

STRUCTURAL AND FUNCTIONAL BRAIN CONNECTIVITY IN MIDDLE-AGED  
CARRIERS OF RISK ALLELES FOR ALZHEIMER'S DISEASE

by

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## ABSTRACT

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Single nucleotide polymorphisms (SNPs) in APOE, COMT, BDNF, and KIBRA have been associated with age-related memory performance and executive functioning as well as risk for Alzheimer's disease (AD). The purpose of the present investigation was to characterize differences in brain functional and structural integrity associated with these SNPs as potential endophenotypes of age-related cognitive decline. I focused my investigation on healthy, cognitively normal middle-aged adults, as disentangling the early effects of healthy versus pathological aging in this group may aid early detection and prevention of AD. The aims of the study were 1) to characterize SNP-related differences in functional connectivity within two resting state networks (RSNs; default mode network [DMN] and executive control network [ECN]) associated with memory and executive functioning, respectively; 2) to identify differences in the white matter (WM) microstructural integrity of tracts underlying these RSNs; and 3) to characterize genotype differences in the graph properties of an integrated functional-structural network. Participants (age 40-60, N = 150) underwent resting state functional magnetic resonance imaging (rs-fMRI), diffusion tensor imaging (DTI), and genotyping. Independent components analysis (ICA) was used to derive RSNs, while probabilistic tractography was performed to characterize tracts connecting RSN subregions. A technique known as functional-

by-structural hierarchical (FSH) mapping was used to create the integrated, whole brain functional-structural network, or resting state structural connectome (rsSC). I found that BDNF risk allele carriers had lower functional connectivity within the DMN, while KIBRA risk allele carriers had poorer WM microstructural integrity in tracts underlying the DMN and ECN. In addition to these differences in the connectivity of specific RSNs, I found significant impairments in the global and local topology of the rsSC across all evaluated SNPs. Collectively, these findings suggest that integrating multiple neuroimaging modalities and using graph theoretical analysis may reveal network-level vulnerabilities that may serve as biomarkers of age-related cognitive decline in middle age, decades before the onset of overt cognitive impairment.

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## LIST OF ABBREVIATIONS

A $\beta$	beta-amyloid
AD	Alzheimer's disease
AFNI	Analysis of Functional NeuroImages
APOE	apolipoprotein E
BDNF	brain-derived neurotrophic factor
BOLD	blood oxygen level dependent
COMT	catechol-O-methyl transferase
DTI	diffusion tensor imaging
DMN	default mode network
DOF	degrees of freedom
DRS-2	Mattis Dementia Rating Scale Second Edition
ECN	executive control network
EPI	echo-planar imaging
FA	fractional anisotropy
FSH	functional-by-structural
FSL	FMRIB Software Library
GDS	Geriatric Depression Scale
ICA	independent components analysis
KIBRA	kidney and brain protein
MCI	mild cognitive impairment
MD	mean diffusivity
Met	methionine

MMSE	Mini-Mental Status Exam
MRI	magnetic resonance imaging
PET	positron emission tomography
PFC	prefrontal cortex
RD	radial diffusivity
ROI	region of interest
rsfMRI	resting state functional magnetic resonance imaging
RSN	resting state network
rsSC	resting state structural connectome
SNP	single nucleotide polymorphism
TPDT	transverse patterning discriminations test
Val	valine
vMWT	virtual Morris Water Task
WM	white matter

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# Structural and Functional Brain Connectivity in Middle-Aged Carriers of Risk Alleles for Alzheimer's Disease

## **Neuropathology Associated with Healthy Aging and Alzheimer's Disease**

Alzheimer's disease (AD) is the sixth leading cause of death in the United States and will affect an estimated 13.8 million people by the year 2050 (Alzheimer's Association, 2014). This disease is characterized by profound declines in memory, executive functioning, and ability to perform activities of daily living (McKhann et al., 2011), resulting in reduced quality of life for both patients and their caregivers. Although research is underway to identify potential treatments for AD, we do not yet fully understand the underlying causes of the disorder or the most appropriate targets for treatment. Furthermore, although delaying the onset of AD by five years would save an estimated \$367 billion in direct healthcare costs (Alzheimer's Association, 2016), it is challenging to identify who may benefit most from early diagnosis and intervention efforts. Thus, it is imperative that we identify biomarkers of AD that are detectable early in the aging process, before the onset of overt cognitive symptoms and irreversible brain damage.

Both normal aging and AD are associated with structural brain changes, and there is significant spatial overlap in the regions affected by healthy and pathological aging. For instance, a longitudinal study of healthy adults aged 20 to 77 reported significant regional volume reductions in the hippocampus, caudate nucleus, temporal lobes, prefrontal cortex (PFC), and prefrontal white matter (WM) over a five-year follow-up interval (Raz et al., 2005). Healthy, non-demented older adults in this sample showed a faster rate of regional volume loss compared to younger individuals. A similar regional pattern of atrophy is observed in patients in preclinical stages of AD (Chételat et al., 2005; Fan, Batmanghelich, Clark, Davatzikos, & Alzheimer's Disease Neuroimaging Initiative, 2008; MacDonald, Cohen, Stenger, & Carter, 2000; Misra,

Fan, & Davatzikos, 2009). Patients with mild cognitive impairment (MCI), a transitional state on the continuum from normal aging to AD, have accelerated rates of atrophy compared to clinically normal older adults (Driscoll et al., 2009) and eventually exhibit involvement of the entire neocortex in the later stages of AD (MacDonald et al., 2000). Despite this, distinguishing healthy brain aging from the earliest stages of pathological aging remains a challenge, especially at a single time point. Indeed, a study using pattern classification to differentiate MCI from normal aging reported that approximately 1/3 of MCI patients had patterns of regional atrophy that could not be distinguished from those of cognitively normal individuals of the same age (Fan et al., 2008).

Other indices of structural brain integrity also fail to accurately distinguish between healthy and pathological aging. Diffusion tensor imaging (DTI) studies have shown that healthy older adults have lower fractional anisotropy (FA) and higher mean diffusivity (MD) in WM tracts than younger adults, suggesting that aging may compromise WM microstructural organization (see Sullivan & Pfefferbaum, 2006, for review). These effects are observed particularly in frontal regions, including the anterior cingulum, genu of the corpus callosum, and fronto-parietal tracts (Chua, Wen, Slavin, & Sachdev, 2008). MCI patients do not appear to differ from healthy older adults in the WM microstructural organization of these frontal regions (Bosch et al., 2012; Fellgiebel et al., 2004; Kantarci et al., 2001; Nir et al., 2013; Stahl et al., 2007), although several studies report MCI-associated differences in the diffusion parameters of posterior WM (Bosch et al., 2012; Fellgiebel et al., 2005; Y. Zhang et al., 2007). These findings are complicated by the fact that MCI is a clinically heterogeneous category (Nordlund et al., 2005) that may comprise patients with different patterns of cognitive impairment who are at different points on the continuum between normal cognition and AD. One study that divided the

MCI category into early and late MCI found that although DTI measures could distinguish between healthy aging and late stage MCI, individuals with early MCI did not differ from healthy, non-demented older adults in their WM integrity (Nir et al., 2013). This further illustrates the difficulty in identifying preclinical biomarkers of risk for age-related cognitive decline.

Given the overlap in the pattern of structural brain changes associated with normal aging and AD, these neuroimaging measures have weak predictive utility to differentiate healthy aging from early disease stages (Devanand et al., 2005; Rowe et al., 2013). Research investigating focal alterations in brain integrity has largely failed to identify useful biomarkers to classify individuals at risk for AD before the onset of clinical symptoms. For example, a study using data from the Alzheimer's Disease Neuroimaging Initiative examined the accuracy of common neuroimaging biomarkers to predict which patients with MCI would convert to AD and which would remain cognitively stable (Prestia et al., 2013). Hippocampal volumes had 46% sensitivity to predict conversion to AD and 76% specificity to exclude patients with stable MCI, while regional cerebral hypometabolism had 33% sensitivity and 58% specificity. Although PET imaging of amyloid deposition has been shown to yield high sensitivity (93.5%) to predict conversion to AD, it suffers from a relatively high false positive rate that makes it problematic for use in clinical practice (S. Zhang et al., 2012). Furthermore, these studies have been conducted on patients already diagnosed with MCI; our ability to predict the likelihood of developing AD among healthy older adults who do not yet show signs of cognitive impairment is likely to be even poorer. Given the complex etiology and pathogenesis of AD, taking a multi-modal, integrative, network-level neuroimaging approach has the potential to reveal features associated with risk for cognitive decline that may be overlooked in more traditional region-of-

interest (ROI) analyses (Gomez-Ramirez & Wu, 2014; Seeley, Crawford, Zhou, Miller, & Greicius, 2009).

The application of a branch of mathematics called graph theory to neuroimaging data has gained considerable attention for its potential ability to yield novel information about the human connectome (Sporns, Tononi, & Kötter, 2005). A neuroimaging graph comprises a set of nodes and edges, with nodes representing discrete brain regions and an edge representing the connectivity between two nodes. Thus, highly complex data can be subjected to graph analysis to obtain meaningful metrics of network topology. Initial graph theoretical analyses of brain networks indicated that the brain has a “small world” topology, which is characterized by high local efficiency to support segregated or specialized modules as well as global integration to facilitate integrated information processing (Achard & Bullmore, 2007; Bassett & Bullmore, 2006). Patients with MCI and AD show loss of “small world” properties in graph theoretical analyses (Brier et al., 2014; Sanz-Arigita et al., 2010; Stam, Jones, Nolte, Breakspear, & Scheltens, 2007), suggesting that the global network topology is disrupted by AD neuropathology. Furthermore, as neurodegenerative conditions such as AD may preferentially target critical nodes, or “hubs,” of the brain (Buckner et al., 2009; Greicius, Srivastava, Reiss, & Menon, 2004), early disruptions to global or local network efficiency may be sensitive biomarkers of AD risk. Although patients with MCI and AD have been shown to have lower local and global efficiency of functional and structural networks compared to healthy elderly individuals (Lo et al., 2010; Supekar, Menon, Rubin, Musen, & Greicius, 2008; X. Zhao et al., 2012), no known studies have investigated these metrics in middle-aged individuals at risk for AD.

The field of neuroimaging genetics provides a rich source of information about neurobiological features associated with genetic polymorphisms that increase the risk for disease. A neuroimaging genetics approach can be particularly useful for studying early brain changes associated with AD, as a cascade of neuropathological changes precedes the development of memory changes or other clinical symptoms (Jack et al., 2010). In particular, A $\beta$  deposition (Aizenstein et al., 2008; Mintun et al., 2006) and vascular dysfunction (Iturria-Medina et al., 2016) may predate the onset of clinical symptoms by decades. As a result, it is important to characterize differences in brain structure and function in middle-aged adults who may already be undergoing neuropathological changes despite manifesting no cognitive impairment. By studying network-level brain integrity in this middle-aged population, we may identify differences that predict risk for AD years before the onset of cognitive impairment, providing a potential window for prevention or early intervention efforts before aberrant processes or irreversible damage have already taken place.

### **Functional and Structural Connectivity as Endophenotypes of AD**

The overt clinical phenotype of AD is complex and comprised of neurocognitive, neurobehavioral, and psychiatric symptoms (McKhann et al., 2011). Given this complexity, it is challenging to link the end clinical phenotype of AD to its specific genetic underpinnings. Using endophenotypes, or intermediate phenotypes, can fill in the gaps between genetic variability and higher-level behavioral phenotypes (Gottesman & Gould, 2003). Indices of structural and functional brain integrity have been proposed as potential endophenotypes of AD (Braskie, Ringman, & Thompson, 2011). To be established as an endophenotype, a marker must meet the following criteria (Gershon & Goldin, 1986; Gottesman & Gould, 2003): the endophenotype must be 1) associated with illness in the population; 2) heritable; 3) primarily state-independent

(e.g., manifest regardless of whether the illness is active); and 4) amenable to reliable measurement. As outlined below, measures of functional and structural connectivity meet these criteria and are viable potential endophenotypes of age-related cognitive decline.

### **AD is associated with altered functional and structural connectivity**

AD is associated with alterations in functional and structural connectivity. Resting state functional connectivity (rs-fMRI) is used to characterize synchronous patterns of blood oxygen level dependent (BOLD) signal that occur when the brain is in a task-free state. These patterns are thought to reflect the intrinsic connectivity of resting state networks (RSNs), which exhibit coherent spontaneous activity between anatomically separated regions (Biswal, Yetkin, Haughton, & Hyde, 1995; Greicius, Krasnow, Reiss, & Menon, 2003; Mazoyer et al., 2001; Raichle et al., 2001). Studies from multiple research groups and across different study populations have consistently found around eight to 12 RSNs in the adult brain (Beckmann, DeLuca, Devlin, & Smith, 2005; Damoiseaux et al., 2006; Smith et al., 2009; see van den Heuvel & Hulshoff Pol, 2010, for review). Two of these networks, the default mode network (DMN) and executive control network (ECN), show disrupted functional connectivity in patients with MCI or AD, suggesting that they may be sensitive to AD-related pathology (Agosta et al., 2012; Balthazar, de Campos, Franco, Damasceno, & Cendes, 2014; Damoiseaux, Prater, Miller, & Greicius, 2012; Petrella, Sheldon, Prince, Calhoun, & Doraiswamy, 2011).

### ***DMN***

The DMN is a task negative network that emerges when the brain is at rest, showing decreased activity during cognitively demanding tasks (Greicius et al., 2003; Raichle et al., 2001). The DMN includes the posterior and anterior cingulate cortex, inferior parietal lobe, medial PFC, and the hippocampal formation (Greicius et al., 2003; Raichle et al., 2001; Smith et

al., 2009). Connectivity of the DMN has been associated with self-referential thought (Greicius et al., 2003; Mason et al., 2007), and the brain regions comprising the DMN support episodic memory, particularly autobiographical memory and memory retrieval processes (Sestieri, Corbetta, Romani, & Shulman, 2011; Spreng & Grady, 2010; Spreng, Mar, & Kim, 2009). Altered DMN connectivity has been reported in a variety of clinical populations, including major depressive disorder (Sheline et al., 2009; Zhu et al., 2012), anxiety disorders (Andreescu, Sheu, Tudorascu, Walker, & Aizenstein, 2014; Lanius et al., 2010; X. H. Zhao et al., 2007), schizophrenia (Calhoun et al., 2011; Garrity et al., 2007), and traumatic brain injury (Bonnelle et al., 2011; Sharp et al., 2011), with the degree of DMN connectivity often relating to severity of clinical symptoms (Bonnelle et al., 2011; Greicius et al., 2007; Lanius et al., 2010; Zhou et al., 2012).

DMN connectivity has been proposed as a biomarker that may distinguish healthy aging from AD (Greicius et al., 2004). Data from the Baltimore Longitudinal Study of Aging suggests that during healthy aging, regional blood flow within subregions of the DMN remains relatively stable compared to non-DMN regions (Beason-Held, Kraut, & Resnick, 2009). However, patients with MCI and AD show disrupted connectivity of the DMN (Balthazar et al., 2014; Damoiseaux et al., 2012), including aberrant coupling of the hippocampus with the rest of the DMN (Greicius et al., 2004). Furthermore, disrupted DMN connectivity is associated with poorer episodic memory performance (Celebi et al., 2016; Dunn et al., 2014; L. Wang et al., 2006; Wu et al., 2011; Yuan et al., 2016), higher burden of amyloid plaques (Mormino et al., 2011; Sheline, Raichle, et al., 2010), and higher likelihood of converting from MCI to AD (Petrella et al., 2011).

### *ECN*

A second network, the ECN, is associated with ability to sustain cognitive control and flexibly employ strategies during cognitively demanding tasks (Dosenbach et al., 2007; Seeley et al., 2007). The ECN includes dorsolateral PFC, ventrolateral PFC, dorsomedial PFC, and lateral parietal cortices (Smith et al., 2009). This network is distinguishable from the left and right frontoparietal networks, which also emerge when the brain is at rest and are associated with executive abilities (Dosenbach et al., 2007; Seeley et al., 2007; Smith et al., 2009). Whereas the frontoparietal control network may support cognitive flexibility and initiation (Spreng, Stevens, Chamberlain, Gilmore, & Schacter, 2010; Vincent, Kahn, Snyder, Raichle, & Buckner, 2008), the ECN is a primarily frontal network associated with sustained cognitive control (Dosenbach et al., 2007). As impaired cognitive control is one of the clinical features of AD (Duke & Kaszniak, 2000), altered ECN connectivity may be a biomarker of risk for AD.

While the trajectory of ECN connectivity during the course of healthy aging is unknown, one longitudinal investigation has reported decreased ECN connectivity during aging and a decline in the functional segregation between the ECN and DMN (Ng, Lo, Lim, Chee, & Zhou, 2016). However, relatively few studies have focused on ECN connectivity in patients with AD. One study reported higher ECN connectivity in AD patients compared to healthy controls, with lower connectivity associated with poorer performance on neuropsychological tests of executive functioning (Agosta et al., 2012). Another has reported lower connectivity within the ECN in AD patients compared to healthy older adults (Geerligs, Renken, Saliassi, Maurits, & Lorist, 2015). These disparate findings are not entirely surprising, as several studies have reported that AD patients may show higher frontal connectivity early in the disease course – a potential compensatory mechanism – before eventually exhibiting a loss of frontal connectivity as the disease progresses (G. Allen et al., 2007; Huang et al., 2010; Supekar et al., 2008; L. Wang et al.,

2006). Thus, as age, disease severity, and other sample characteristics may affect ECN connectivity in AD and result in conflicting findings, it is important to better understand ECN connectivity in healthy, middle-aged individuals who are not yet showing overt clinical symptoms of AD.

Importantly, the anatomical subregions that comprise the DMN and ECN include brain areas known to show greater atrophy (see Ewers et al., 2011, for review) and higher A $\beta$  burden (Braak & Braak, 1991, 1997; Jack et al., 2008; Li et al., 2008) in AD patients, including the precuneus/posterior cingulate cortex, PFC, posterior parietal cortex, and parahippocampal gyrus. Thus, the brain regions making up these RSNs may be particularly vulnerable to early pathological changes that may affect network functional connectivity. This makes them strong candidates to explore as potential endophenotypes of AD.

Given that RSNs exhibit synchronous activity between anatomically separated brain regions, they may share underlying structural connections. DTI studies have revealed robust WM structural connections between subregions of the DMN (Andrews-Hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010; Damoiseaux & Greicius, 2009; Greicius, Supekar, Menon, & Dougherty, 2009; Horn, Ostwald, Reisert, & Blankenburg, 2014) and other RSNs (Hermundstad et al., 2013; Skudlarski et al., 2008), indicating that the functional organization of RSNs corresponds to the underlying structural architecture of the brain. This aspect of network-level connectivity is important to probe more deeply, as AD leads to a profound disruption of WM pathways in the brain (Bartzokis et al., 2004; Douaud et al., 2013; Rose et al., 2000). Patients with MCI and AD typically show a pattern of lower FA and higher MD in WM tracts throughout the brain, with particularly robust effects observed in the corpus callosum and tracts involving the medial temporal lobe, frontal lobe, and posterior cingulate cortex (see Amlie  $\&$  Fjell, 2014,

pp., for review). Lower FA and higher MD reflect differences in the microstructural properties of WM, which may include lower myelination, reduced axonal density, or disruption of axon structure (Jones, Knösche, & Turner, 2013). Furthermore, microstructural differences in critical WM tracts connecting subregions of the DMN have been associated with degree of episodic memory and language impairment in AD patients (Weiler et al., 2014).

In healthy adults, integrity of WM tracts reaches full maturity in the third and fourth decades of life, begins to decline during middle age, and enters a more precipitous trajectory of decline after age 60 (Kochunov et al., 2012; Westlye et al., 2010). Given this trajectory of declining WM integrity during midlife and the prominence of WM alterations in age-related cognitive decline, differences in structural connectivity may be potential endophenotypes of AD.

#### **Heritability of measures of functional and structural connectivity**

Measures of brain organization that are disrupted during the AD process have been shown to be heritable. A meta-analysis of 48 twin studies reported high heritability for volumes of the whole brain (82.8%), frontal gray (64.8%) and white matter (84%), and the hippocampus (53.2-58.5%) (Blokland, de Zubicaray, McMahon, & Wright, 2012). Genetic factors also contribute significantly to network-level characteristics, including indices of WM microstructural organization (Chiang et al., 2009; Chiang, McMahon, et al., 2011; Shen et al., 2014) and resting state functional connectivity (Fu et al., 2015; Glahn et al., 2010; Korgaonkar, Ram, Williams, Gatt, & Grieve, 2014; Sinclair et al., 2015). The heritability of network-level indices of brain integrity suggests that these measures may be potentially good endophenotypes of AD.

#### **Functional and structural connectivity are state-independent and reliable**

To meet criteria as potential endophenotypes of age-related cognitive decline, measures must also be state-independent and reliable. State independence refers to the requirement that the

trait manifest whether or not the end phenotype (cognitive impairment) is “active.” Thus, all individuals at genetic risk, not just those who have already developed cognitive impairment, should show differences in the trait (During, Osorio, Elahi, Mosconi, & de Leon, 2011). Although studies of middle-aged adults are limited to date, healthy, non-demented older adults who carry risk alleles for cognitive impairment show differences in functional connectivity (Heise et al., 2014; Z. Liu et al., 2017; Machulda et al., 2011; Sheline, Morris, et al., 2010) and WM connectivity (Cai et al., 2017; Felsky et al., 2014; Kohannim et al., 2012) compared to non-carriers. Thus, these indices of brain connectivity may be considered state independent, as they manifest in individuals at genetic risk, not just those with the end phenotype of cognitive impairment.

Furthermore, accumulated evidence suggests that networks derived from rs-fMRI (Blautzik et al., 2013; Cao et al., 2014; Franco, Mannell, Calhoun, & Mayer, 2013; Shah, Cramer, Ferguson, Birn, & Anderson, 2016; Zuo & Xing, 2014) and DTI (Boekel, Forstmann, & Keuken, 2017; Bonilha et al., 2015; Heiervang, Behrens, Mackay, Robson, & Johansen-Berg, 2006; Pfefferbaum, Adalsteinsson, & Sullivan, 2003; J. Y. Wang, Abdi, Bakhadirov, Diaz-Arrastia, & Devous, 2012) show high test-retest reliability. Acceptable test-retest reliability of DMN connectivity measures in older adults have been observed even after a one-year follow-up interval (Guo et al., 2012). High reliability has been demonstrated both for traditional connectivity measures as well as graph theoretical measures of global network organization (Braun et al., 2012; Cao et al., 2014).

Collectively, this evidence suggests that measures of functional and structural connectivity meet the criteria to be potential endophenotypes of age-related cognitive impairment. Not only do the DMN and ECN comprise regions known to be vulnerable to AD

neuropathology, but they are also associated with performance on neuropsychological measures of memory and executive functioning, respectively. As impairments in memory and executive functioning are hallmark behavioral symptoms of AD, investigating the brain integrity of carriers of risk alleles associated with these cognitive domains may yield viable endophenotypes of AD.

### **Genes Associated with Cognitive Phenotypes of Alzheimer's Disease**

Numerous genome-wide association studies and candidate gene studies have identified single nucleotide polymorphisms (SNPs) associated with cognitive abilities and risk for AD. The current project focused on associations between functional and structural brain network alterations and SNPs in four candidate genes that have been previously associated with age-related differences in memory and executive functioning. This offers a targeted strategy for identifying endophenotypes of cognitive changes associated with AD.

#### **Apolipoprotein E (APOE)**

Presence of the APOE  $\epsilon$ 4 allele (chromosome 19q13.2) is one of the most well established risk factors for AD. ApoE is a lipid transporter expressed throughout the brain and liver. Two SNPs, rs7412 and rs429358, segregate  $\epsilon$ 4 carriers and non-carriers. Presence of the  $\epsilon$ 4 allele increases risk of AD in a dose-dependent manner, with  $\epsilon$ 3/ $\epsilon$ 4 carriers having a 3.68 times greater risk and  $\epsilon$ 4/ $\epsilon$ 4 carriers having a seven-fold greater risk than  $\epsilon$ 3 homozygotes (Bertram, McQueen, Mullin, Blacker, & Tanzi, 2007). The  $\epsilon$ 4 allele is associated with disrupted myelin structure, mitochondrial function, cholinergic activity, and vasculature (see D. H. Kim et al., 2014, for review).

A growing body of evidence suggests that APOE may be an example of antagonistic pleiotropy (Han et al., 2007), in which alleles have a differential effect on evolutionary fitness at different points in the lifespan. For example, younger  $\epsilon$ 4 carriers have higher IQs (Yu, Lin, Chen,

Hong, & Tsai, 2000), greater educational achievement (Hubacek et al., 2001), and better episodic memory (Han et al., 2007; Mondadori et al., 2007), executive functioning (Han et al., 2007), and verbal fluency (Alexander et al., 2007) than non- $\epsilon 4$  carriers. In older adults, however, this relationship is reversed. A meta-analysis showed that older  $\epsilon 4$  carriers performed significantly worse on measures of global cognitive ability, episodic memory, executive functioning, and perceptual speed than non-carriers, with age increasing the magnitude of episodic memory impairment (Wisdom, Callahan, & Hawkins, 2011).

The relationship between APOE and functional brain network connectivity mirrors the general pattern of  $\epsilon 4$ -associated cognitive findings observed across the lifespan. Consistent with the beneficial role of APOE  $\epsilon 4$  on cognition in younger adulthood, young  $\epsilon 4$  carriers have higher default mode network (DMN) connectivity than non-carriers (Filippini et al., 2009; Fleisher et al., 2009). In contrast, investigations in healthy elderly and early AD have reported lower connectivity in  $\epsilon 4$  carriers, including functional disconnection between the hippocampus and the posterior cingulate cortex, precuneus, dorsal anterior cingulate cortex, and middle temporal cortex (Machulda et al., 2011; Sheline, Morris, et al., 2010). These effects are larger in older individuals (Heise et al., 2014) and are observed even in the absence of amyloid plaques (Sheline, Morris, et al., 2010). Only one known study has investigated APOE-related differences in resting state connectivity in middle age, reporting that  $\epsilon 4$  carriers have lower DMN connectivity than non-carriers (Goveas et al., 2013). Thus, the effects of the APOE  $\epsilon 4$  allele in middle age may more closely resemble the pattern observed in older adults than younger individuals and may be indicative of preclinical dysfunction in functional networks that precedes overt cognitive impairment.

APOE is also associated with differences in the microstructural organization of WM. Older  $\epsilon 4$  carriers have lower fractional anisotropy (FA) and higher mean diffusivity (MD), indicating microstructural disorganization, in the WM of the parahippocampal gyrus (Honea, Vidoni, Harsha, & Burns, 2009).  $\epsilon 4$  carriers also have shorter fiber bundle lengths in the uncinate fasciculus, a WM tract that connects the temporal lobe to the orbitofrontal cortex (Salminen et al., 2013). No known studies report the direction or magnitude of APOE-associated differences in WM microstructural integrity in middle-aged populations, making this an important area for additional research.

### **Catechol-O-methyl Transferase (COMT)**

Polymorphism of the COMT gene, located on chromosome 22q11.2, affects dopamine pathways in the PFC (Meyer-Lindenberg et al., 2006). In particular, a functional SNP in codon 158 of the gene transcript leads to substitution of methionine (Met) for valine (Val) in the resulting protein sequence. This Val158Met polymorphism (rs4680) alters activity of the COMT enzyme, which degrades catecholamine neurotransmitters in the synaptic cleft. The low-activity *met* allele results in slower dopamine degradation, and thus higher dopamine levels in PFC, compared to the high-activity *val* allele (Chen et al., 2004). Val158Met is associated with differences in cognition; younger and older carriers of the low-activity *met* allele have better executive functioning (Barnett, Jones, Robbins, & Müller, 2007; deFrias et al., 2005; Papenberg et al., 2013; Wishart et al., 2011) and episodic memory abilities (Barnett et al., 2007; de Frias et al., 2004; Papenberg et al., 2013) than *val* carriers. Both of these cognitive domains are commonly affected by AD, making COMT polymorphism a strong candidate to search for endophenotypes of AD-related cognitive changes.

COMT polymorphism also impacts brain connectivity, although the direction of these effects is not clear. Several studies in healthy adults have reported that COMT *val* carriers have higher functional connectivity between the PFC and other cortical regions at rest (Baeken et al., 2014; Meyer et al., 2016; Tunbridge, Farrell, Harrison, & Mackay, 2013), while others have reported lower PFC connectivity among *val* carriers (B. Liu et al., 2010; Tian et al., 2013). However, the majority of extant studies have investigated healthy younger adults, making it important to understand how COMT polymorphism may affect structural and functional connectivity during the aging process.

### **Brain-Derived Neurotrophic Factor (BDNF)**

The gene encoding brain-derived neurotrophic factor (BDNF) is located on chromosome 11p13 and is expressed in the hippocampus and throughout the cerebral cortex (Murer et al., 1999). A member of the nerve growth factor family, BDNF is important for neuronal differentiation and survival as well as synaptic plasticity (Lu & Chow, 1999; McAllister, Katz, & Lo, 1999). A Val to Met substitution at codon 66 (Val66Met; rs6265) has been linked to differences in memory and brain integrity. The *met* allele is associated with poorer memory in healthy younger adults (Egan et al., 2003; Hariri et al., 2003; Lamb, Thompson, McKay, Waldie, & Kirk, 2015). This is consistent with meta-analytic evidence that *met* carriers have smaller hippocampal volumes than *val* carriers (Hajek, Kopecek, & Höschl, 2012). In older samples, findings are equivocal, with some studies reporting poorer episodic memory and greater risk for AD in *met* carriers (Kennedy et al., 2015; Miyajima et al., 2008) while others suggest that *val* carriers are more susceptible to these effects (Ventriglia et al., 2002; Voineskos et al., 2011). Longitudinal evidence is limited, although one longitudinal study reported that *met* carriers with

MCI showed greater declines in memory and hippocampal volume compared to *val* carriers, indicating that BDNF may be implicated in the AD neuropathological process (Lim et al., 2014).

BDNF Val66Met has also been associated with differences in white matter microstructural organization, although findings are inconsistent. In a large cohort of younger adult twin pairs, *val* carriers had lower fractional anisotropy (FA) in the fornix, corpus callosum, left posterior thalamic radiation, and left inferior fronto-occipital fasciculus (Chiang, Barysheva, et al., 2011), suggesting compromised WM integrity. At least one study has corroborated this report of less coherent WM microstructural integrity in *val* carriers, while others report lower WM integrity in *met* carriers (Kennedy, Rodrigue, Land, & Raz, 2009) or no differences between the alleles (Montag, Schoene-Bake, Faber, Reuter, & Weber, 2010). As observed with the effects of BDNF polymorphism on episodic memory performance, this inconsistent pattern of results may be explained by an age by genotype interaction. In a cross-sectional study of adults aged 18 to 82, poorer WM microstructural organization of association fiber tracts connecting to the medial temporal lobe was observed in younger *met* carriers but older *val/val* carriers (Voineskos et al., 2011). The pattern of episodic memory performance in this sample followed the same pattern, with younger *met* carriers and older *val/val* carriers showing compromised memory performance. Characterizing the association between BDNF polymorphism and brain connectivity in a middle-aged sample may inform our understanding of the age-associated effects of BDNF polymorphism on brain integrity.

### **Kidney and Brain Expressed Protein (KIBRA)**

Several genome-wide association studies have identified associations between a T to C substitution in the ninth intron of KIBRA (rs17070145) and episodic memory (Papassotiropoulos et al., 2006; Pawlowski & Huentelman, 2011). KIBRA is expressed in the hippocampus and

plays a role in synaptic plasticity (Johannsen, Duning, Pavenstädt, Kremerskothen, & Boeckers, 2008). Carriers of the T allele outperform CC carriers on episodic memory tasks (Milnik et al., 2012), an effect that has been replicated in younger adults (Papassotiropoulos et al., 2006) and healthy elderly individuals (Bates et al., 2009; Schaper, Kolsch, Popp, Wagner, & Jessen, 2008; Witte, Köbe, Kerti, Rujescu, & Flöel, 2016). Furthermore, T carriers have a lower risk for late-onset AD than CC carriers (Burgess et al., 2011; Corneveaux et al., 2010).

Neuroimaging studies have reported that T carriers have larger hippocampal volumes (Palombo et al., 2013; Witte et al., 2016) as well as higher functional activation of the hippocampus during episodic memory tasks (Kauppi, Nilsson, Adolfsson, Eriksson, & Nyberg, 2011). Reports on the effects of KIBRA polymorphism on network connectivity are sparse. One study of Han Chinese younger adults reported that C-allele (i.e., risk allele) carriers had higher connectivity of the posterior cingulate cortex with the medial PFC within the DMN (D. Wang et al., 2013). Characterizing effects of KIBRA polymorphism on network-level functional and structural connectivity of the DMN in middle-aged individuals may better illustrate the effects of this gene on risk for AD.

### **Imaging Genetics of Brain Connectivity to Establish Endophenotypes of AD**

The four candidate genes selected for inclusion in the proposed study are associated with age-related impairment in memory and executive functioning. Although several of these SNPs have been associated with focal brain differences in younger or older adults, there has been a paucity of research investigating genetic differences in middle age. Characterizing genetic differences in brain integrity in middle adulthood has an advantage over studying older individuals, as middle-aged adults at risk for developing AD have not yet begun to experience cognitive impairment. Furthermore, identifying endophenotypes of AD in healthy, cognitively

normal middle-aged adults may provide opportunities for early detection and intervention efforts before clinical symptoms of AD begin to manifest.

As reviewed above, many of the imaging genetics studies investigating polymorphism in APOE, COMT, BDNF, and KIBRA in older adults have focused on focal brain changes or gross measures of neuropathology. However, subtle changes in WM microstructure (Jernigan et al., 2001; Kochunov et al., 2012; Kodiweera, Alexander, Harezlak, McAllister, & Wu, 2016; Westlye et al., 2010) and functional network connectivity (E. A. Allen et al., 2011; He et al., 2013; Zuo et al., 2010) may begin in middle age, making measures of structural and functional connectivity potentially more sensitive markers of risk for age-related cognitive impairment in middle-aged individuals. The candidate genes included in the present study have been associated with differences in temporal and prefrontal regions compromised during early stages of AD. Thus, studying the DMN and ECN, which include these vulnerable regions, represents a strong strategy for identifying genetic differences in network-level structural and functional integrity.

The aims were designed to provide a comprehensive description of genetic differences in functional and structural network integrity in middle age, both on a local level (e.g. individual target RSNs) and global level (e.g., whole brain connectivity). My primary aims were threefold:

1. To identify genotype differences in the functional connectivity of the DMN and ECN.

*Hypothesis:* APOE and BDNF risk allele carriers will have lower functional connectivity of the DMN and ECN, differences associated with COMT polymorphism will be seen primarily in the ECN, and differences associated with KIBRA in the DMN.

2. To identify genotype differences in the microstructural organization of WM tracts connecting subregions of the DMN and ECN

*Hypothesis:* APOE and BDNF risk allele carriers will have poorer microstructural organization (i.e., lower FA and AD, higher MD and RD) of WM tracts connecting subregions of the DMN and ECN, differences associated with COMT polymorphism will be observed in WM tracts connecting the ECN, and differences associated with KIBRA in the DMN.

3. To identify genotype differences in the graph properties of a whole-brain, integrated functional-structural network.

*Hypothesis:* Risk allele carriers for all SNPs will have lower global and local efficiency of the integrated functional-structural network. Risk allele carriers' networks will also be less resilient to targeted hub failure.

As the application of graph theory to neuroimaging is an emerging science, it is important to establish that these measures are associated with behavior. Thus, I also completed an exploratory aim designed to determine the relationship between graph theoretical measures of brain integrity and performance on two hippocampus-dependent learning and memory tasks:

Exploratory Aim 1: To examine the associations between the graph properties of a whole-brain, integrated functional-structural network and performance on learning and memory tasks, the virtual Morris Water Task (vMWT) and the Transverse Patterning Discriminations Task (TPDT).

*Hypothesis:* Higher global and local efficiency will be associated with better performance on the vMWT and TPDT.

## **Method**

### **Participants**

Participants ( $N = 150$ ) were community-dwelling adults aged 40 to 60 years ( $M = 49.9$ ,  $SD = 6.0$ ; 60 men). Exclusion criteria included: (a) self-reported cognitive or memory complaints; (b) Mini-Mental Status Exam (MMSE) (Folstein, Folstein, & McHugh, 1975) score  $\leq 24$ ; (c) Mattis Dementia Rating Scale Second Edition (DRS-2) (Jurica, Leitten, & Mattis, 2004) score  $\leq 135$ ; (d) Geriatric Depression Scale (GDS) (Yesavage et al., 1982)  $> 10$ ; (e) history of central nervous system disease (e.g., dementia, stroke, Parkinson's disease, epilepsy, other neurological disease); (f) history of severe cardiac disease (e.g., myocardial infarction, coronary bypass surgery, angioplasty); (g) history of metastatic cancer; (h) history of serious psychiatric disorder or substance use disorder; (i) any contraindication to MRI. All participants provided written informed consent and received financial compensation for their participation. The study was carried out in accordance with guidelines set by the institutional review boards at the University of Wisconsin-Milwaukee and the Medical College of Wisconsin.

### **Cognitive Assessment Measures**

Participants completed several cognitive tasks and questionnaires. The following measures were used to exclude participants with possible cognitive impairment or depressed mood:

#### **Mini-Mental Status Examination (MMSE)**

The MMSE (Folstein et al., 1975) is a brief screening tool used to assess global mental status. The 11-question measure (possible scores from 0 to 30) assesses orientation, attention and concentration, registration, recall, and language. Scores below 24 have been shown to be effective in identifying individuals with possible cognitive impairment. One person was excluded based on this cutoff.

#### **Mattis Dementia Rating Scale 2 (DRS-2)**

The DRS-2 is a validated measure of overall cognitive functioning (possible scores from 0 to 144) (Jurica et al., 2004). It yields five subscales that provide information about attention, initiation/perseveration, construction, conceptualization, and memory. Scores below 135 are indicative of possible cognitive impairment; this cutoff was used to ensure that the study population had no overt cognitive impairment. Four participants fell below this cutoff and were excluded from further analysis.

### **Geriatric Depression Scale (GDS)**

The GDS (Yesavage et al., 1982) is a 30-item measure that assesses symptoms of depression in middle-aged and older populations. Scores above 10 indicate possible Major Depressive Disorder. One participant reported a GDS score greater than 10 and was excluded from further analysis.

Participants also completed two hippocampus-dependent learning and memory tasks:

### **Virtual Morris Water Task (vMWT)**

The vMWT (Astur, Ortiz, & Sutherland, 1998; Moffat & Resnick, 2002) is a translational version of a rodent task (R. G. Morris, 1984; R. G. Morris, Garrud, Rawlins, & O'Keefe, 1982) designed to assess place learning and memory. The vMWT (NeuroInvestigations, Inc., Lethbridge, AB, Canada) was administered on a Dell computer with a 17-inch monitor. The virtual environment consisted of a circular pool located in the center of a square room. Four distal cues (e.g., window, painting) were the only visual features of the virtual environment that could be used to disambiguate spatial locations. Participants began each trial within the pool, which consisted of opaque blue water. They navigated through the environment using the up arrow key to control forward movement and the left and right arrow keys to rotate their position.

Backward navigation was not possible. Participants were given a practice trial in a different virtual environment to give them the opportunity to learn how to use the keys to navigate.

The vMWT consisted of five blocks of learning trials with four trials in each block. At the beginning of each learning trial, participants were placed in a random location in the pool. A square platform was hidden beneath the surface of the opaque water, and participants were instructed to find the platform as quickly as possible. Once they crossed over the platform, it elevated above the pool and remained elevated for 10 seconds until the next trial began. During this time, participants were able to rotate on the platform to view their position within the room, although they were not explicitly instructed to do so. A limit of 60 seconds was allotted for each hidden platform trial. After this time, the platform became visible and participants received a visual message on the screen instructing them to move to the platform as quickly as possible. Latency and path length were calculated for each trial. Heading error toward the platform was calculated as the angular deviation from a straight path to the center of the platform from the participant's starting position. Heading error was measured at the first occurrence that participant distance was greater than 25% of the pool diameter from the starting position. Total latency, distance, and heading error were summed across learning trials to create summary measures of vMWT performance.

### **Transverse Patterning Discriminations Test (TPDT)**

The TPDT is a non-linear learning task that is dependent on the hippocampus (Alvarado & Rudy, 1992; Driscoll & Sutherland, 2005; Rickard & Grafman, 1998; Rickard, Verfaellie, & Grafman, 2006). The TPDT consisted of six phases conducted in a stepwise fashion. Non-nameable black stimuli were presented on a white background. Each trial began with a fixation cross displayed in the center of the screen for 1 second. Two stimuli appeared on the screen and

participants responded by pressing a response key to indicate the left or right stimulus of the displayed pair. Correct responses were indicated by a beeping tone and the word “Correct” displayed in green on the screen. Incorrect responses were indicated by a buzzing tone and the word “Incorrect” displayed in red. The display was then cleared for a 2-second inter-trial interval before the next stimulus pair appeared. Participants were told to try to get as many correct as possible but were not explicitly instructed about the response contingencies.

Phases 1-3 of the TPDT consisted of elemental discriminations. Phase 1 consisted of the stimulus pair A+B-. In phase 2, stimulus pair C+D- was presented in addition to A+B-. Phase 3 consisted of three sets of elemental discriminations: A+B-, C+D-, E+F-. Phases 4-6 of the TPDT consisted of transverse patterning discriminations. Phase 4 consisted of the stimulus pair G+H-. Phase 5 consisted of G+H- and H+I-. In phase 6, the transverse discriminations included G+H-, H+I-, and I+G-. For each phase, training continued until participants achieved 11 correct out of 12 trials. A maximum of 400 trials was allotted to complete all six phases.

### **Genotyping**

A small amount of blood was drawn from participants in order to obtain DNA. Four SNPs were selected for inclusion (out of 96 SNPs assayed) based on existing literature regarding their role in age-related cognitive impairment. These include SNPs that make up the common  $\epsilon 2$ ,  $\epsilon 3$ , and  $\epsilon 4$  APOE genotypes, COMT Val158Met polymorphism, BDNF Val66Met polymorphism, and the KIBRA T to C substitution in the ninth intron (see Table 1).

SNP ID	Chr.	Position (bp)	Expected GMAF	Observed GMAF
<i>APOE</i>				
rs7412	Chr19	50103919	0.074	0.157
rs429358	Chr19	50103781	0.149	0.179
<i>COMT</i>				
rs4680	Chr22	18331271	0.390	0.291
<i>BDNF</i>				
rs6265	Chr11	27636492	0.229	0.238
<i>KIBRA</i>				
rs17070145	Chr5	167778369	0.455	0.436

**Table 1. Candidate SNPs.** GMAF: global minor allele frequency. Expected GMAF reports the minor allele frequency from the global population (obtained from the 1000 Genome Project) and reflects the second most frequent allele value. Observed GMAF reflects the minor allele frequency in the current study population.

## Multi-Modal MRI

All MRI data acquisition was conducted on a GE Signa 3T scanner (Waukesha, WI) with a quad split quadrature transmit/receive head coil. Participants were screened for any contraindications to MRI. Imaging sessions lasted 1 hour and 15 minutes. The imaging paradigm included:

### Structural MRI

A ‘spoiled-grass’ (SPGR) sequence (axial acquisition: TR = 35 ms, TE = 5 ms, flip angle = 45°, matrix = 256 x 256, field of view = 24 cm, Nex = 1) was obtained at the beginning of each imaging session.

### Resting state functional MRI (rs-fMRI)

A T2\*-weighted functional scan was obtained with an echo-planar pulse imaging (EPI) sequence (28 axial slices, 20 x 20 cm<sup>2</sup> FOV, 64 x 64 matrix, 3.125 mm x 3.125 mm x 4 mm voxels, TE = 40 ms, TR = 2,000 ms). The 8-minute fMRI scan was acquired under a task-free

condition (i.e., resting state): subjects were instructed to relax with eyes closed and to “not think about anything in particular.”

### **Diffusion tensor imaging (DTI)**

A 3-minute, 30 seconds DTI sequence was acquired with a spin echo single shot, echo-planar imaging sequence with sensitivity (SENSE = 2.5) encoding (2.2 mm isotropic voxels, 212 x 212 mm FOV, 96 x 96 acquired matrix), TR/TE = 6338/69 ms, 60 slices for whole brain coverage, with diffusion gradients applied along 32 non-collinear directions at a b-factor of 700 s/mm<sup>2</sup>, including one minimally weighted image with b = 0 s/mm<sup>2</sup>.

### **Data Processing and Analysis**

#### **Sample size**

I calculated a required sample size using G\*Power for ANCOVA, assuming genotype as a predictor variable and age as a covariate. As APOE ε4 homozygotes are rare, I powered the study to detect APOE genotype differences using a dominant model (i.e., ε4 homozygotes and heterozygotes vs. non-ε4 carriers); all other SNPs have a sufficient frequency to use an additive model. A study by Koch and colleagues (Koch et al., 2012) found a moderate effect ( $d = .34$ ) of APOE status on DMN connectivity. To achieve a similar effect size assuming power of .80 and alpha = .05, I require a total N of 124. Thus, the sample size is adequate to power the analyses and detect simple effects using a dominant genetic model for APOE and an additive model for COMT, BDNF, and KIBRA SNPs.

#### **Neuroimaging data processing**

##### ***Resting state fMRI data processing***

fMRI image preprocessing was carried out using Analysis of Functional NeuroImages (AFNI) (Cox, 1996) and FMRIB Software Library (FSL) (Smith et al., 2004) based on the rs-

fMRI preprocessing pipeline employed in the Human Connectome Project (Smith et al., 2013). Preprocessing included: 1) removal of the first four EPI volumes; 2) slice timing correction; 3) despiking; 4) registration of each volume to the first volume; and 5) removal of non-brain tissue from EPI volumes. A bias field-corrected T1-weighted image was skull stripped and segmented into gray matter, white matter, and cerebrospinal fluid using FAST (Y. Zhang, Brady, & Smith, 2001). EPI volumes were averaged to create a mean EPI image that was coregistered to the T1-weighted image using affine registration with 6 DOF with FLIRT (Jenkinson, Bannister, Brady, & Smith, 2002). This transform was concatenated with a structural-to-MNI nonlinear warp field, permitting a single resulting warp to be applied to resample EPI into 2-mm MNI space. White matter and CSF masks were downsampled to match EPI resolution. Ordinary Least Squares regression (AFNI 3ddeconvolve) was used to regress out motion parameters and their derivatives as well as time-series from white matter and CSF masks. A highpass filter of .01 Hz was applied to remove low-frequency drift. Data were spatially smoothed using a 6-mm FWHM Gaussian filter.

After preprocessing, each subject's 4D dataset underwent linear decomposition through independent component analysis (ICA) using FSL's MELODIC (Beckmann et al., 2005), yielding a set of statistically independent time-courses and associated spatial maps. Results were visually inspected by two independent raters to identify artefactual components. Inter-rater agreement for identification of artefacts was high (Cohen's  $\kappa = .85$ ). Individual subjects' data was denoised by regressing out these artefactual components. Denoised data were entered into group ICA and resulted in 19 independent components. Relevant components were identified using a template-matching procedure (Greicius et al., 2007) to select the "best-fit" component based on a validated template of the DMN and ECN (Smith et al., 2009).

Group differences in patterns of resting state connectivity were identified using dual regression (Filippini et al., 2009), which generates subject-specific versions of the spatial maps and associated time series. First, for each subject, the group-average set of spatial maps is regressed into the subject's 4D space-time dataset. Next, those time series are regressed (as temporal regressors) into the same 4D dataset. This results in a set of subject-specific spatial maps, one per group-level spatial map. These maps were fed into FSL's randomise (Winkler, Ridgway, Webster, Smith, & Nichols, 2014) for nonparametric permutation inference. Genotype was the independent variable, with age as a covariate. Separate models were constructed for each of the SNPs of interest.

### ***DTI data processing***

DTI data processing was carried out using FSL. The B0 image was skull-stripped using BET (Smith, 2002), and the resulting mask was applied to the other images. Eddy current-induced distortions and subject movements were corrected using FSL's "eddy" tool (Andersson & Sotiropoulos, 2016). A probability distribution of fiber direction was generated at each voxel using BEDPOSTX (Behrens, Berg, Jbabdi, Rushworth, & Woolrich, 2007; Behrens et al., 2003) to be used in probabilistic tractography. Seed regions for probabilistic tractography were derived from the group spatial maps obtained from ICA. Within each RSN of interest, coordinates of peak connectivity were extracted. An 8-mm kernel was dilated around each peak coordinate to create a spherical seed ROI to ensure adequate penetration of the WM to achieve successful probabilistic fiber tracking.

ProbtrackX (Behrens et al., 2007; Behrens et al., 2003) was used to construct WM tracts between each combination of seed and target regions. ProbtrackX builds a distribution of the likely tract location and path by repeatedly sampling from the voxelwise diffusion directions

calculated by BEDPOSTX. For each pair of ROIs, 5000 streamlines per seed voxel were calculated with a 0.5mm step length and a curvature threshold of 0.2 to eliminate pathways with an implausibly sharp curvature. Only streamlines that passed through the target waypoint mask were retained. For each pair of seeds, tractography was run in both directions (i.e., once to obtain seed1–seed2 and again to obtain seed2–seed1). Resulting tracts were normalized by dividing by the waytotal, which represents the total number of streamlines sent from the seed ROI, and then averaged. The resulting tract was thresholded to exclude the lowest 10% of fibers and binarized. These binarized masks were used to extract the following diffusion metrics: fractional anisotropy (FA), a measure of the “directionality” of the WM tract; mean diffusivity (MD), reflecting total diffusion within a voxel; axial diffusivity, the first eigenvalue, measuring diffusion in the principle fiber direction; and radial diffusivity (RD), the average of the second and third eigenvalues, reflecting diffusion in the non-principle fiber directions.

### ***FSH mapping***

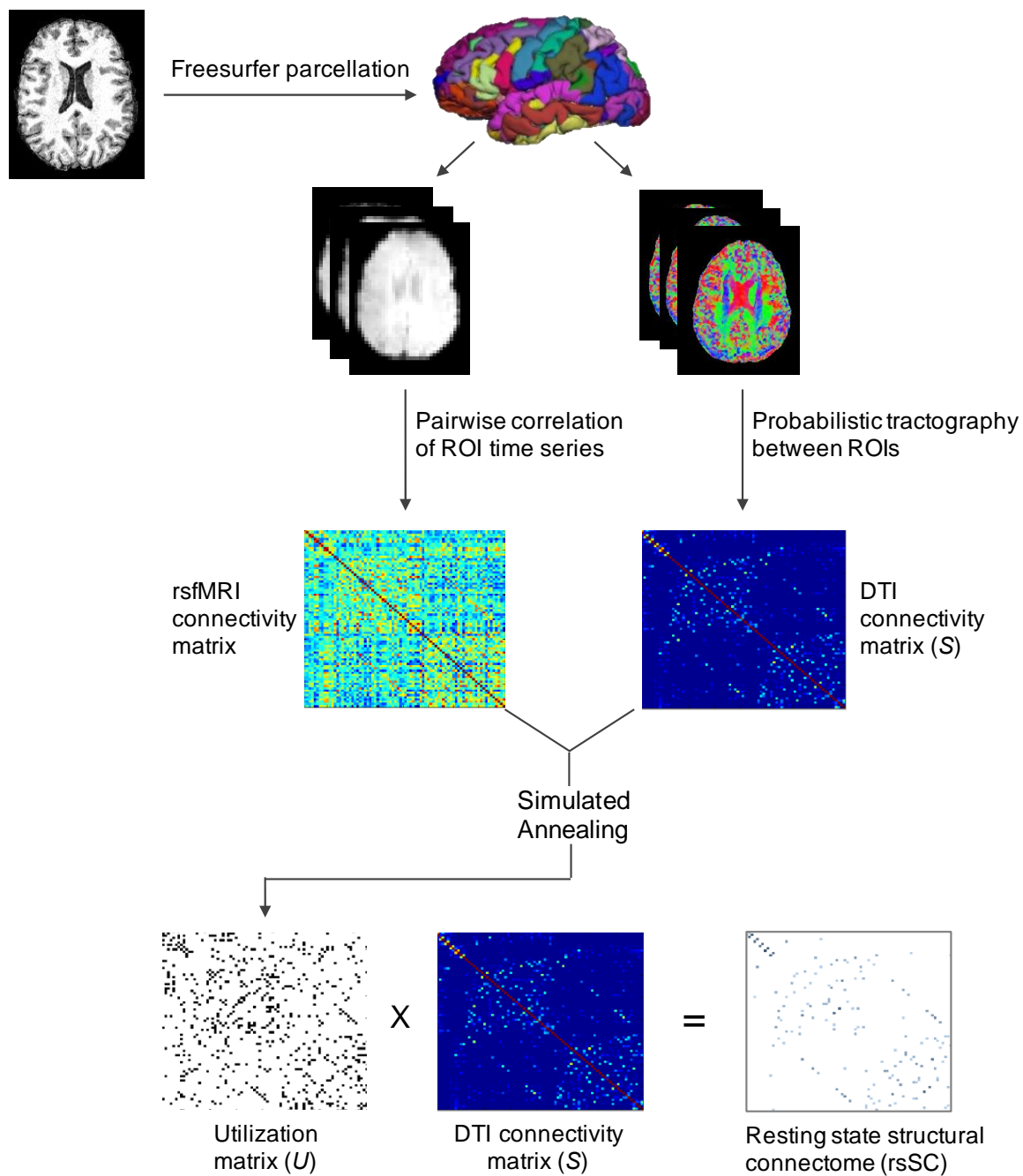
#### *Deriving the rsSC*

Functional by structural hierarchical (FSH) mapping was employed to integrate the functional and structural data into a single graph (Ajilore et al., 2013; Leow et al., 2012). FSH mapping begins with subject-specific functional and structural connectivity matrices. Freesurfer cortical parcellation and subcortical segmentation (Dale, Fischl, & Sereno, 1999; Fischl et al., 2002; Fischl et al., 2004) were performed to define 80 ROIs. These ROIs were registered to MNI and diffusion space, respectively, using affine registration with 6 DOF using FLIRT (Jenkinson et al., 2002). To create the functional connectivity matrices, the mean timecourse from each ROI was extracted from the preprocessed resting state fMRI data. These timecourses were correlated to create an 80x80 functional connectivity matrix. To create the structural connectivity matrices,

probabilistic tractography was performed between each ROI pair using Probtrackx (Behrens et al., 2007; Behrens et al., 2003). The resulting structural connectivity matrix was normalized by dividing each matrix row by the waytotal for its corresponding seed ROI. The functional and structural connectivity matrices were then  $z$ -transformed before being entered into the FSH mapping pipeline.

The FSH mapping pipeline has been reported elsewhere (Ajilore et al., 2013; Leow et al., 2012) and is illustrated in Figure 1. This technique is used to derive functional connectivity-informed structural connectivity. As not all white matter tracts are equally utilized during a given state captured by fMRI, functional connectivity data may be used to infer the underlying pattern of white matter engagement that occurs during a particular resting state. The resulting resting state-informed structural connectome (rsSC) reflects the structural network underlying the observed functional connectome.

Briefly, FSH mapping assumes that higher levels of rs-fMRI correlation reflect stronger structural interactions between two regions. This may be through direct or indirect neuroanatomical WM connections. Thus, the degree of rs-fMRI correlation between two regions decreases as the graph distance of the structural connectivity between the regions increases. FSH mapping assumes that this relationship mathematically follows an exponential decay function. For each node pair in the structural connectivity matrix, the edge reflects the existence of an underlying neuroanatomical WM connection (which may be direct or indirect). This WM connection may or may not be used when the brain is in a particular resting state. Thus, it is possible to construct a utilization matrix  $U$  that represents the pattern of WM engagement in the functional resting state.



**Figure 1. Functional-by-structural hierarchical (FSH) mapping processing pipeline.**

To reduce mathematical complexity, FSH mapping assumes all-or-nothing utilization of each edge in this matrix. Accordingly, each WM connection is either utilized or not in a given

functional state (i.e.,  $U_{(i,j)} = 1$  indicates that the WM structural connection between nodes  $i$  and  $j$  are utilized during the resting state;  $U_{(i,j)} = 0$  indicates that the WM connection is not utilized). A given connection between two nodes is considered “utilized” if including this anatomical connection better predicts the overall resting state fMRI correlation. For instance, consider that matrix  $S$  denotes the structural connectivity matrix, which contains the modulated graph distance of the WM connection between each node pair. If  $S$  is multiplied by the utilization matrix  $U$  in an entry-by-entry fashion, the resulting matrix  $U \circ S$  represents the resting state-informed structural connectome (rsSC).

To create the utilization matrix  $U$ , FSH mapping uses simulated annealing, a probabilistic technique to arrive at the optimal solution for a given function. FSH mapping begins by setting all edges in  $U$  to 1, indicating full utilization of the WM structural connectome in the functional resting state. Thus, in this initial state,  $U \circ S = S$ , as the structural connectivity matrix is fully utilized. FSH mapping then calculates the nonlinear fit between the rs-fMRI connectivity matrix  $F$  and  $U \circ S$ . The sum of the absolute value of the residuals ( $|r|$ ) of this function reflects the goodness of fit of the observed rs-fMRI connectivity with the predicted rs-fMRI connectivity given by the rsSC. To arrive at the optimal solution for  $U$ , simulated annealing randomly chooses one element of  $U$  and changes its value (since  $U$  is originally set to all 1s, the first iteration will change  $U_{(i,j)}$  to 0). If the new state yields a lower summed residual with respect to an artificial cooling temperature, indicating a better fit between  $F$  and  $U \circ S$ , the new value of  $U_{(i,j)}$  is retained. This perturbation was repeated 20,000 times, and the temperature was gradually reduced using a simulated annealing cooling function until the global minimum was reached. This global minimum represents the optimal solution for  $U$  to maximize the goodness of fit between the observed rs-fMRI  $F$  and the rsSC ( $U \circ S$ ). Because the final solution for  $U$  may differ slightly

based on which element  $U_{(i,j)}$  is chosen for the first perturbation, the entire FSH cooling algorithm was run 100 times per group using randomly selected start seeds. These results were summed to create a probability distribution of the optimal solution  $U$  for each group. This was thresholded to retain the top 25% of utilized nodes, yielding the final group  $U$  matrix. A weighted rsSC was then created by multiplying each participant's structural connectivity matrix  $S$  by the binarized group  $U$  matrix.

As FSH mapping is very computationally intense, the procedure was performed on a subset of participants for each SNP. APOE and BDNF were evaluated using a dominant genetic model, while KIBRA and COMT were evaluated by comparing homozygous minor allele carriers to homozygous major allele carriers. Within each SNP, groups were matched on age and sex.

#### *Graph analysis of the rsSC*

Graph metrics of network organization are partially dependent on the wiring cost (i.e., the number of edges) in a graph (Ginestet, Nichols, Bullmore, & Simmons, 2011). To ensure that findings were not contingent on wiring cost, the rsSC was thresholded to retain between 10% and 50% of the strongest weights in the graph at 1% increments. Between-group differences in the graph measures at each of these wiring costs were determined through non-parametric permutation tests with 5000 iterations, with a significance threshold of  $p < .05$ .

The Brain Connectivity Toolbox (Rubinov & Sporns, 2010) was used to derive graph properties of the rsSC. I used two measures to evaluate the network topography of the rsSC for each group: 1) global efficiency, which is the average inverse shortest path length in the network and is a measure of network integration and 2) local efficiency, which is the efficiency of node neighborhoods, defined by evaluating which of a node's neighbors are neighbors of each other.

Local efficiency is a measure of network segregation, in which densely interconnected groups of brain regions (e.g., “clusters” or “modules”) emerge.

#### *Resilience analysis of the rsSC*

Resilience refers to a network’s ability to withstand perturbations or failures. I performed a random and targeted failure analysis for each group rsSC. In the random failure analysis, the network’s resilience was evaluated as nodes were removed from the network at random. The size of the largest connected component was used as a measure of network resilience (Ajilore et al., 2014). To ensure that results do not depend on which nodes were randomly selected to fail, I ran 5000 iterations of this random failure analysis.

In the targeted failure analysis, network nodes were rank ordered in terms of node centrality, or “hubness.” Four centrality metrics were used to calculate a robust measure of node centrality (Bolt, Nomi, Rubinov, & Uddin, 2017): 1) degree centrality, defined as the number of connections of each node; 2) betweenness centrality, the fraction of all shortest paths within a network that contain a given node; 3) eigenvector centrality, a measure of which nodes are connected to other highly connected nodes; and 4) participation coefficient, the proportion of intermodular connections of a given node. These metrics were calculated for each node in each rsSC at thresholds ranging from 10% to 50% of the strongest graph weights. Ranks for each node across these four metrics were summed to create a rank-ordered list of all rsSC nodes by their centrality or “hubness.” The targeted failure analysis removed nodes in order of their centrality, beginning with the most central node. Resilience was evaluated after the removal of each additional node.

## Results

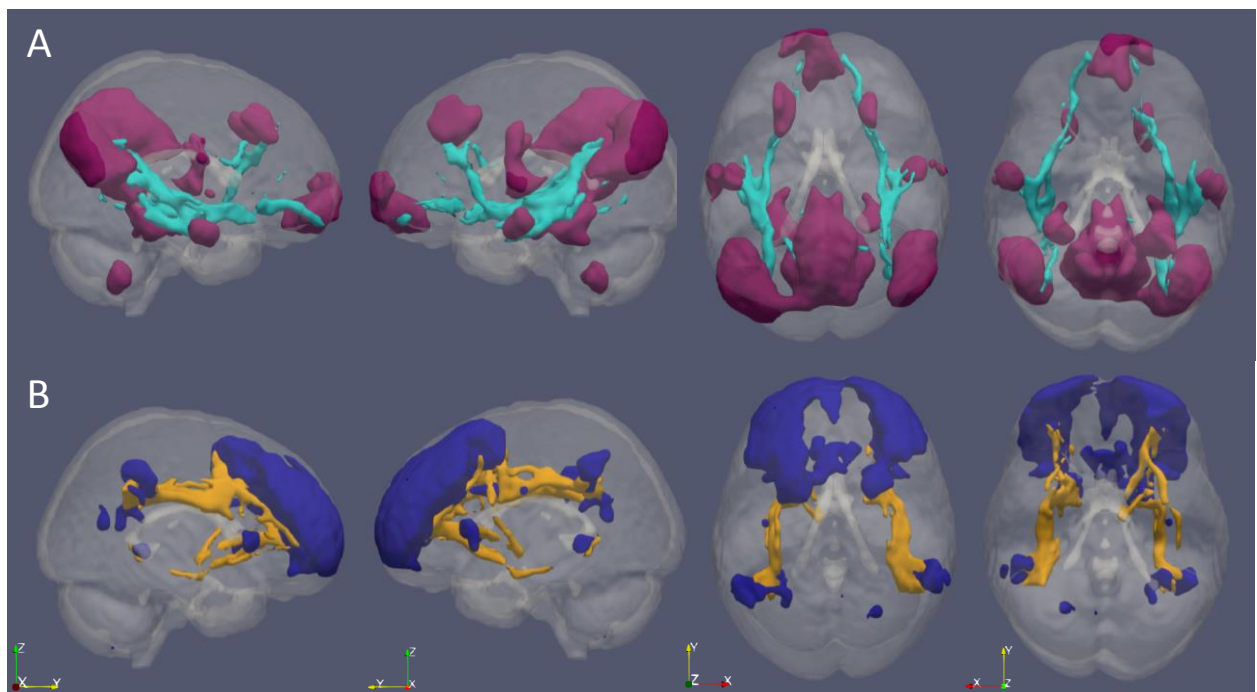
Demographic characteristics of participants are reported in Table 2. Differences in age, education, DRS-2, MMSE, and GDS scores were assessed via two-sample *t*-tests for SNPs analyzed using a dominant model (i.e., APOE) and via one-way ANOVA for SNPs analyzed using an additive model (i.e., COMT, BDNF, KIBRA). Differences in the distribution of sex across the SNPs were analyzed using  $\chi^2$  tests. None of these demographic characteristics significantly differed by genotype ( $p$ 's > .05).

	<i>APOE</i>		<i>COMT</i>			<i>BDNF</i>			<i>KIBRA</i>		
	rs7412 and rs429358		rs4680			rs6265			rs17070145		
	$\epsilon 4$ carriers (N = 40)	non- $\epsilon 4$ carriers (N = 100)	<i>met/met</i> (N = 32)	<i>val/met</i> (N = 51)	<i>val/val</i> (N = 34)	<i>met/met</i> (N = 8)	<i>val/met</i> (N = 25)	<i>val/val</i> (N = 73)	TT (N = 16)	CT (N = 64)	CC (N = 56)
Age (yrs)	51.1 (6.1)	49.4 (6.2)	50.8 (6.0)	49.3 (6.0)	49.5 (6.8)	50.7 (5.8)	48.2 (6.9)	49.7 (6.0)	50.4 (5.3)	49.6 (6.4)	50.2 (6.4)
Sex (M:F)	39:57	15:25	13:18	18:32	13:21	3:5	14:11	26:45	6:10	25:37	21:33
Educ. (yrs)	15.4 (2.5)	15.2 (2.4)	15.0 (2.1)	15.3 (2.5)	15.5 (2.8)	16.0 (2.0)	15.8 (2.4)	15.2 (2.5)	15.6 (2.4)	15.3 (2.5)	15.1 (2.4)
DRS-2	139.9 (2.3)	139.9 (2.3)	140.1 (2.4)	139.9 (2.4)	140.1 (2.2)	140.0 (2.6)	139.7 (2.0)	139.8 (2.4)	139.5 (2.1)	139.9 (2.5)	140.0 (2.3)
MMSE	28.5 (1.1)	28.8 (1.3)	28.6 (1.1)	28.9 (1.2)	28.8 (1.1)	28.3 (1.6)	28.4 (1.2)	28.9 (1.1)	29.1 (.9)	28.9 (1.0)	28.5 (1.4)
GDS	1.8 (2.3)	2.4 (2.7)	2.3 (2.4)	2.3 (2.7)	2.1 (2.6)	3.14 (3.34)	1.6 (1.9)	2.4 (2.7)	3.3 (3.2)	2.3 (2.7)	1.9 (2.3)

**Table 2. Demographic characteristics by genotype.** Educ.: education. DRS-2: Mattis Dementia Rating Scale-2. MMSE: Mini-Mental Status Examination. GDS: Geriatric Depression Scale. Within each SNP, groups did not differ on any of these demographic characteristics ( $p$ 's > .05).

## ICA and Probabilistic Tractography to Characterize the DMN and ECN

The ICA-derived best fit component for the DMN included clusters in the medial frontal pole, superior frontal gyrus, middle temporal gyrus, parahippocampal gyrus, and lateral occipital cortex (Figure 2A). The best fit component for the ECN (Figure 2B) included a large cluster comprising the frontal pole and dorsolateral PFC as well as bilateral clusters in the superior frontal gyrus and supramarginal/angular gyrus. Voxels of peak activity within the DMN and ECN were used to derive seeds for probabilistic tractography (Table 3). Tracts connecting subregions of the DMN included portions of the inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, cingulum bundle, anterior thalamic radiation, uncinate fasciculus, and fornix (Figure 2). Tracts connecting subregions of the ECN included the anterior thalamic radiation, superior longitudinal fasciculus, and dorsal portions of the cingulum bundle.



**Figure 2. Functional and structural connectivity of the DMN and ECN.** (A) 3D rendering of the best-fit component for the default mode network (DMN; maroon) and white matter (WM) tracts connecting subregions of the network (light blue). (B) Best-fit component for the executive control network (dark blue) and WM tracts connecting subregions of the network (gold).

	Coordinates (MNI)		
	<i>x</i>	<i>y</i>	<i>z</i>
DMN			
Precuneus	2	-58	34
Left lateral occipital cortex	-44	-74	24
Right lateral occipital cortex	48	-68	22
Frontal pole	45	93	29
Left superior frontal gyrus	-20	28	38
Right superior frontal gyrus	24	26	38
Left middle temporal gyrus	-56	-10	-16
Right middle temporal gyrus	56	-8	-16
Left parahippocampal gyrus	59	46	27
Right parahippocampal gyrus	28	-34	-16
ECN			
Left frontal pole	-32	50	10
Right frontal pole	32	50	10
Left superior frontal gyrus	-22	6	56
Right superior frontal gyrus	22	8	56
Left supramarginal/angular gyrus	-50	-52	42
Right supramarginal/angular gyrus	52	-48	42

**Table 3. Seed coordinates for probabilistic tractography.** DMN: default mode network. ECN: executive control network. Seed coordinates reflect voxel of peak activity for each cluster within the network.

## Genetic Differences in Brain Integrity

### APOE

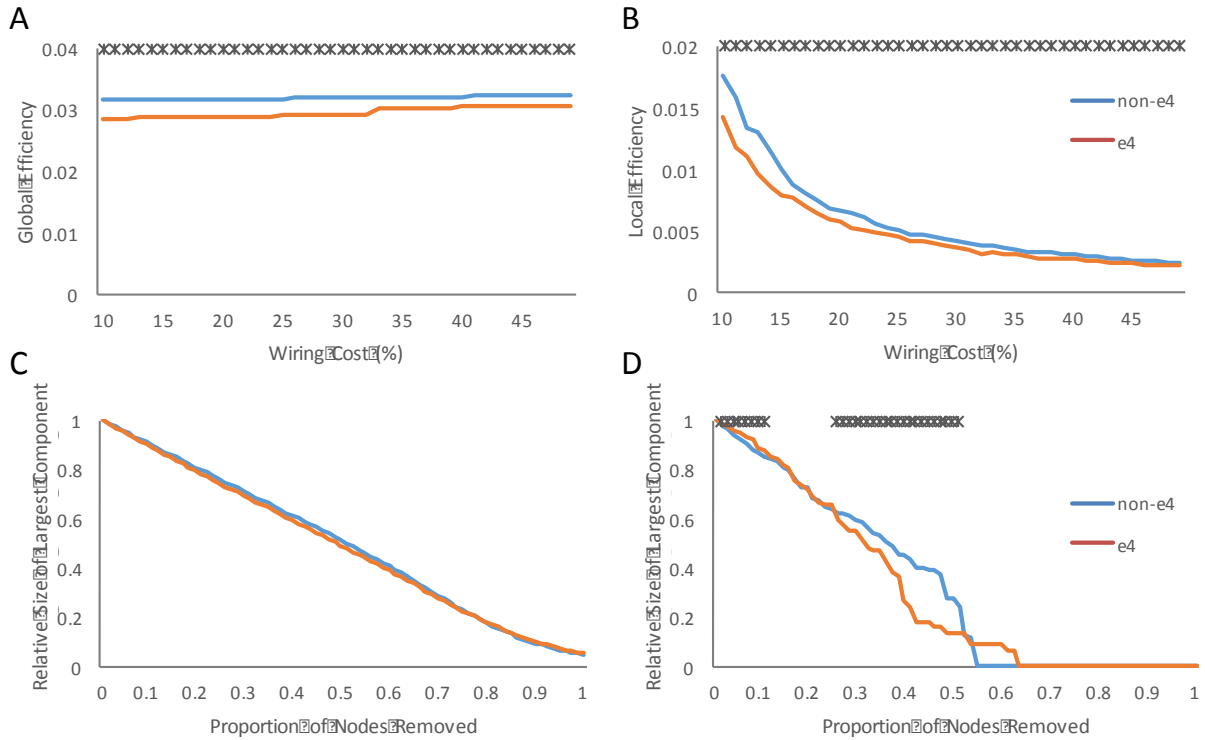
#### *Functional and structural connectivity of the DMN and ECN*

APOE polymorphism was not significantly associated with functional connectivity or WM microstructural organization of the DMN or ECN after controlling for age ( $p$ 's > .05).

#### *Connectivity of the resting state structural connectome (rsSC)*

APOE  $\epsilon$ 4 carriers had significantly lower global efficiency and local efficiency than non- $\epsilon$ 4 carriers across all evaluated wiring costs (Figure 3). In the random failure analysis, resilience did not differ between groups when nodes were removed at random. For the targeted failure analysis,  $\epsilon$ 4 carriers maintained higher resilience than non- $\epsilon$ 4 carriers until approximately 10% of

network hubs were removed. After that point,  $\epsilon 4$  carriers had significantly lower resilience than non- $\epsilon 4$  carriers as progressively more central nodes were removed.



**Figure 3. APOE polymorphism and rsSC topology and resilience.** APOE  $\epsilon 4$  allele carriers have lower (A) global efficiency and (B) local efficiency compared to non- $\epsilon 4$  carriers. There were no differences between groups in the (C) random failure analysis, while (D) targeted failure analysis showed lower resilience to hub removal among  $\epsilon 4$  carriers. \*denotes  $p < .05$

## COMT

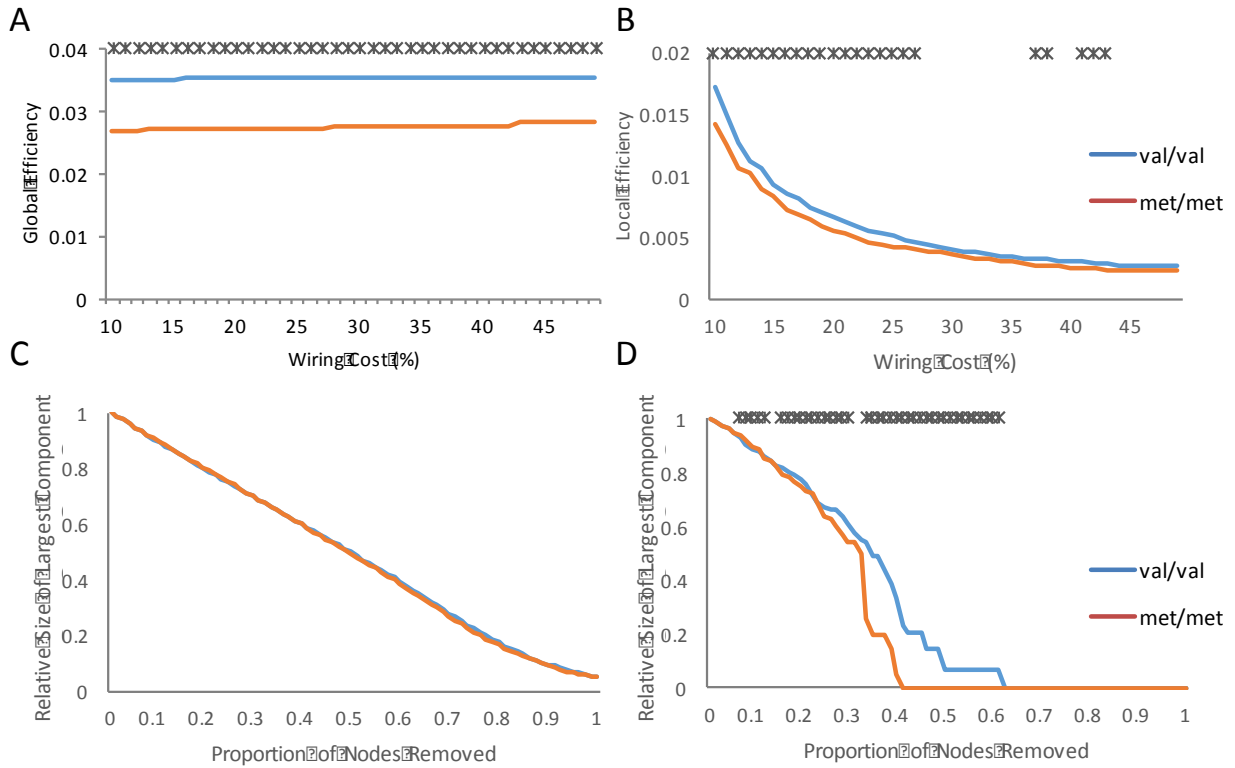
### *Functional and structural connectivity of the DMN and ECN*

COMT polymorphism was not significantly associated with functional connectivity or WM microstructural organization of the DMN or the ECN after controlling for age ( $p$ 's  $> .05$ ).

### *Connectivity of the resting state structural connectome (rsSC)*

COMT *val/val* carriers had significantly global efficiency than *met/met* carriers across all evaluated wiring costs (Figure 4). *Val/val* carriers also had higher local efficiency than *met/met* carriers at wiring costs ranging from 10% to 27%. There were no group differences in the

random failure analysis. In the targeted failure analysis, *val* homozygotes maintained higher resilience than *met* homozygotes until the networks collapsed.



**Figure 4. COMT polymorphism and rsSC topology and resilience.** COMT rs4680 *met/met* carriers have lower (A) global efficiency and (B) local efficiency compared to *val/val* carriers. There were no differences between groups in the (C) random failure analysis, while (D) targeted failure analysis showed lower resilience to hub removal among *met/met* carriers. \*denotes  $p < .05$

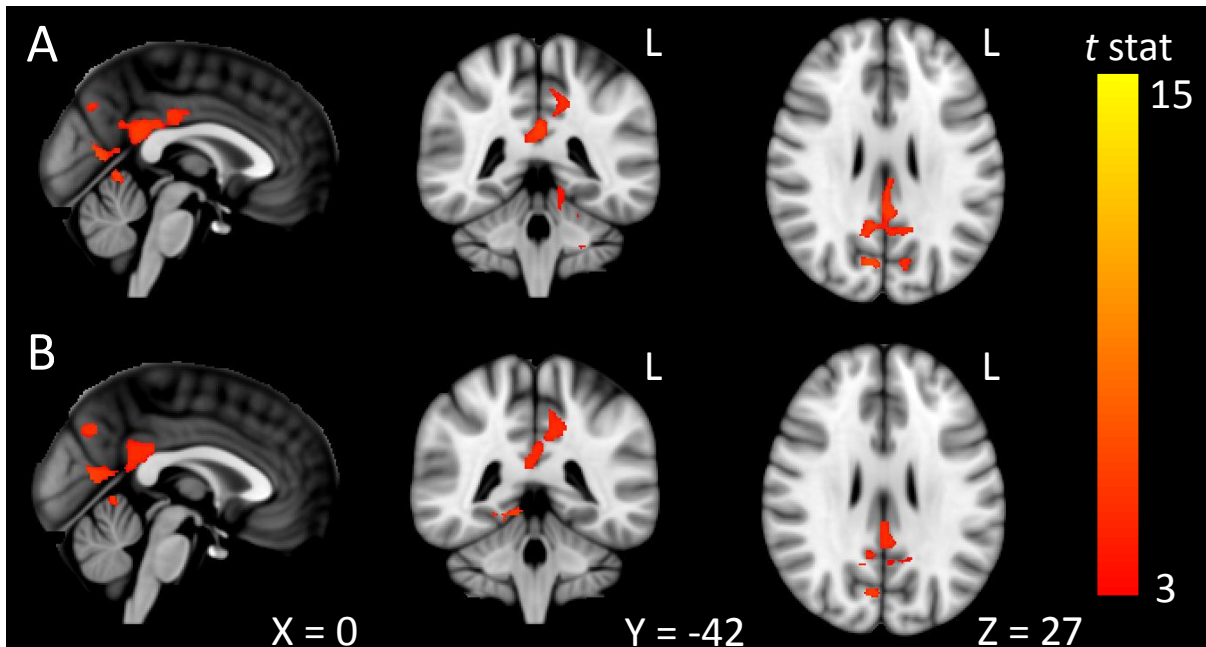
## BDNF

### *Functional and structural connectivity of the DMN and ECN*

BDNF polymorphism was significantly associated with functional connectivity within the DMN. *Met/met* carriers had significantly higher connectivity than *val/met* carriers in the precuneus and posterior cingulate gyrus ( $p < .05$ , FWE-corrected using threshold-free cluster enhancement) (Figure 5). *Met/met* carriers also had higher connectivity than *val/val* carriers in the right precuneus and right parahippocampal gyrus. There were no differences in DMN

connectivity between *val/met* and *val/val* carriers. There were no group differences in ECN connectivity.

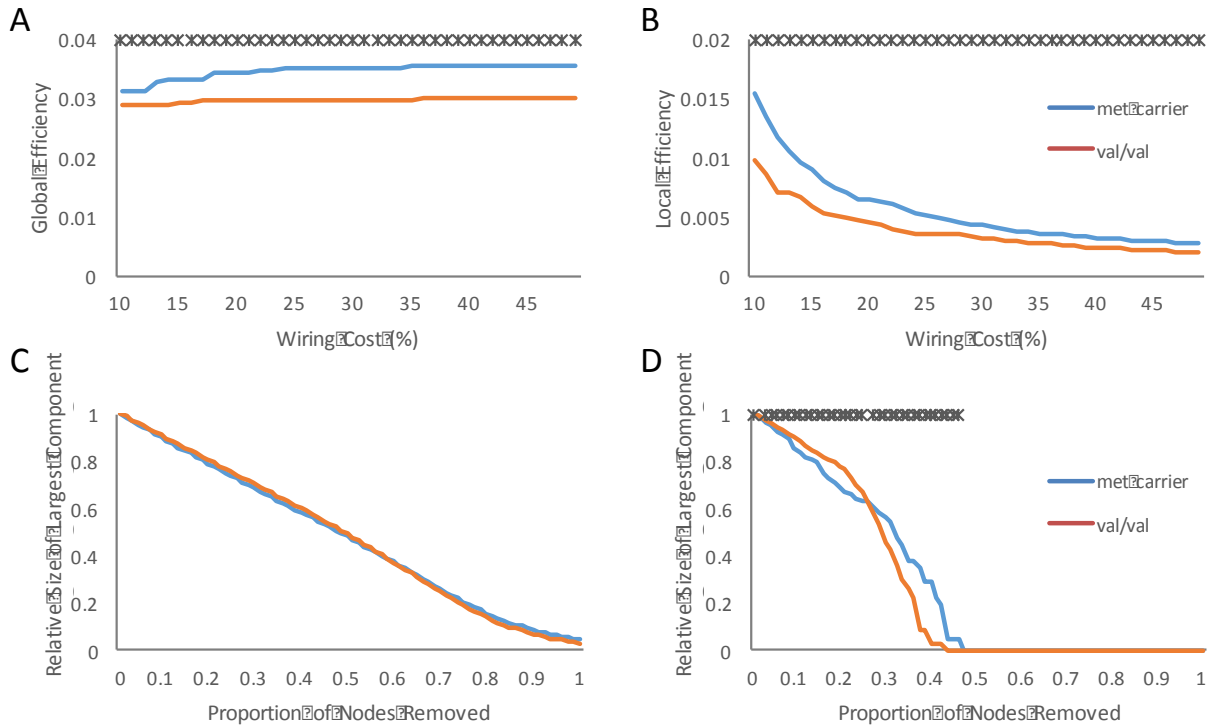
BDNF polymorphism was not significantly associated with WM microstructural organization of the DMN or ECN.



**Figure 5. Differences in DMN functional connectivity between BDNF risk allele carriers.** BDNF *met/met* carriers had higher functional connectivity within the DMN compared to (A) *val/met* carriers and (B) *val/val* carriers,  $p < .05$  (FWE-corrected using threshold-free cluster enhancement).

#### *Connectivity of the resting state structural connectome (rsSC)*

BDNF *met* carriers had higher global efficiency and local efficiency at all evaluated wiring costs (Figure 6). There were no group differences in resilience for the random failure analysis. In the targeted failure analysis, *val/val* carriers maintained higher resilience than *met* carriers until approximately 25% of central nodes were removed. After that point, *met* carriers maintained higher resilience until the networks failed.



**Figure 6. BDNF polymorphism and rsSC topology and resilience.** BDNF rs6265 val/val carriers had lower (A) global efficiency and (B) local efficiency compared to met carriers. There were no differences between groups in the (C) random failure analysis, while (D) targeted failure analysis showed lower resilience to hub removal among val/val carriers. \*denotes  $p < .05$

## KIBRA

### *Functional connectivity of the DMN and ECN*

After controlling for age, there were no significant associations between KIBRA polymorphism and functional connectivity of the DMN or ECN.

### *Structural connectivity of the DMN*

#### *WM microstructural organization of the DMN*

KIBRA polymorphism was associated with FA,  $F(2, 122) = 5.176, p = .007$ , and RD,  $F(2, 120) = 4.073, p = .019$ , within the WM tracts comprising the DMN (Figure 7). Follow-up  $t$ -tests indicated that TT carriers had higher FA ( $t(69) = 2.316, p = .02$ ) and lower RD ( $t(68) = 1.952, p = .05$ ) than CT carriers. TT carriers also had higher FA ( $t(66) = 2.536, p = .014$ ) and

lower RD ( $t(65) = 2.197, p = .032$ ) than CC carriers. There were no differences in FA or RD between CT and CC carriers, and AD did not differ between any of the groups.

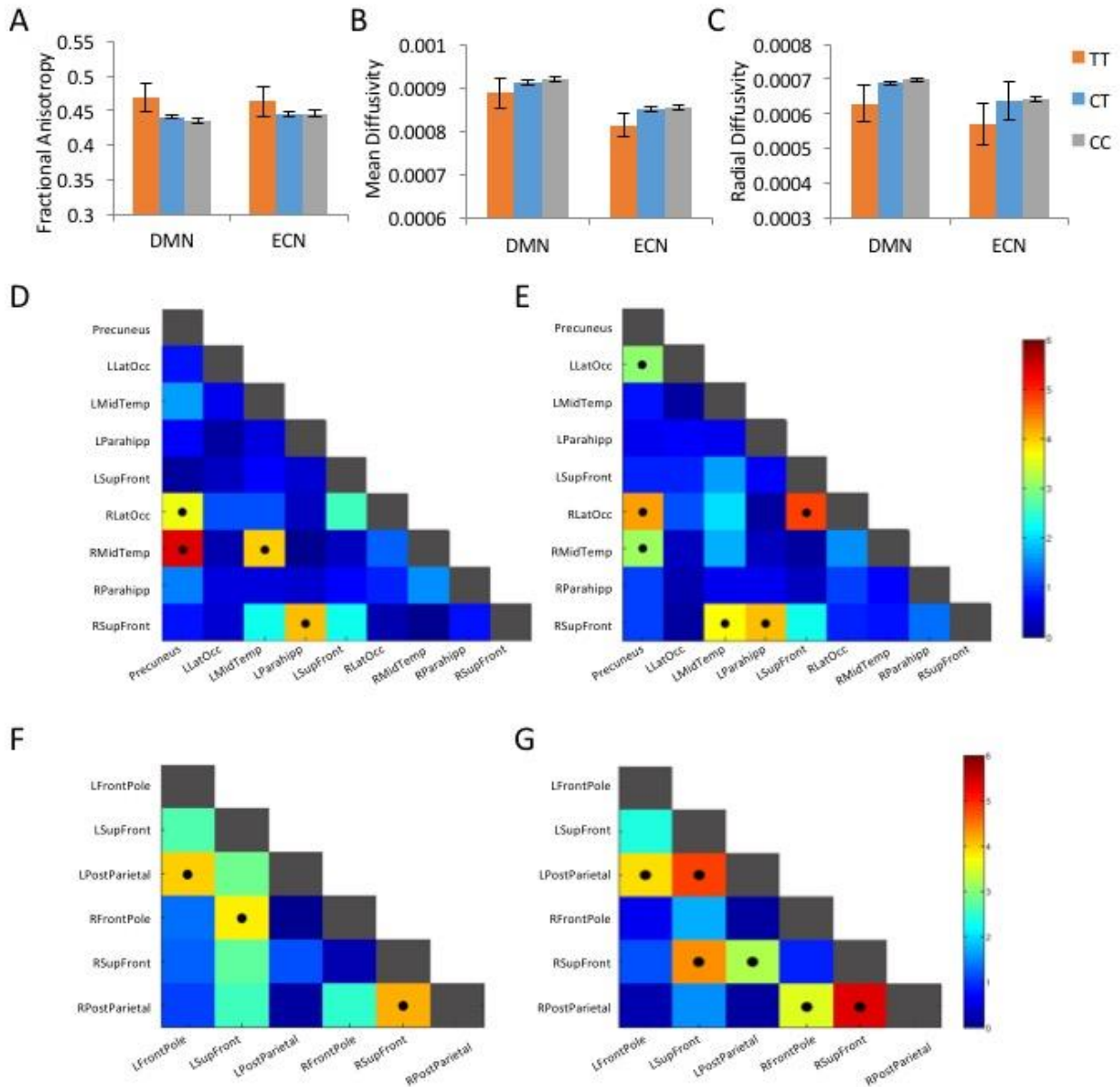
Analysis of individual tracts making up the DMN showed that this association between KIBRA polymorphism and FA was observed in tracts connecting the precuneus to the right lateral occipital cortex ( $F(2,89) = 3.611, p = .031$ ) and right middle temporal gyrus ( $F(2,99) = 5.211, p = .007$ ); the tract connecting the right superior frontal cortex to left parahippocampal gyrus ( $F(2,116) = 4.051, p = .02$ ); and the tract connecting the left and right middle temporal gyrus, ( $F(2,110) = 3.945, p = .022$ ). Associations between KIBRA polymorphism and RD were observed in tracts connecting the precuneus to the left lateral occipital cortex ( $F(2,85) = 3.168, p = .047$ ), right lateral occipital cortex ( $F(2, 87) = 4.267, p = .017$ ), and right middle temporal gyrus ( $F(2, 97) = 3.002, p = .05$ ); tracts connecting the right superior frontal cortex to the left middle temporal gyrus ( $F(2, 101) = 3.704, p = .028$ ) and left parahippocampal gyrus ( $F(2, 116) = 4.102, p = .019$ ); and the tract connecting the left superior frontal cortex to right lateral occipital cortex ( $F(2, 92) = 4.786, p = .011$ ).

#### *WM microstructural organization of the ECN*

KIBRA polymorphism was associated with MD,  $F(2, 119) = 3.85, p = .024$ , and RD,  $F(2, 119) = 4.163, p = .018$ , within the WM tracts comprising the ECN (Figure 7). Follow-up  $t$ -tests indicated that TT carriers had lower MD ( $t(68) = 2.182, p = .033$ , and lower RD ( $t(68) = 2.154, p = .035$ ) compared to CT carriers. TT carriers also had lower MD ( $t(64) = 2.407, p = .019$ , and lower RD ( $t(68) = 2.168, p = .034$ ) compared to CC carriers. There were no differences in MD or RD between CT and CC carriers, and AD did not differ between any of the groups.

Analysis of the individual tracts making up the ECN showed that the association between KIBRA polymorphism and MD was observed in tracts connecting the left frontal pole to the left

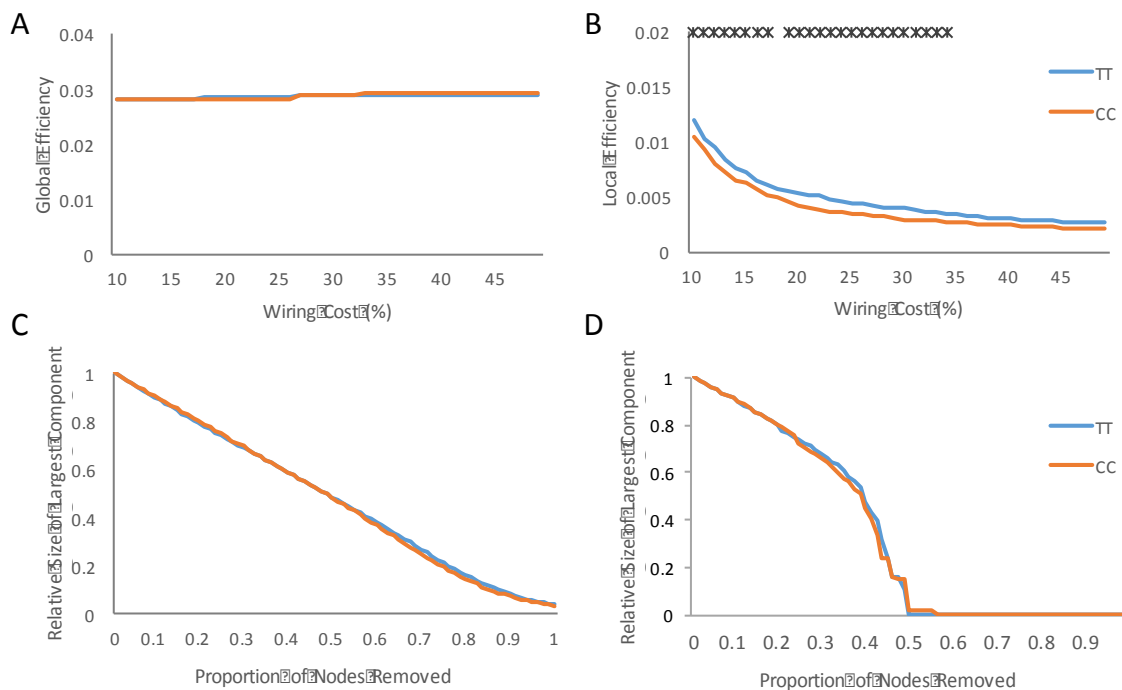
posterior parietal cortex ( $F(2, 93) = 3.965, p = .022$ ), the right frontal pole to left superior frontal cortex ( $F(2, 113) = 3.783, p = .026$ ), and the right superior frontal cortex to right posterior parietal cortex ( $F(2, 118) = 4.153, p = .018$ ). Associations between KIBRA polymorphism and RD were observed in the tract connecting the left frontal pole to left posterior parietal cortex ( $F(2, 93) = 3.914, p = .023$ ); tracts connecting the right frontal pole to right posterior parietal cortex ( $F(2, 88) = 3.493, p = .035$ ), left posterior parietal cortex ( $F(2, 72) = 3.225, p = .046$ ), and left superior frontal cortex ( $F(2, 113) = 4.842, p = .01$ ); tracts connecting the left superior frontal cortex to left posterior parietal cortex ( $F(2, 110) = 4.841, p = .01$ ) and right superior frontal cortex ( $F(2, 124) = 4.315, p = .015$ ); and the tract connecting the right superior frontal cortex to right posterior parietal cortex ( $F(2, 118) = 5.352, p = .006$ ).



**Figure 7. KIBRA polymorphism and microstructural organization of WM of the DMN and ECN.** KIBRA rs17070156 T-allele carriers have (A) higher fractional anisotropy of the default mode network (DMN), (B) lower mean diffusivity (MD) of the ECN, and (C) lower radial diffusivity of the DMN and ECN. T-allele carriers had higher FA (D) and lower MD (E) in specific tracts connecting subregions of the DMN as well as lower MD (F) and RD (G) in tracts of the ECN. Color bar denotes strength of effects as measured by ANOVA *F*-statistic, with significant effects denoted by a black dot.

### Connectivity of the resting state structural connectome (rsSC)

There were no differences between KIBRA TT and CC carriers on global efficiency across any of the evaluated wiring costs ( $p$ 's > .05) (Figure 8). However, KIBRA TT carriers had higher local efficiency for wiring costs ranging from 10 to 35%. There were no differences between groups for the random failure analysis or the targeted failure analysis.

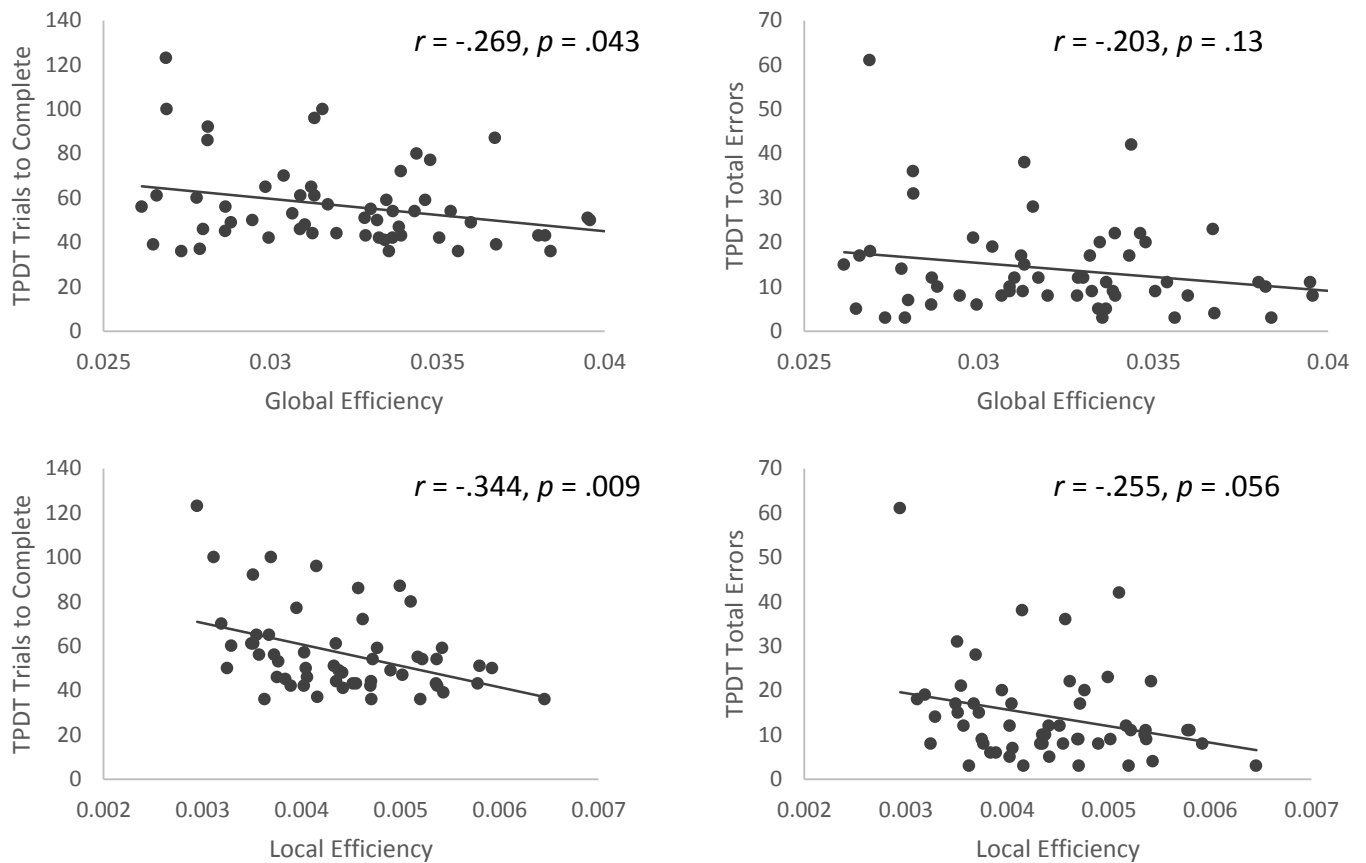


**Figure 8. KIBRA polymorphism and rsSC topology and resilience.** KIBRA rs17070145 TT carriers did not differ from CC carriers in (A) global efficiency but had (B) greater local efficiency. There were no differences between groups in the (C) random failure analysis or (D) targeted failure analysis. \*denotes  $p < .05$

### Graph Theoretical Measures and Cognitive Performance

Simple linear correlation was used to examine the associations between graph theoretical measures (global and local efficiency) and performance on the vMWT and TPDT. There were no significant associations between vMWT summary variables and graph theoretical measures. For

the TPDT, higher global efficiency was associated with fewer trials to complete transverse patterning discriminations,  $r = -.269, p = .043$ . Higher local efficiency was associated with fewer trials to complete the transverse patterning discriminations,  $r = -.344, p = .009$ , with a marginally significant association between local efficiency and number of errors made on the TPDT,  $r = -.255, p = .056$ .



**Figure 9. Graph theoretical measures and cognitive performance.** Higher global efficiency was associated with (A) fewer trials to complete the TPDT though the association with (B) total errors was non-significant. Greater local efficiency was associated with (C) fewer trials to complete the TPDT and (D) fewer errors.

## **Discussion**

The goal of the present study was to investigate measures of functional and structural brain connectivity as potential endophenotypes of AD in healthy, non-demented middle-aged individuals. I report a pattern of significant differences between individuals at elevated genetic risk for AD compared to non-risk allele carriers when investigating the functional and structural connectivity of two RSNs hypothesized to be affected by AD neuropathology. An even more striking pattern of findings was observed when using graph theoretical measures to characterize the properties of an integrated, whole-brain structural-functional network. These graph theoretical analyses revealed robust differences in network topology and resilience to targeted node failure among APOE, COMT, BDNF, and KIBRA risk allele carriers. Together, these findings suggest that despite being years or even decades from potentially exhibiting overt cognitive impairment, non-demented, middle-aged carriers of AD risk alleles exhibit compromised network integrity that may serve as a potential endophenotype of risk for cognitive impairment or AD.

### **Network Connectivity as an Endophenotype of AD**

Establishing endophenotypes of AD is of significant public health relevance, given the immense financial and social burden of the disease. Unfortunately, given the considerable overlap in brain changes observed in normal and pathological aging (Chua et al., 2008; Fan et al., 2008; Misra et al., 2009; Nir et al., 2013), identifying those who may benefit most from early diagnosis and intervention remains a challenge. Prior studies investigating potential endophenotypes of AD have largely focused on focal brain differences, including regional gray matter volume (Drzezga et al., 2009; Honea, Swerdlow, Vidoni, Goodwin, & Burns, 2010; Karas et al., 2004), microstructural properties of specific WM tracts (Chiang, Barysheva, et al., 2011;

Honea et al., 2009; Salminen et al., 2013), regional hypometabolism (Drzezga et al., 2005; Mosconi et al., 2004; Reiman et al., 2005), and deposition of amyloid and tau (Drzezga et al., 2009; J. C. Morris et al., 2010; Okello et al., 2009). Despite decades of neuroimaging research in this area, these investigations have largely failed to find reliable, sensitive biomarkers with adequate prognostic accuracy (Prestia et al., 2013; S. Zhang et al., 2012).

Given this difficulty in establishing reliable endophenotypes of AD using traditional neuroimaging methods, network-level indices of brain integrity have been proposed as potentially more sensitive and specific predictors of AD risk. However, extant studies demonstrating disrupted network connectivity have largely focused on older adults or those who have already developed MCI or early AD (Agosta et al., 2012; Balthazar et al., 2014; Damoiseaux et al., 2012; Geerligs et al., 2015; Petrella et al., 2011; Seo, Lee, Lee, Park, Sohn, Lee, et al., 2013; Supekar et al., 2008). The present study is the first known demonstration of differences in network-level connectivity in non-demented, middle-aged individuals at genetic risk for AD but who currently show no overt cognitive impairment. My findings suggest that there may be subtle genotype-related differences in brain connectivity that are evident during middle age, providing a potential biomarker of risk for AD that is detectable years or even decades before the onset of cognitive symptoms. Given that the neuroimaging modalities employed are non-invasive and task-free, they are particularly well suited for use in a clinical setting.

Critically, I found the most robust pattern of genotype differences when investigating the graph properties of the rsSC, an integrated functional-structural network. Across all SNPs of interest, risk allele carriers had lower “small world” properties, including global and local efficiency, and were less resilient to targeted removal of hub regions. The results of the targeted

failure analysis are particularly intriguing, as progressive removal of hub regions mimics the AD neuropathological process. The poor resilience of risk allele carriers to this type of network attack suggests that their compromised global network topology may make them more vulnerable to AD neuropathology.

These findings also point to the need to use more sophisticated measures of brain integrity to capture the earliest changes associated with potential neuropathology. Although I observed several genotype-related differences in functional and structural connectivity of RSNs when using traditional analysis methods, my most striking findings emerged when combining whole-brain rs-fMRI and DTI data into an integrated functional-structural graph. Despite the popularity of multi-modal imaging paradigms, most studies continue to analyze each modality in parallel, rather than combining them. Some multi-modal neuroimaging studies use fMRI to guide fiber tracking (Broser, Groeschel, Hauser, Lidzba, & Wilke, 2012; Greicius et al., 2009; Yang et al., 2009) or investigate the functional connectivity associated with a structural network derived from diffusion-weighted imaging (Douaud, Filippini, Knight, Talbot, & Turner, 2011; Pinotsis, Hansen, Friston, & Jirsa, 2013). However, techniques that truly integrate fMRI and DTI data into a single, functional-structural network are still developing and have not been widely employed (Bowman, Zhang, Derado, & Chen, 2012; Calamante, Smith, Liang, Zalesky, & Connelly, 2017; Venkataraman, Rathi, Kubicki, Westin, & Golland, 2010). Some of the proposed methods model structural by functional connections, but these are limited by the fact that regions may show strong functional connections despite having no direct structural connection (Honey et al., 2009). Furthermore, many existing methods consider structural connectivity to be static, while functional connectivity is presumed to be dynamic (Ajilore et al., 2013). It is likely that structural

connections are dynamically utilized to produce functional activity, meaning that a method to combine fMRI and DTI data should model the data accordingly.

The use of functional-by-structural hierarchical (FSH) mapping in the present investigation is one of its major strengths. FSH mapping provides information about the utilization of WM connections during a particular functional state, permitting the creation of an integrated functional-structural “resting state structural connectome” (Ajilore et al., 2013; Leow et al., 2012). Additionally, it has greater flexibility than other existing methods because of its ability to model both direct and indirect structural connections that may produce a functional state. Only when studying the graph properties of the rsSC did I observe robust differences in network topology across the SNPs of interest. The complex, multifactorial nature of AD makes it essential that we continue to develop techniques such as FSH mapping, allowing us to meaningfully integrate multiple neuroimaging modalities to increase the sensitivity to detect very early network aberrations associated with risk for AD.

### **Effects of Risk Genes on Network Connectivity in Middle Age**

I focused my analyses on four genes that have been previously associated with cognitive impairment or risk for AD. In the present study, risk allele carriers for each SNP of interest showed differences in the connectivity of the DMN or ECN or in the graph properties of the integrated rsSC.

#### **APOE**

Although APOE is the best characterized genetic risk factor for AD, the time course and mechanisms by which it elevates AD risk remain poorly understood. Contrary to my hypotheses, I did not observe any differences in the functional or structural connectivity of the DMN or ECN between APOE  $\epsilon$ 4-carriers and non-carriers. This is not entirely unsurprising, as APOE appears

to be an example of antagonistic pleiotropy in which the  $\epsilon 4$  allele confers a benefit during younger adulthood but becomes deleterious later in the aging process (Han et al., 2007). Consistent with this hypothesis, younger  $\epsilon 4$  carriers have higher DMN connectivity than non-carriers (Filippini et al., 2009; Fleisher et al., 2009), whereas healthy older  $\epsilon 4$  carriers and those with early AD show lower DMN connectivity (Heise et al., 2014; Machulda et al., 2011; Sheline, Morris, et al., 2010). Some evidence also suggests that younger  $\epsilon 4$  carriers have better WM integrity than non- $\epsilon 4$  carriers (Dowell et al., 2013), while poor WM integrity is well documented in older  $\epsilon 4$  carriers (Honea et al., 2009; M. J. Kim, Seo, Kim, Lee, & Na, 2016; Salminen et al., 2013; S. Zhang et al., 2015). As middle age represents the transition between younger and older adulthood, middle-aged  $\epsilon 4$  carriers may exhibit a range of effects, with some maintaining higher DMN connectivity and WM microstructural organization than non- $\epsilon 4$  carriers and others beginning to show age-related decreases in functional and structural connectivity.

Although I did not observe differences in functional and structural connectivity of the DMN or ECN, I report robust APOE  $\epsilon 4$ -associated differences in the topology of the rsSC. Non- $\epsilon 4$  carriers had higher global and local efficiency than  $\epsilon 4$  carriers. This pattern is suggestive of a higher small world topology among non- $\epsilon 4$  carriers. A small world topology balances the need for efficient local communication and global information transfer while minimizing the energy needs associated with a densely wired network (Achard & Bullmore, 2007). Prior studies using networks derived from rs-fMRI (J. Wang, Wang, He, Yu, & Wang, 2015; X. Zhao et al., 2012), DTI (Brown et al., 2011), cortical thickness (Goryawala et al., 2014), and [ $^{18}\text{F}$ ] fluorodeoxyglucose positron emission tomography (PET) (Seo, Lee, Lee, Park, Sohn, Choe, et al., 2013) have reported that healthy elderly  $\epsilon 4$  carriers and those with AD have disrupted small world properties compared to non- $\epsilon 4$  carriers. However, to my knowledge, this is the first study

to report  $\epsilon 4$ -associated differences in global network topology in middle age. These findings suggest that subtle differences in network properties, including lower global and local efficiency, may emerge several decades before the onset of clinical symptoms of AD.

Furthermore, I report that middle-aged APOE  $\epsilon 4$  carriers are less able to withstand targeted node failure, which replicates the neuropathological process of AD. Well-connected hub regions, often found in heteromodal association areas (Buckner et al., 2005), are preferentially targeted by the AD process. Specifically, hub regions are among the first to undergo amyloid deposition, demonstrate hypometabolism, and begin to atrophy (Buckner et al., 2009; Greicius et al., 2004; Lo et al., 2010; Sperling et al., 2009). Although the rsSC of APOE  $\epsilon 4$  carriers was resilient to random node removal, removing nodes in order of their “hub-ness” caused network failure more rapidly than for non- $\epsilon 4$  carriers. This provides further evidence that healthy, middle-aged APOE  $\epsilon 4$  carriers already show network-level vulnerabilities that may make them more susceptible to AD pathogenesis.

### **COMT**

Although not considered a direct risk factor for AD, COMT Val158Met polymorphism is associated with differences in executive functioning, one of the primary cognitive domains affected in AD (McKhann et al., 2011). I found that carriers of the high-activity *val* allele of COMT rs4680, which is associated with lower prefrontal dopamine, had higher global and local efficiency of the rsSC compared to *met/met* carriers. Although the *met* allele is commonly reported as conferring an advantage in executive functioning for younger (Bruder et al., 2005; Egan et al., 2001; Enoch, Waheed, Harris, Albaugh, & Goldman, 2009) and older (deFrias et al., 2005; Nagel et al., 2008) individuals, numerous studies have failed to find any differences between *val* and *met* carriers (Blanchard, Chamberlain, Roiser, Robbins, & Müller, 2011; Bolton

et al., 2010; Wardle, de Wit, Penton-Voak, Lewis, & Munafò, 2013) or report higher executive functioning among *val* carriers (O'Hara et al., 2006; Tsuchimine, Yasui-Furukori, Kaneda, & Kaneko, 2013; Y. Wang et al., 2013).

Although several studies have reported that adult *val* carriers have higher functional connectivity between the PFC and other cortical regions at rest (Baeken et al., 2014; Meyer et al., 2016; Tunbridge et al., 2013) and during low-load working memory tasks (Sambataro et al., 2009), studies investigating COMT polymorphism and WM microstructure in healthy adults have largely failed to find significant effects (Kohannim et al., 2012; Papenberg et al., 2015). My results suggest that *val/val* carriers may have an advantage in the global organization of an integrated functional-structural network, as they exhibit higher global efficiency and local efficiency than *met/met* carriers. *Val/val* carriers' networks were also more resilient to targeted failure analysis. However, given equivocal findings regarding which COMT allele is associated with the greatest risk for age-related cognitive decline, more evidence is needed to establish whether the observed differences in network organization may serve as a biomarker for cognitive impairment or AD.

## **BDNF**

Numerous studies have reported that BDNF polymorphism is associated with differences in episodic memory performance (Egan et al., 2003; Hajek et al., 2012; Hariri et al., 2003; Miyajima et al., 2008), one of the hallmark symptoms of AD. Like APOE, BDNF Val66Met appears to be another example of pleiotropy, in which the gene polymorphism exhibits different effects throughout the lifespan. In younger individuals, the *val* allele is associated with better episodic memory (Egan et al., 2003; Hariri et al., 2003; Lamb et al., 2015) and larger hippocampal volume (Hajek et al., 2012). However, in older adults, the *val* allele may be

deleterious, as it has been associated with poorer cognitive performance and lower WM microstructural integrity (Gajewski, Hengstler, Golka, Falkenstein, & Beste, 2011; Ventriglia et al., 2002; Voineskos et al., 2011).

In this middle-aged sample, BDNF *met/met* carriers had higher functional connectivity than *val/met* and *val/val* carriers in several regions within the DMN, including the precuneus, posterior cingulate gyrus, and right parahippocampal gyrus. These regions are commonly cited as hub regions that are particularly vulnerable to early pathological changes associated with AD. Consistent with these differences in functional connectivity, I also report that *met/met* carriers had higher global efficiency and local efficiency of the rsSC compared to *val/val* carriers. Although *val/val* carriers maintained resilience to the removal of the first several hubs in a targeted failure analysis, their networks ultimately failed more quickly than *met/met* carriers'. This suggests that although *val/val* carriers have enough distributed network resources to withstand some brain insult, they quickly reach a tipping point after which they experience a precipitous decline. This interpretation is consistent with a longitudinal study that found that *val/val* carriers maintained their cognitive performance through age 65 but experienced a more precipitous decline during their 70s (Erickson et al., 2008).

### **KIBRA**

The KIBRA rs17070145 T allele has been associated with better episodic memory in two genome-wide association studies (Papassotiropoulos et al., 2006; Pawlowski & Huentelman, 2011), an effect that has been verified in independent samples of younger (Papassotiropoulos et al., 2006; Preuschhof et al., 2010) and older (Almeida et al., 2008; Bates et al., 2009; Schaper et al., 2008) adults. A meta-analysis also reported that the T allele is also associated with better working memory (Milnik et al., 2012). Furthermore, several reports suggest that T carriers have

a lower risk for late-onset AD than CC carriers (Burgess et al., 2011; Corneveaux et al., 2010). Here, I report that middle-aged KIBRA T allele carriers had significantly better WM microstructural integrity of tracts connecting subregions of the DMN and ECN, despite showing no differences in functional connectivity within these networks.

WM tracts connecting PFC to temporal regions and posterior parietal cortex showed the most prominent genotype-related effects in the present sample. Temporal-prefrontal projections, including the uncinate fasciculus and anterior thalamic radiation, have emerged as critical WM tracts for episodic memory (Aggleton, Pralus, Nelson, & Hornberger, 2016; Hiyoshi-Taniguchi et al., 2015; Lockhart et al., 2012; Niogi et al., 2008; Sexton et al., 2012). Similarly, microstructural integrity of the superior longitudinal fasciculus and dorsal cingulum bundle, the tracts connecting subregions of the ECN in this study, may be important for executive control of memory (Darki & Klingberg, 2015; Gold, Powell, Xuan, Jicha, & Smith, 2010; Urger et al., 2015). Thus, differences in the WM microstructural organization of these tracts may explain the stronger episodic and working memory performance among KIBRA T allele carriers. As this is the first known study to investigate associations between KIBRA rs17070145 and WM integrity, future studies are needed to better understand the dynamics of age-related changes in WM tracts as well as associations with cognitive performance.

Graph theoretical analysis of the whole-brain integrated functional-structural network revealed higher local efficiency in KIBRA TT carriers but no differences in global efficiency. This suggests KIBRA TT carriers may have a more modular network structure that prioritizes local segregation while maintaining the overall global integration of the brain network. However, the lack of association between KIBRA polymorphism and resilience to targeted node failure

suggests that despite having lower local efficiency, KIBRA CC carriers do not show particular vulnerability to network failure during middle age.

### **Graph Theoretical Measures and Cognitive Performance**

Graph theoretical measures are thought to capture topographic features of complex networks that are not captured by traditional neuroimaging methods (Sporns et al., 2005). However, for these measures to be valid and clinically useful tools, they should also correlate with cognitive performance. Several studies have demonstrated that graph theoretical measures are associated with degree of cognitive impairment in AD. For example, shorter average path lengths, indicating higher network efficiency and integration, are associated with higher MMSE scores in AD patients (deHaan et al., 2008; Stam et al., 2007). Another study found that individuals with greater small world characteristics had lower clinical dementia rating (CDR) scores, indicating less functional impairment (Brier et al., 2014). Graph theoretical measures, including lower path length and higher clustering coefficients, have also been associated with better performance on neuropsychological tests, including measures of episodic memory (Lo et al., 2010; Tijms et al., 2014).

In the present investigation, I performed an exploratory analysis examining the association between FSH mapping-derived graph theoretical measures and performance on two hippocampus-dependent memory tasks. Both global and local efficiency were associated with better performance on both spatial and non-spatial hippocampus-dependent tasks. These associations between graph theoretical measures and hippocampus-dependent learning and memory bolster my argument that the topology of an integrated functional-structural network may serve as an early endophenotype of AD.

### **Study Limitations**

This study is not without its limitations. The study was powered to detect moderate genetic effects of SNPs on functional and structural brain integrity. Although I had adequate power to perform analyses using a dominant genetic model for APOE and an additive model for COMT, BDNF, and KIBRA SNPs, I was not able to study gene-gene or gene-environment interactions with the current sample size. Additionally, the number of SNPs and complexity of the neuroimaging analyses leave the study vulnerable to inflated Type I error due to multiple comparisons. Replication of these effects in an independent cohort will be important to establish graph theoretical measures of network integrity as potential endophenotypes of AD.

It is also important to note that the rsSC was constructed to represent the utilization of structural connections during a particular resting state. Thus, the pattern of connectivity represented by the rsSC may not generalize to other, task-based cognitive states. Additionally, the FSH model itself has several limitations. For example, due to the need for a parsimonious model of functional-by-structural connectivity, FSH mapping does not account for feedback, inhibitory interactions, or deactivation of network connections (Leow et al., 2012). Despite this, FSH mapping has several advantages over other methods of integrating fMRI and DTI data: it assumes that structural connections are dynamically utilized, rather than static; it accounts for non-linear relationships between structural and functional connectivity; and it allows a particular functional connection to be modeled by both direct and indirect (multi-step) structural connections (Ajilore et al., 2013; Leow et al., 2012). Furthermore, FSH mapping has been shown to be more sensitive than whole-brain functional connectivity or structural connectivity alone in detecting differences between clinical populations and healthy controls (Ajilore et al., 2013).

Finally, this study is limited by its cross-sectional design. Although I identified differences in global network topology that may make APOE, COMT, BDNF, and KIBRA risk

allele carriers less resilient to targeted node failure, I cannot determine if these are long-standing developmental differences in brain organization or whether they represent the beginning of AD-related pathology. Furthermore, I lack prospective data to determine which of the risk allele carriers in the current sample will actually go on to develop AD. Longitudinal studies characterizing the transition from middle age to older adulthood are needed to better understand the dynamics of connectivity changes that may serve as biomarkers of risk for age-related cognitive decline.

### **Summary and Conclusions**

In conclusion, I report several genotype-related differences in functional and structural connectivity in specific RSNs that have been previously shown to be affected in MCI and AD. More striking, however, is my finding that all of the risk alleles studied were associated with impairments in the topology of an integrated functional-structural network. In addition to showing lower “small world” characteristics, risk allele carriers were less resilient to targeted failure of central network nodes, which mimics the AD neuropathological process. This suggests that conventional neuroimaging methods that separately characterize functional or structural connectivity in discrete networks may be inadequate to detect early changes associated with AD. Rather, integrating multiple imaging modalities and using graph theoretical analysis may capture subtle differences in network topology that are associated with risk for cognitive impairment or AD. To my knowledge, this is the first investigation that identifies global network differences in a middle-aged population, establishing a potential early endophenotype of cognitive impairment or AD.



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- Zuo, X. N., Kelly, C., Di Martino, A., Mennes, M., Margulies, D. S., Bangaru, S., . . . Milham, M. P. (2010). Growing together and growing apart: regional and sex differences in the lifespan developmental trajectories of functional homotopy. *J Neurosci*, *30*(45), 15034-15043. doi:10.1523/JNEUROSCI.2612-10.2010
- Zuo, X. N., & Xing, X. X. (2014). Test-retest reliabilities of resting-state FMRI measurements in human brain functional connectomics: a systems neuroscience perspective. *Neurosci Biobehav Rev*, *45*, 100-118. doi:10.1016/j.neubiorev.2014.05.009

## CURRICULUM VITAE

### EDUCATION AND TRAINING

- Alpert Medical School of Brown University 2017 –  
Clinical Psychology Internship Training Program  
Neuropsychology Track
- University of Wisconsin-Milwaukee, Milwaukee, WI  
Ph.D. candidate in Clinical Psychology  
Expected 2018  
Dissertation title: *Structural and Functional Brain Connectivity in Middle-Aged Carriers of Risk Alleles for Alzheimer's Disease*  
Multicultural Knowledge of Mental Health Practices Certificate 2015
- University of Chicago, Chicago, IL 2010  
M.A. in the Social Sciences, Cognitive Psychology concentration  
Thesis title: *Effects of Emotional Content and Aging on Source Memory for Autobiographical Events*  
Summa cum Laude
- Marquette University, Milwaukee, WI 2009  
B.S. with Honors in Physiological Sciences and Psychology,  
Magna cum Laude

### RESEARCH SUPPORT

- F31 AG050407 (NIH/NIA) Korthauer (PI); Driscoll (Sponsor)  
08/01/16 – 07/31/17  
Brain network connectivity and genetic risk for Alzheimer's disease
- University of Wisconsin-Milwaukee Graduate Summer Research Fellowship  
05/15/14 – 08/20/14  
Contributions of structural brain integrity to spatial navigation in middle age.

### RESEARCH PUBLICATIONS (PEER REVIEWED)

- Korthauer, L.E.**, Nowak, N.T., & Driscoll, I. (2017). Cognitive correlates of spatial navigation: Associations between executive functioning and the virtual Morris Water Task. *Behavioural Brain Research*, 317(15): 470-478.
- Korthauer, L.E.**, Nowak, N.T., Moffat, S.D., Ferrucci, L., Resnick, R.M., & Driscoll, I. (2016). Correlates of virtual navigation performance in older adults. *Neurobiology of Aging*, 39, 118-127.

Zhang, A., Ajilore, O., Zhan, L., Gadelkarim, J., **Korthauer, L.**, Yang, S., Leow, A., & Kumar, A. (2013). White matter tract integrity of anterior limb of internal capsule in major depression and type 2 diabetes. *Neuropsychopharmacology*, 38(8): 1451-1459.

Gallo, D.A., **Korthauer, L.E.**, McDonough, I.M., Teshale, S., & Johnson, E.L. (2011). Age-related positivity effects and autobiographical memory detail: Evidence from a past/future source memory task. *Memory*, 19(6): 641-52.

## **RESEARCH PUBLICATIONS (IN PREP AND UNDER REVIEW)**

**Korthauer, L.E.**, Driscoll, I, Goveas, J., Espeland, M., Shumaker, S., Garcia, L., Rapp, S., Tindle, H., Salmoirago-Blotcher, E., Rossom, R., Wassertheil-Smoller, S., Zaslavsky, O., Cochrane, B., Sink, K., & Masaki, K. (under review). The relationship between depressed mood and subtypes of mild cognitive impairment and dementia in post-menopausal women.

**Korthauer, L.E.**, Zhan, L., Ajilore, O., & Driscoll, I. (in preparation). APOE e4 carriers show disrupted topology of the resting state structural connectome in middle age.

**Korthauer, L.E.**, Blujus, J.K., & Driscoll, I. (in preparation). Genetic risk for Alzheimer's disease does not predict cognitive performance in middle age.

**Korthauer, L.E.**, Driscoll, I, Goveas, J., Espeland, M., Shumaker, S., Ockene, J., Rapp, S., Tindle, H., Salmoirago-Blotcher, E., Cochrane, B., Sink, K., Resnick, S., & Vaughan, L. (in preparation). The association between state affect and incidence of mild cognitive impairment and dementia in post-menopausal women.

## **BOOK CHAPTERS**

**Korthauer, L.E.** & Driscoll, I. (in press). APOE as a risk factor for age-related cognitive impairment: neuropsychological and neuroimaging findings. In Encyclopedia of Health Psychology. Paul, R. & Baker, L.M. (Eds.) Wiley: New York.

## **CONFERENCE PRESENTATIONS**

**Korthauer, L.E.**, Blujus, J., Frahmand, M., Scherkenbach, H., Awe, E., Prost, R., Resnick, S., & Driscoll, I.\* (2017). Brain integrity associated with cognitive performance but not polymorphisms in genes related to cognitive impairment and Alzheimer's disease in a healthy, middle-aged sample. Poster presented at the Alzheimer's Association International Conference, London, UK. \*presenting author

**Korthauer, L.E.**, Sabsevitz, D.S., Mahoney, E.J., Bauer, P., Quasney, E.E., Umfleet Glass, L., Swanson, S.J., & Binder, J.R. (2017). Regional subcortical volumes are associated

- with pre-operative memory performance in left anterior temporal lobectomy (ATL) patients. Poster presented at the 45<sup>th</sup> annual meeting of the International Neuropsychological Society, New Orleans, LA.
- Korthauer, L.E.**, Nowak, N.T., Scherkenbach, H., Awe, E., Frahmand, M., & Driscoll, I. (2016). *KIBRA* polymorphism and hippocampus-associated integrity in middle age: a multi-modal neuroimaging investigation. Poster presented at the 46<sup>th</sup> annual meeting of the Society for Neuroscience, San Diego, CA.
- Korthauer, L.E.**, Goveas, J., Espeland, M.A., Shumaker, S.A., Garcia, K.R., Ockene, J., Tindle, H., Salmoirago-Blotcher, E., Cochrane, B., Sink, K.M., Vaughan, A.L., Rapp, S., Resnick, S.M., & Driscoll, I. (2016). Negative affect associated with increased incidence of mild cognitive impairment and dementia in nondepressed postmenopausal women. Poster presented at the Alzheimer's Association International Conference, Toronto, Ontario, Canada.
- Korthauer, L.E.**, Sabsevitz, D.S., Umfleet Glass, L., Quasney, E., Binder, J.R., Mueller, W.M., Raghavan, M., & Swanson, S.J. (2016). Predictors of visual memory outcome following anterior temporal lobectomy (ATL). Poster presented at the 14<sup>th</sup> Annual Meeting of the American Academy of Clinical Neuropsychology, Chicago, IL.
- Korthauer, L.E.**, Nowak, N.T., Frahmand, M., & Driscoll, I. (2016). Contributions of executive functioning to spatial navigation performance. Poster presented at the 44<sup>th</sup> annual meeting of the International Neuropsychological Society, Boston, MA.
- Mahoney, E.J., **Korthauer, L.E.**, Quasney, E., Umfleet, L., Binder, J.R., Sabsevitz, D., & Swanson, S. (2016). The relationship between perceived and objective memory change following temporal lobectomy. Poster presented at the 44<sup>th</sup> annual meeting of the International Neuropsychological Society, Boston, MA.
- Korthauer, L.E.**, Nowak, N.T., Awe, E., & Driscoll, I. (2015). Associations between pattern separation and structural brain integrity in middle age. Poster presented at the 45<sup>th</sup> annual meeting of the Society for Neuroscience, Chicago, IL.
- Frahmand, M., **Korthauer, L.E.**, Nowak, N.T., & Driscoll, I. (2015). Cognitive factors affecting spatial navigation. Poster presented at the 45<sup>th</sup> annual meeting of the Society for Neuroscience, Chicago, IL.
- Nowak, N.T., Doshi, J., **Korthauer, L.E.**, Awe, E., Davatzikos, C., & Driscoll, I. (2015). Virtual water maze performance in middle-aged adults. Poster presented at the 45<sup>th</sup> annual meeting of the Society for Neuroscience, Chicago, IL.
- Korthauer, L.E.**, Nowak, N.T., Awe, E., & Driscoll, I. (2014). Assessment of virtual Morris Water Maze performance and white matter microstructural integrity in middle age. Poster presented at the 44<sup>th</sup> annual meeting of the Society for Neuroscience, Washington, D.C.

**Korthauer, L.E.**, Nowak, N.T., Moffat, S.D., Ferrucci, L., Resnick, R.M., & Driscoll, I. (2013). Longitudinal assessment of virtual Morris Water Maze performance and associations with regional brain volumes in older adults. Poster presented at the 43rd annual meeting of the Society for Neuroscience, San Diego, CA.

**Korthauer, L.E.**, Charlton, R.A., Kumar, A., & Lamar, M. (2012). The impact of white matter hyperintensities on cognitive function in aging and late-life depression. Poster presented at the 40<sup>th</sup> annual meeting of the International Neuropsychological Association, Montreal, Quebec, Canada.

Lamar, M., Charlton, R.A., **Korthauer, L.E.**, & Kumar, A. (2012). Aspects of metabolic syndrome across the lifespan: Implications for brain structure and function. Poster presented at the 19th annual Cognitive Neuroscience Society Meeting, Chicago, IL.

Grajewski, M., Penney, D.L., Davis, R., **Korthauer, L.**, Kumar, A., & Lamar, M. (2011). Magnifying graphomotor output to highlight intention: A closer look at performance using a digitized clock drawing test. Poster presented at the 31st annual meeting of the National Academy of Neuropsychology, Marco Island, FL.

**Korthauer, L.E.** & Blumenthal, E.M. (2008). Disruption of oogenesis in *drop-dead (drd) mutants*. Poster presented at the 50<sup>th</sup> annual Drosophila Research Conference, Chicago, IL.

## CLINICAL EXPERIENCE

*Clinical Psychology Resident, Rhode Island Hospital*

Clinical supervisors: Drs. Geoffrey Tremont, Jennifer Davis, Andrea Sartori

July 2017 –

- Conduct outpatient and inpatient neuropsychological assessments in academic medical setting

*External Practicum Student, Zablocki Veterans Administration Medical Center*

Clinical supervisors: Drs. Kathleen Patterson, Eric Larson, Angela Gleason, Melissa

Lancaster

June 2016 – June 2017

- Conduct neuropsychological assessments in veteran patient population
- Case conceptualization and writing integrated reports (approx. 1 report/week)

*External Practicum Student, Medical College of Wisconsin*

Clinical supervisors: Drs. Sara Swanson, Julie Bobholz, David Sabsevitz, Laura Umfleet

June 2015 – August 2016

- Conduct neuropsychological assessment of patients with memory disorders, traumatic brain injury, multiple sclerosis, epilepsy, learning disability, and other disorders

- Case conceptualization and writing integrated reports (approx. 1 report/week)

*Graduate Student Therapy Trainee, University of Wisconsin-Milwaukee Psychology Clinic*

Clinical supervisors: Drs. Christopher Martell and Robyn Ridley

June 2014 – September 2015

- Assess and treat depressive disorders using empirically-supported Behavioral Activation approach
- Use cognitive behavioral therapy (CBT) to treat clients with mood, anxiety, and adjustment disorders

*Graduate Student Trainee, University of Wisconsin-Milwaukee Psychology Clinic*

Clinical supervisors: Drs. Bonnie Klein-Tasman and Han-Joo Lee

August 2012 – August 2013

- Conduct clinical diagnostic interviews with clients with a diverse range of mental health problems, including mood, anxiety, and personality disorders
- Conduct psychodiagnostic assessments for individuals with learning disabilities, ADHD, and other cognitive problems

*Graduate Student Psychoeducational Assessment, Central City Cyberschool*

Clinical supervisor: Dr. Bonnie Klein-Tasman, August 2013 – June 2014

- Assess cognitive performance, academic achievement, and emotional functioning in at-risk students at an inner city charter school

*Graduate Student Vertical Team Member, University of Wisconsin-Milwaukee*

Spring 2015: General Cognitive Behavioral Therapy Team, Dr. Robyn Ridley

Spring 2015: Behavioral Activation for Depression Team, Dr. Christopher Martell

Fall 2014: General Cognitive Behavioral Therapy Team, Dr. Robyn Ridley

Fall 2014: Behavioral Activation for Depression Team, Dr. Christopher Martell

Spring 2014: OCD and Anxiety Disorders Team, Dr. Shawn Cahill

Fall 2013: Behavioral Activation for Depression Team, Dr. Christopher Martell

Spring 2013: Behavioral Intervention for Tic Disorders Team, Dr. Douglas Woods

Fall 2012: OCD and Anxiety Disorders Team, Dr. Shawn Cahill

## **TEACHING EXPERIENCE**

*Teaching Assistant, Department of Psychology, University of Wisconsin-Milwaukee*

Spring 2015: Physiological Psychology, Dr. Ira Driscoll

Fall 2014: Research Methodology, Dr. Sue Lima

Spring 2014: Physiological Psychology, Dr. Ira Driscoll

Fall 2013: Research Methodology, Dr. Sue Lima

Spring 2013: Research Methodology, Dr. Marcellus Merritt

Fall 2012: Research Methodology, Dr. Sue Lima

## **HONORS AND AWARDS**

Alzheimer's Association International Conference Travel Fellowship (2016)  
American Academy of Clinical Neuropsychology Student Poster Merit Award (2016)  
Glenn/AFAR Scholarship for Research in the Biology of Aging, First Alternate (2016)  
University of Wisconsin-Milwaukee Graduate Student Excellence Fellowship (2015-2016)  
University of Wisconsin-Milwaukee Distinguished Graduate Student Fellowship (2015-2016)  
University of Wisconsin-Milwaukee Chancellor's Graduate Student Award (2012-2014)  
Gammex Research Award (2009)  
Marquette University Dean's List (2005-2009)  
Undergraduate Achievement Award, Marquette University (2006-2008)  
National Merit Scholar (2005)  
Wisconsin Academic Excellence Award (2005)

## **AFFILIATIONS**

American Academy of Clinical Neuropsychology, Student Affiliate, 2015 –  
Association of Graduate Students in Neuropsychology at UW-Milwaukee, President, 2014 –  
Sigma Xi, Student Affiliate, 2013 –  
Society for Neuroscience, Student Affiliate, 2013 –  
Society for Clinical Neuropsychology (APA Division 40), Student Affiliate 2012 –  
International Neuropsychological Society, Student Affiliate, 2010 –