased RD in mice that were genetically modified to be myelin-deficient, which corresponds to the positive correlation between RD and demyelination severity observed in human post mortem tissue samples of multiple sclerosis patients (Klawiter et al., 2011).

Human studies of normal aging *in vivo* reveal various patterns of diffusivity that are expected to reflect different mechanisms of neuropathology (Bennett et al., 2010; Burzynska et al., 2010; Madden et al, 2012), with FA and AD linked to axonal damage and MD and RD linked to demyelination. The most consistent and spatially prominent DTI findings are decreased FA and increased RD in older adults relative to younger adults, with region specific increases (and sometimes decreases) in MD and AD (Bennett et al., 2010; Burzynska et al., 2010). Decreased FA and increased RD is most commonly observed across white matter tracts traversing the frontal lobe during normal aging

(Madden et al., 2012), supporting the theory that the increased metabolic activity of OLs in late-myelinating association pathways makes them more vulnerable to oxidative damage. Madden et al. (2012) noted that a concurrent decrease in FA and increase in RD likely represents pathology of both the axon and myelin sheath. Results from the present study suggest that genetic differences in *SOD2* do not contribute to axonal pathology but specifically influence myelin disruption in healthy older adults.

The lack of cognitive differences between *SOD2* groups may be due to several factors. First, the average age of the sample was only 63 years old, and therefore the genetic impact on age-related cognitive decline may not have been sufficient to influence group differences. Previous research by Tucker-Drob and Briley (2014) demonstrated that approximately one third of between-subject variability in cognitive changes between ages 65-96 is explained by genetic differences, whereas no cohesive pattern of indicators could explain the variability in cognitive aging between ages 50-65. This is in agreement with the resource-modulation hypothesis, which theorizes that increased depletion of brain resources modulates the impact of common genetic variants on cognition, and therefore the impact of such variants becomes more significant with advanced age (Lindenberger et al., 2008). Many studies have provided support for this model by revealing modest or non-existent genetic effects in young adults relative to older adults (for review see Papenberg, Lindenberger, & Backman, 2015). The resource-modulation hypothesis is closely related to the concept of cognitive reserve, which may also have contributed to the lack of significant cognitive effect between *SOD2* groups. Cognitive reserve refers to the use of pre-existing cognitive processing strategies to perform normally despite considerable neuropathology (Stern, 2009). Education is a common

proxy measure of cognitive reserve that is positively correlated with cognitive outcomes (Le Carret et al., 2003). Participants in the present study were highly educated (≈ 16 years), and therefore alterations in the ATR and CB among CC genotypes may have been functionally attenuated due to a high level of cognitive reserve. Finally, the lack of cognitive effect is consistent with previous genetic studies within this cohort that have reported negative findings with regard to cognition (Salminen et al., 2013, Salminen et al., 2014).

Despite the absence of a direct effect of *SOD2* on cognitive function, multiple regression analyses revealed a significant moderating effect of the CC genotype between the CB and processing speed, with a more robust interaction in the CHC compared to the CGC. Previous research suggests that alterations in the CHC are more closely linked to pathological aging and AD compared to alterations in the CGC (Catheline et al., 2010; Choo et al., 2010; Fellgiebel et al., 2005; Firbank et al., 2007; Nir et al., 2013; Santiago et al., 2015). Accordingly, Laukka et al. (2013) revealed weaker associations between age-related changes in the CHC and reduced processing speed when cognitively "normal" older adults were excluded for prodromal dementia (assessed retrospectively from longitudinal follow up). The CHC is a fiber pathway within the Papez circuit that connects the posterior cingulate cortex (PCC) with the medial temporal lobe (Yu et al., 2014), the latter of which harbors the hippocampal region, entorhinal, and parahippocampal cortices (Squire, Stark, & Clark, 2004). Each of these structures is vulnerable to AD pathology, particularly the accumulation of oxidative end products and reduced antioxidant capacity in the hippocampus. Both aging and genetically determined SOD2 deficiencies promote oxidative stress in the hippocampus, thereby leading to

reductions in cognitive function (Huang, Leu, & Zou, 2015). Relatedly, the PCC is a primary connectivity hub for major cortical networks (Buckner et al., 2009; Greicius, Supekar, Menon, & Dougherty, 2009), allowing information processing across disparate brain systems. Disrupted functional connectivity of the PCC has been associated with reduced processing speed in aging individuals (Andrews-Hanna et al., 2007; Damoiseaux et al., 2008), which may explain the link between the increased RD in the CHC and slower processing speed in CC genotypes of *SOD2*. It is possible that some individuals with the CC genotype were in a prodromal stage of disease at the time of scanning which influenced the strength of the moderation. Longitudinal studies are needed to evaluate annual changes in the relationship between the CB and processing speed among CC genotypes.

In contrast to my hypothesis, *CAT-262* was not significantly related to white matter or cognition in this cohort of individuals. Although this was unexpected, previous research has reported conflicting results regarding the impact of this SNP on various health conditions. First, a clear risk allele for brain dysfunction has not been defined. Some studies have shown that the minor T allele is protective against diabetic neuropathy, acoustic neuroma, and later presentation of neurological manifestations of Wilson's disease (Chistiakov et al., 2006; Gromadzka et al., 2014; Rajaraman et al., 2008; Zotova et al., 2004). However, other studies have reported an increase risk for breast and prostate cancer (Hu et al., 2015; Saadat & Saadat, 2015), chronic hepatitis B (Liu et al., 2015), alcohol dependency (Plemenitas et al., 2015), ulcerative colitis (Khodayari et al., 2013), and asthma (Babusikova, Jesenak, Evinova, Banovcin, & Dobrota, 2014; Taniguchi et al., 2014). Additional research investigations reported no

association between *CAT-262* and sporadic AD (Capurso et al., 2010), hypertension (Petrovic, 2014), and depression (Galecki, Szemraj, Zboralski, Florkowski, & Lewinski, 2010). Forseberg et al. (2001) revealed differences in allelic expression across organ tissues (Forseberg et al., 2001), which may explain the discrepancy of allelic risk in the abovementioned studies.

Results from the present study may indicate that lower levels of CAT are not sufficient to impact brain structure and function in a healthy adult sample. Although CAT and SOD2 are recognized as the two primary catalytic antioxidants involved in the reduction of ROS, glutathione peroxidase (GPx) works synergistically with CAT to facilitate the breakdown of H_2O_2 to oxygen and water (Bastaki et al., 2005). Results from *in vitro* studies have shown that GPx overexpression protects against experimental stroke, and may be more neuroprotective than SOD2 or CAT (Hoehn, Yenari, Sapolsky, & Steinberg, 2003; Toussaint, Houbion, & Remacle, 1993). GPx1 is the most common isoform of GPx and is encoded by the Pro197Leu SNP (rs105040) in the *GPx1* gene (Crawford et al., 2012). The Leu allele has been associated with earlier mortality (Zeikova et al., 2012) and lobar intracerebral hemorrhage (Pera et al., 2008), yet research regarding the Pro197Leu SNP and brain integrity is limited. Given the convergent mechanisms of GPx and CAT, alterations in brain microstructure and cognition may depend on the presence of risk alleles from both *CAT-262* and *GPx1* Pro197Leu. This theory is consistent with evidence that the interaction between GPx and CAT promotes resistance to H_2O_2 -cell death in mature OLs (Baud et al., 2004).

In the present study genotyping was only completed for *SOD2* and *CAT-262* to facilitate data reduction. *CAT-262* was selected over *GPx1* Pro197Leu due to the weight

of literature emphasizing the importance of CAT in redox reactions and the increased prevalence of the prospective risk allele in Caucasians and African Americans (77% and 98% respectively, versus ≈ 30% for the Leu allele in both races; dbSNP). Additional work is needed to determine if the combination of risk factors from *CAT-262* and *GPx1* is associated with brain abnormalities in a similar sample of healthy older adults.

Limitations

A few limitations of this study should be acknowledged. First, this study did not include a plasma or cerebrospinal fluid (CSF) biomarker of oxidative stress or antioxidant enzyme activity and therefore the functional impact of *SOD2* and *CAT-262* on brain microphysiology remains unknown. While previous studies have measured antioxidant activity from plasma and serum, the relationship between central and peripheral levels of enzyme activity is not consistent (Reiter, 1995; Harish et al., 2013). Alternatively, the enzyme 8-hydroxy-2-deoxyguanosine (8-oxo-dG) is a commonly used peripheral marker of mtDNA damage that has shown to predict brain atrophy in neurodegenerative conditions such as the human immunodeficiency virus (Kallianpur et al., 2016). Examination of 8-oxo-dG in conjunction with *SOD2* may provide useful information regarding underlying mechanisms of neuropathology in CC genotypes.

Second, the use of AD and RD is controversial due to potential misalignment of the principal diffusion direction to underlying tissue structure. Misalignment is most likely to occur in areas of crossing fibers and low anisotropy (often from severe pathology), and can lead to inaccurate biophysical interpretations of what is truly axonal degeneration versus demyelination (Madden et al., 2012; Wheeler-Kingshott & Cercignani, 2009). Interpretation that increased RD in the present study represents

demyelination is based on previously identified patterns of DTI changes that correspond to histological data (Burzynska et al., 2010). While it is possible that increased RD in the ATR also reflects axonal damage given the established correlations between demyelination and axonal degeneration (Klawiter et al., 2011; Schmierer et al., 2008), the weight of literature regarding diffusivity patterns and oxidative mechanisms suggests that RD changes were likely driven by demyelination. Neuropathological data are required to address this hypothesis.

Third, participants were recruited using advertisements for "healthy cognitive aging" and as such there may have been a sampling bias for individuals who were already concerned about their cognitive health. While a sampling bias may have influenced the level of cognitive performance exhibited by this cohort as a whole, it is unlikely that this would have influenced genetic differences in brain outcomes. Finally, the present study was cross-sectional and therefore the impact of *SOD2* and *CAT-262* on intraindividual brain changes remains unknown.

Conclusion

The work presented herein is highly significant as it is the first *in vivo* examination of brain outcomes among healthy older adults with genetic risk variants of *SOD2* and *CAT-262*. While our results do not support a role for *CAT-262* in "normal" brain aging, the CC genotype of *SOD2* appears to confer risk for tract-specific alterations in the Papez circuit that are related to slower processing speed. Knowledge of these associations should facilitate research aimed at developing intervention strategies for individuals at risk for SOD2 deficiencies, whether by exogenous antioxidant supplementation or modification of lifestyle factors that reduce the burden of oxidative

stress in the aging brain. Future studies utilizing PET imaging will further elucidate the relationship between *SOD2* and metabolic disturbances in the Papez circuit, particularly in the ATR and CB. Longitudinal studies examining a slightly older cohort (≥ age 65) will be beneficial for determining the degree to which these antioxidant defense genes influence intraindividual variability in normal brain aging.

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Table 1. Descriptive Characteristics for the Primary Aims

SOD2 **(N = 52)**	CC (*n* =26)	TT (*n* = 26)	*p* value
Age (*M*, *SD*)	64.5 (8.2)	61.8 (7.2)	0.215
Years of Education (*M*, *SD*)	14.9 (2.6)	15.2 (2.6)	0.669
Sex *(n*) (Male, Female)	9, 17	6, 20	0.358
Race (% Caucasian)	76.9	69.2	0.754
Hypertension (% Yes)	30.8	19.2	0.337
CAT-262 (% CC genotype)	57.7	61.5	0.777
ICV (*M, SD*)	1077395.8 (170141.1)	989557.8 (97487.9)	0.053
CAT-262 **(N = 96)**	CC (*n* = 60)	CT/TT (*n* = 34)	*p* value
Age (*M*, *SD*)	62.5 (8.3)	64.5 (7.3)	0.236
Years of Education	15.8 (2.4)	15.5 (2.5)	0.614
Sex *(n*) (Male, Female)	20, 40	14, 20	0.447
Race (% Caucasian)	68.3	88.2	0.052
Hypertension (% Yes)	26.7	26.5	0.984
SOD2 (% CC genotype)	48.4	52.4	0.777
ICV (*M, SD*)	1048182.05 (191627.6)	1039461.13 (147178.5)	0.852

*p < .05

Table 2. Descriptive Characteristics for the Secondary Aims

***SOD2* Recessive Model**	CC (*n* =26)	CT/TT (*n* = 68)	*p* value
Age (*M*, *SD*)	64.50 (8.23)	63.16 (8.27)	0.481
Years of Education (*M*, *SD*)	14.88 (2.57)	15.86 (2.40)	0.053
Sex *(n*) (Male, Female)	9, 17	25, 43	0.846
Race (% Caucasian)	76.9	75.0	0.623
Hypertension (% Yes)	30.8	25.0	0.571
CAT-262 (% CC genotype)	57.7	66.2	0.444
ICV (*M, SD*)	1077395.8 (170141.1)	1032688.4 (177432.9)	0.375
***SOD2* Dominant Model**	CC/CT (*n* = 68)	TT (*n* = 26)	*p* value
Age (*M*, *SD*)	63.7 (8.2)	61.8 (7.2)	0.296
Years of Education	15.9 (2.4)	15.2 (2.6)	0.243
Sex *(n*) (Male, Female)	28, 40	6, 20	0.102
Race (% Caucasian)	77.9	69.2	0.149
Hypertension (% Yes)	29.4	19.2	0.318
CAT-262 (% CC genotype)	64.7	61.5	0.775
ICV (*M, SD*)	1073316.9 (199095)	989557.8 (97487.9)	0.075
***SOD2* Additive Model**	CC (*n* = 26)	CT (*n* = 42)	TT (*n* = 26)	*p* value
Age (*M*, *SD*)	64.5 (8.2)	63.3 (8.3)	61.8 (7.2)	0.480
Years of Education	14.9 (2.6)	16.5 (2.1)	15.2 (2.6)	0.017*
Sex *(n*) (Male, Female)	9, 17	19, 23	6, 20	0.178
Race (% Caucasian)	76.9	78.6	69.2	0.175
Hypertension (% Yes)	30.8	28.6	19.2	0.595
CAT-262 (% CC genotype)	57.7	69.0	61.5	0.613
ICV (*M, SD*)	1077395.8 (170141.1)	1070427.7 (220858.2)	989557.8 (97487.9)	0.205

*p < .05. For the additive model, Tukey's HSD revealed significant differences in years of education between CC and CT genotypes (p = .042). CC and CT groups did not differ significantly from TT groups (p = .956, p = .083, respectively).

Fig.1. Significant multivariate main effects were observed for tract-specific alterations in RD when individuals were grouped according to recessive and additive models. After applying the FDR correction, group differences in the ATR remained significant for the recessive model **(A)**, but not the additive model **(B)**. *Note.* Values were graphed according to raw RD values for visualization purposes. The p values indicated are those after the log10 transformation.

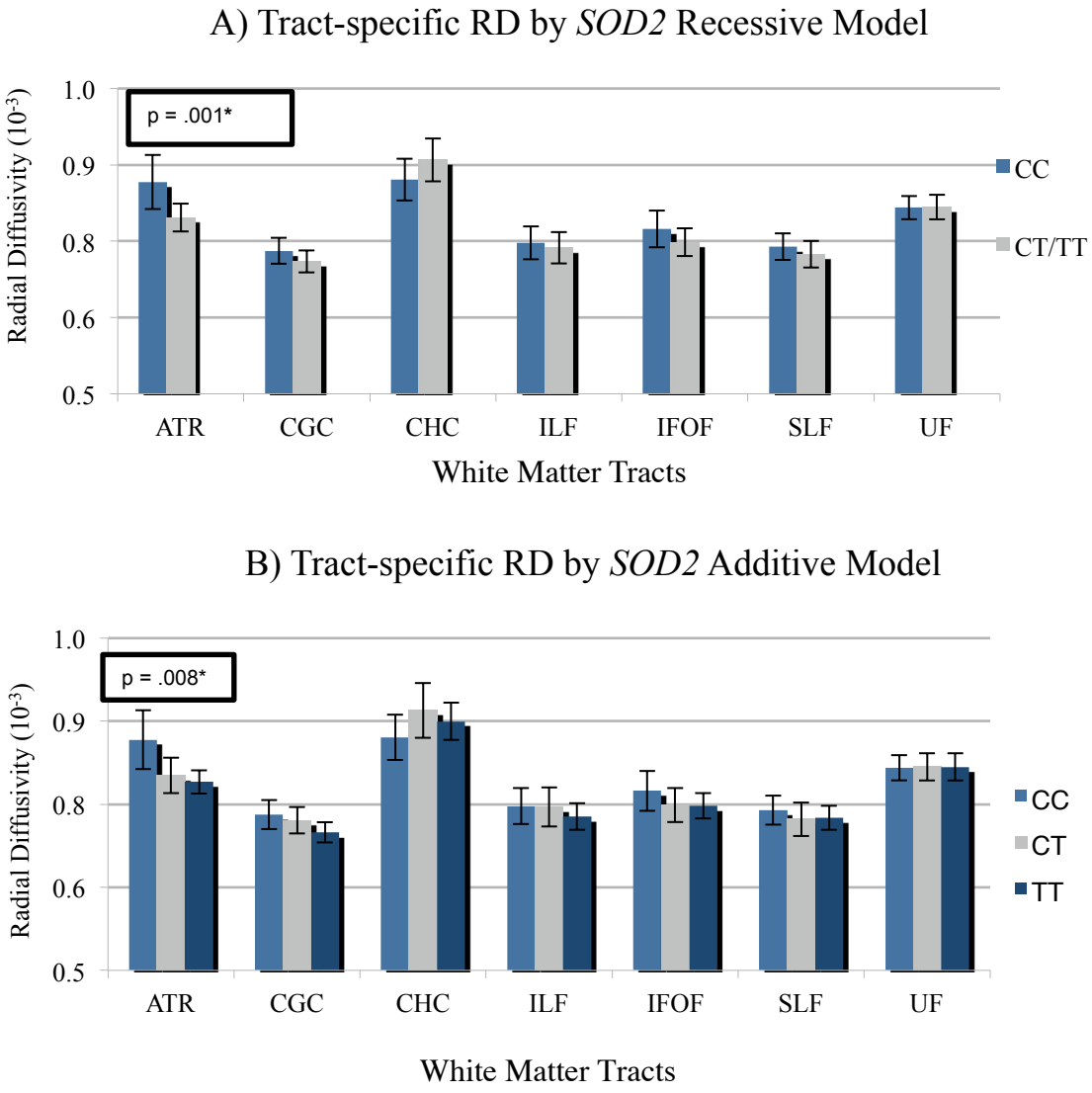
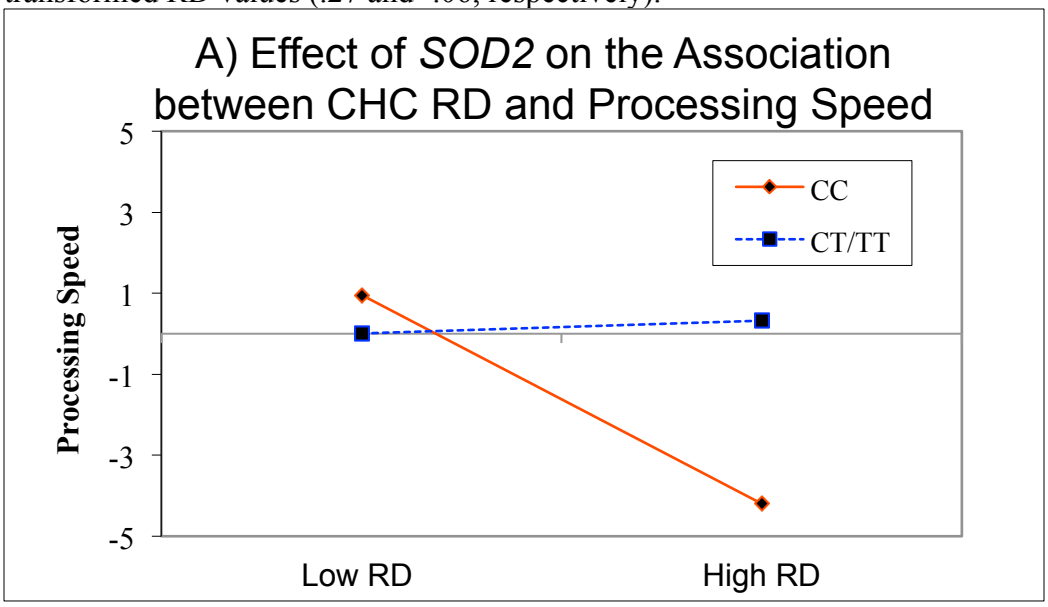


Table 3. Significant Main Effects between White Matter Tracts and Processing Speed

	R^2	F	p	f^2
ATR				
AD	.17	13.55	**<.001***	.20
RD	.13	9.40	**.003***	.15
CGC				
AD	.10	7.20	**.009***	.11
RD	.19	15.59	**<.001***	.23
ILF				
FA	.24	20.82	**<.001***	.32
RD	.19	15.61	**<.001***	.23
IFOF				
FA	.21	17.14	**<.001***	.27
AD	.10	7.31	**.009***	.11
RD	.21	17.29	**<.001***	
SLF				
AD	.14	10.63	**.002***	.16
RD	.11	7.99	**.006***	.12
UF				
AD	.17	13.31	**.001***	.20
RD	.14	10.80	**.002***	.16

*p < .05, bolded p values survived FDR correction (total of 42 comparisons).

Fig.2. Moderation of the CC genotype on RD in the CHC **(A)** and FA in the CGC **(B)** on processing speed. Endpoints were plotted according to maximum and minimum log transformed RD values (.27 and -.06, respectively).



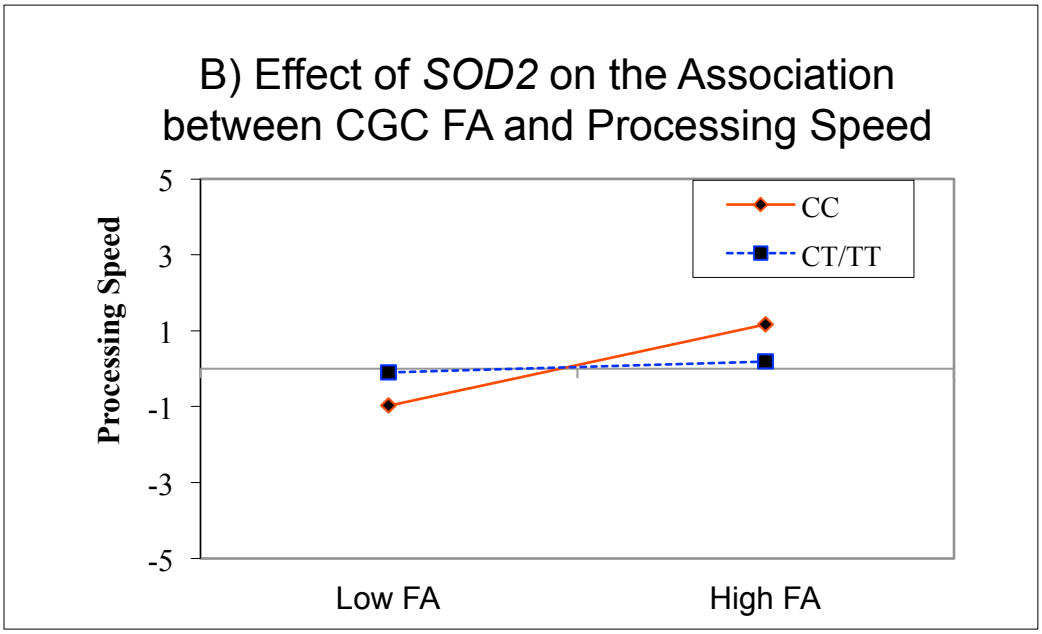


Table 4. Significant Main Effects between White Matter Tracts, Executive Function, and Memory

A) Executive Function	R^2	F	p	f^2
ATR				
AD	.08	5.67	.020*	.09
CGC				
RD	.07	4.10	.047*	.08
ILF				
FA	.24	20.82	**<.001***	.32
RD	.06	4.31	.042*	.06
IFOF				
FA	.17	12.78	**.001***	.20
RD	.12	8.80	.004*	.14
SLF				
AD	.09	5.97	.017*	.10
UF				
AD	.08	5.21	.026*	.09
B) Memory	R^2	F	p	f^2
ILF				
FA	.06	4.32	.041*	.07

*p < .05, bolded p values survived FDR correction (total of 42 comparisons).