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Network Analysis of Cognitive Symptom Domains in Alzheimer's Disease (AD)

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NETWORK ANALYSIS OF COGNITIVE SYMPTOM DOMAINS IN ALZHEIMER'S DISEASE (AD)

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Abstract

Network Analysis of Cognitive Symptom Domains in Alzheimer's Disease (AD)

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Alzheimer's Disease (AD) is a degenerative neurological disease process that results in cognitive and functional declines and ultimately results in death. The pattern and course of cognitive and functional decline has been well characterized in AD, however little is known about the interactions between the symptoms. Network Analysis is a recently developed mathematical approach of examining the interactions between symptoms, by exploring the covariance of symptoms. The current study utilized network analysis to examine the multivariate structural dependencies among cognitive domains known to be affected in Alzheimer's disease. The sample consisted of 864 older adults (60-90 years old), selected from the National Alzheimer's Coordinating Center (NACC) Database, that were assessed over four serial cognitive assessments, each conducted approximately one year apart. The sample was divided into two groups (432 per group). Both groups were cognitively normal at baseline assessment, with one group remaining cognitively normal (Control group) and one going on to develop either Mild Cognitive Impairment (MCI) or Dementia due to AD (Converter group) over the course of the four assessments. The participants completed a neuropsychological assessment with tests known to be sensitive to AD, which included a global screeners, measures of attention, processing speed, executive function, episodic

memory, and language. The relationship between performance on these measures was examined using Network Analysis. The Converter group was also subdivided by sex and the networks of men and women were compared. It was hypothesized that there would be differences in the network structure of these cognitive test between the groups both before criteria for a cognitive diagnosis was made, as well as after the Converter group was diagnosed with AD. It was also hypothesized that the network structure of cognitive tests would differ for men and women with AD. Finally, it was hypothesized that the network structure of these cognitive tests would differ over time for the Converter group. Results indicate that there are differences in the network structure of cognitive tests between the Control and Converter groups even before diagnosis and that this difference becomes more significant over time. However there is not a significant difference between men and women in the Converter group, in terms of network structure. Finally within the Converter group, while the difference in network structure appears to become more prominent over time, it is not significantly difference over the four years assessed in the current study. These findings provide a clearer understanding the impact of AD on the changes in cognitive functioning and further efforts of early detection, with the goals of improved intervention and prevention.

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Dedications

I dedicate this work to all those who have supported me throughout this process. My accomplishments are shared with those who have been with me on this journey and could not have have been possible without the love and support of those around me.

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Chapter 1: Introduction

Alzheimer's Disease (AD) is degenerative neurological disease process that affects over 5 million older adults in the United States each year. Costs of AD have risen to over 170 billion dollars annually. As the average age of the population in the United States increases, this disorder may soon reach epidemic proportion (Alzheimer's Association, 2010; Hebert, Scherr, Bienias, Bennett, & Evans, 2003). The neuropathological changes associated with AD affect a number of brain regions and include the formation of senile plaques and neurofibrillary tangles that result in atrophy of the medial temporal lobes, an area associated with memory and semantic knowledge (Hyman, Van Hoesen, Damasio, & Barnes, 1984). The typical disease progression is characterized by declines in cognitive and functional abilities. These declines occur over an average of 10 years and often result in full debilitation that ultimately leads to death due to related health complications (Hebert et al., 2003).

The diagnostic criteria and classification of AD has evolved over time and the latest edition of the Diagnostic Statistical Manual (DSM-5) includes the diagnoses of Major or Mild Neurocognitive Disorder with specification of certainty (i.e. possible or probable) and etiology (e.g., AD, vascular, dementia with Lewy bodies, etc.) (American Psychiatric Association, 2013). There is extensive research that has explored the typical pattern and course of progression of cognitive declines in dementia. However, there have been few studies that explore the relationship between the symptoms domains and the relationship between those domains and individual factors. Furthermore, none have done so using network analysis.

Network analysis is a statistical method of examining the inter-connection of individual cognitive symptom domains, and determining if some domains are more central than others (Borsboom, 2017). Network analysis also allows for the evaluation of the degree to which

individual factors such as sex or years of education influence the structure of the network. Network analysis also allows for examining if there is a particular symptom domain that is more central in the network or if one symptoms domain drives global increases in the other symptom domains. Furthermore, the use of time series network analysis allows for examining how the network structure changes over the course of time. Using network analysis to examine changes in cognition over time would contribute to the overall knowledge of how AD progresses, and the impact of individual factors on that progression. This has significant implications for understanding the progression of AD and treatment planning. As such, the current study seeks to explore the differences in network structure of cognitive symptoms known to decline in AD between individuals with normal cognition, mild neurocognitive disorder (MCI) due to AD, and major neurocognitive disorder due to AD (dementia). The current study also seeks to more clearly characterize the differences in the progression of AD between men and women by comparing changes in the network structure longitudinally for individuals with mild (MCI) or major neurocognitive disorder (Dementia) due to AD. Additionally, we will aim to establish how the network structure of cognitive abilities, affected in AD, differs for those with MCI or Dementia due to AD, as compared to those with normal cognitive functioning. Findings will not only contribute to the current understanding of the course and progression of cognitive decline in AD, results will also increase understanding of the relationship between the cognitive domains affected in AD and how they change in relation to one another. Findings may help to better understand factors that contribute to individual differences in pattern and course of cognitive decline observed in AD.

Chapter 2: Literature Review

Alzheimer's Disease

Alzheimer's Disease (AD) is degenerative neurological disease process that affects over 5 million older adults in the United states each year, costing over 170 billion dollars annually. With the average age of the population in the United States increasing, concerns have been raised that AD may soon reach epidemic proportion (Alzheimer's Association, 2010; Hebert et al., 2003). As a result, there has been extensive research done to better understand the cause, progression, and impact of AD. From a neurocognitive standpoint, the pattern and course of cognitive decline seen in AD is rather consistent (Bondi, Edmonds, & Salmon, 2017a). While there are some occasions when the cognitive and behavioral presentation is atypical, most commonly, individuals present with impairments in memory that progress over time (Bondi, Edmonds, & Salmon, 2017b). Specifically, impairments in encoding and storage of new memories has been found in individuals with AD (Hodges & Patterson, 1995). Using neuropsychological assessments, this pattern of memory impairment can be distinguished from attention based memory impairments (Bondi et al., 2014; Buschke, Sliwinski, Kuslansky, & Lipton, 1997). In addition to memory decline, many individuals also experience language impairments early in the disease process. Loss of sematic knowledge results in word finding difficulties and impairments in sematic fluency (Nebes, 1989; Hodges & Patterson, 1995). Visuospatial abilities (Cronin-Golomb, & Amick, 2001) and executive functions (Bondi, Monsch, Butters, Salmon, & Paulsen, 1993; Lafleche & Albert, 1995; Perry, 1999) are also affected in some individuals.

Ultimately, cognitive declines progress to more global impairment over the course of the disease. Given the progressive nature of the disease, the latest edition of the DSM, Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) includes the diagnoses of Major or Mild Neurocognitive Disorder to distinguish the level of impairment the individual has (American Psychiatric Association, 2013). The distinction between Major or Mild Neurocognitive Disorder are similar in many ways to the previously used criteria for distinguishing Dementia and MCI. Due to these similarities, these terms are often used interchangeably in the literature on AD. In addition to the distinction of Major or Mild Neurocognitive Disorder, the DSM-5 also includes the use of modifiers which indicate the etiological cause of the cognitive decline. Finally, the DSM-5 includes a specifier which indicates the certainty of the etiological cause. For instance, a specifier of "possible" or "probable" is used when the etiology is thought to be AD. Taken together, the diagnostic criteria included in the DSM-5 aims to provide more diagnostic clarity, which in turn provides patients and their loved ones more insight into what should be expected as the disease progresses.

Neurocognitive Disorder

As mentioned above, the lasted edition of the DSM (DSM-5) draws a distinction between Mild and Major Neurocognitive Disorder, with the primary difference being the individual's level of impairment in daily functioning or Activities of Daily Living (ADLs). In order to meet criteria for Mild Neurocognitive Disorder, the individual must:

A. Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on:
    1. Concern of the individual, a knowledgeable informant, or the clinician that

there has been a significant decline in cognitive function; and

2. A substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.

B. The cognitive deficits do not interfere with capacity for independence in everyday activities (i.e., complex instrumental activities of daily living such as paying bills or managing medications are preserved, but greater effort, compensatory strategies, or accommodation may be required).

C. The cognitive deficits do not occur exclusively in the context of a delirium.

D. The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia)

The criteria for Major Neurocognitive disorder are identical, except for criteria B, which states, "the cognitive deficits interfere with independence in everyday activities (i.e., at a minimum, requiring assistance with complex instrumental activities of daily living such as paying bills or managing medications)." As such, for AD, Mild Neurocognitive Disorder is a precursor to Major Neurocognitive Disorder (American Psychiatric Association, 2013; Edmonds et al., 2019; Morris et al., 2001), with the latter diagnosis made once the disease progresses to the level when individuals have lost the ability to care for their daily needs.

Mild and Major Neurocognitive Disorder are umbrella terms that refers to decline in cognition and adaptive (for major) functioning that result from a neurodegenerative process. There have been a number of subtypes identified, each of which is associated with a unique neurodegenerative disease process and the resulting decline in functioning and cognition corresponds to the respective pattern of neurodegeneration. As such, the DSM-5 diagnosis calls

for specification of the etiology subtype. The etiology is determined based on time course, domains affected, associated symptoms, patient health and neurologic history (e.g. history of TBI or psychiatric history) and in some cases, biological markers. The DSM-5 criteria also includes a qualifier of certainty in the etiology and in the case of AD can be possible or probable AD (American Psychiatric Association, 2013). The accuracy of the clinical criteria for probable AD, when diagnosed in a specialized memory disorders centers, generally exceeds 85%. However, despite this level of accuracy, a final diagnosis can only occur after examination of the brain upon autopsy and is based on the density of senile plaques and neurofibrillary tangles. Alzheimer's Disease is among the most prevalent of the degenerative subtypes and is diagnosed primarily based on cognitive, behavioral, and functional symptoms (American Psychiatric Association, 2013). Additionally, there are known biomarkers associated with AD that can aid in identifying AD as the etiology of the neurocognitive disorder.

Pattern and Course of Progression

The declines in cognitive functioning that occur in the early stages of AD are associated with neuropathological changes in the medial temporal lobes and progresses frontally. Because the medial temporal lobes are the brain regions that mediate language and memory, individuals with Alzheimer's Dementia (AD) generally present initially with changes in memory, language, and semantic processing, while cognitive deficits associated with frontal lobe pathology appear later in the course of the disorder. As the disease progresses and disease pathology spreads throughout the brain, impairments become more global in nature. Research has implicated beta amyloid plaques and tau tangles (Braak & Braak, 1991) as the cause of neurodegeneration. For most individuals the neurodegenerative process progresses slowly, and a significant disease load is required before cognitive and behavioral symptoms are observed. The course of the cognitive

decline seen in AD has been well studied, and the typical pattern involves early impairments in learning, memory, and language, with later declines in frontal lobe functions such as attention, working memory, and executive functions (Braak & Braak, 1991). However the relationships between these domains and the affect that decline in one domain has on the others has not been examined.

Sex-related Differences

Sex-related differences have been identified in both the prevalence and rate of progression of AD. The prevalence of AD has been found to be significantly higher in women as compared to men. Specifically, research has found the lifetime risk of dementia due to AD was approximately twice as high in women (12%) as compared to men (6.3%) (Plassman et al., 2007; Seshadri et al., 1997). Most recently, census estimates revealed nearly two-thirds of the older adults diagnosed with AD are women (Hebert, Weuve, Scherr, & Evans, 2013). Researchers have attempted to account for this disparity by examining sex differences in incidence, progression (Hebert, Scherr, McCann, Beckett, & Evans, 2001; Letenneur et al., 1999; Liu et al., 1998; Kivohara et al., 1996; Roberts et al., 2014), and responsiveness to treatments (Mielke, Vemuri, & Rocca, 2014).

One commonly cited explanation for higher prevalence in women is the longer average life span for women as compared to men which results in a longer period of risk. This explanation has been supported by several researchers, including Plassman et al. (2007) who found that when age and education were controlled, women were are no higher risk than men for developing dementia due to AD. Seshadri and colleagues (1997) also accounted for this difference based on the longer life expectancy of women as compared to men. More recently, researcher have argued that the explanation for sex differences in AD is far more complex than

originally thought. Several alternative explanations include hormonal differences, cognitive reserve, education, and other biological explanations (Laws, Irvine, & Gale, 2018). Laws et al. (2018) argue that there is evidence that not only are rates of AD higher in women, but women seem to decline at a more rapid pace, and also show greater impairment than men. These differences cannot be accounted for by longer life span and therefore other factors must be involved.

There have been mixed findings regarding hormonal differences between men and women is as a possible explanations for the sex differences. While, some studies find positive effects, others have found negative effects of hormones on AD. One of the largest studies that has been conducted on the effects of hormones on AD is the Women's Health Initiative Memory Study (WHIMS). This study involved 7479 postmenopausal women (Rapp et al., 2003; Shumaker et al., 2003). Four thousand five hundred and thirty two women with natural menopause (intact uterus) were randomly assigned to groups comparing conjugated equine estrogen (CEE) and medroxyprogesterone (MPA) to a placebo (Rapp et al., 2003). Data from the WHIMS demonstrated a higher incidence of dementia and greater cognitive decline in the group using hormone replacements as compared to the placebo group. In contrast, several RCTs have shown when healthy postmenopausal women treated with 17β –estradiol (E2) were compared to controls, hormone use was associated with less decline in verbal memory (Bagger, Tanko, Alexandersen, Qin, Christiansen, for the PERF Study Group, 2005; Dumas, Hancur-Bucci, Naylor, Sites, & Newhouse, 2008; Silverman et al., 2011; Tierney et al., 2009). The inconsistency between these findings has been explained by using the "healthy-cell bias" (Chen, Nilsen, & Brinton, 2006), which suggests that E2 selectively benefits neurons that are healthy. As a result E2 is protective when initiated while neurons are still healthy, but harmful after

neuronal cell degeneration has begun.

Sex differences in AD have also been explored in terms of metabolic differences. Malpetti and colleagues (2017) examined brain hypo-metabolism differences between men and women in the context of cognitive reserve (e.g. education and occupational level). This study included healthy controls (n = 225) and patients with AD (n = 282), and found, within the AD group, there were differences in the correlations between education and occupation levels and brain hypo-metabolism. Specifically, there was a posterior temporal-parietal association in males and a frontal and limbic association in females. This finding suggests that networks involvement differs between men and women. The metabolic connectivity for both controls and those with AD were similar, however there are differences in network activation. Specifically, there was greater efficiency in the posterior default mode network for males, while the anterior frontal executive network had greater efficiency for females (Malpetti et al., 2017).

In further attempts to better characterize the differences in AD, researchers have looked to the underlying AD pathology for explanations for the observed sex differences (Filon et al., 2016). Filon and colleagues (2016) conducted full neuropathological examinations on 1028 deceased individuals with AD. Results founds no difference by in the age of dementia onset. However, they did find that women were more likely to proceed to very severe cognitive impairments (Mini-Mental State Examination score of 5) as well has more significant neuropathological changes (less than Braak stage VI neurofibrillary degeneration). Regarding the pathological differences, there were not significant differences in the median neuritic plaque densities in men and women, while women did have significantly greater tangle density scores. This study also showed a significant difference in the brain weight between females with AD as compared to controls, while the brain weight differences observed in men was not significant.

This difference remained significant even when accounted for age, disease duration, and comorbid conditions. Based on these findings, Filon and colleagues (2016) argue that women have more severe neurofibrillary degeneration, and greater loss of brain parenchyma, which is one reason for the disparity in the rate of progression and severity of AD.

Neuropathology of Alzheimer's Disease

As discussed above, the neuropathological changes of AD occur in the medial temporal lobes initially and then spreads globally (Korf, Wahlund, Visser, & Scheltens, 2004). The typical disease progression is characterized by decline in cognitive and functional abilities (Hebert et al., 2003). The neuropathological changes associated with AD include the senile plaques and neurofibrillary tangles. The plaques are thought to be formed as a result of mis-folding of a beta amyloid proteins (A-beta), causing toxic amyloid fibrils. This process can begin to occur as many as 20 – 30 years prior to the manifestation of any clinical symptoms of the disease. These abnormal proteins build up in the medial temporal lobes, frontal lobes, anterior cingulate, posterior cingulate, precuneas and striatum (Nestor, Fryer, Smielewski, & Hodges, 2003; Pengas, Hodges, Watson, & Nestor, 2010).This build up eventually sets off a cascade effect resulting in problems with phosphorylation of the microtubule-associated protein (MAP) (Iqbal, Liu, & Gong, 2018). Tau is a type of MAP that stimulates tubulin assembly into microtubules in the brain and is normally occurring in healthy brains (Weingarten, Lockwood, Hwo, & Kirschner, 1975). However when abnormal hyperphosphorylation of tau occurs, this causes the tau to be toxic and contributes to neurodegeneration. The toxic function that occurs as a result of this hyperphosphorylation cannot then compensated for by other MAPs (Liu et al., 2007).Once the hyperphosphorylation occurs, the abnormal tau is polymerized into highly aggregated paired helical filaments (PHFs) and neurofibrillary tangles (NFTs). It is the PHFs and

NFTs that give rise to cell death. The mechanisms that result in the senile plaques and neurofibrillary tangles have been targeted for pharmacological interventions, however a cure has not yet been identified.

Biomarkers

Given these neuropathological underpinnings of AD, researchers have worked to identify biomarkers of AD. Biomarkers, simply put, are measurable variables, either physical, chemical, or anatomical variables that provide insight into the disease state. Specific to AD, two categories of biomarkers discussed in the research include those associated with amyloid accumulation, and those associated with neurodegeneration. The core biomarkers for AD provide evidence of amyloid pathology (Aβ40 / Aβ42 extracellular accumulation) and/or intracellular depositions of neurofibrillary tangles (hyperphosphorylated Tau inclusions). These biomarkers therefore serve to identify neuropathological features of AD in individuals that are still living. Previously, this type of neuropathology could only be detected on biopsy or necropsy (Menéndez González, 2014). In addition to being able to more easily detect these signs of AD pathology in living individuals, use of biomarkers also allows for monitoring the progression of the neuropathology.

Cerebral Spinal Fluid

A number of different methods of measuring these biomarkers have been developed over the past 20-30 years, including cerebral spinal fluid (CSF) testing and neuroimaging. Specifically, given the unique role of CSF in the nervous system, it is well suited for providing information about the state of brain tissue, without using more invasive means. Due to the direct contact of CSF with the extracellular space of the brain, the biochemical changes in the brain are reflected in the CSF (Bouwman et al., 2007a). More specifically, neuropathological processes in the brain, such as those seen in AD result in the release of byproducts into the CSF. Identifying

these byproducts in CSF can provide insight into the cellular changes that are occurring in the brain. Specific to AD pathology, there are three primary CSF biomarkers that have been widely accepted that include total tau (T-tau), phospho-tau (P-tau), and the 42 amino acid form of β-amyloid (Aβ42) (Blennow, 2004; Herukka, Hallikainen, Soininen, & Pirttilä, 2005; Jack et al., 2010). In addition to these well accepted CSF biomarkers for AD, there are a number of other biomarker candidates that are currently being explored, although additional evidence is needed to support their use. Accumulation of β-amyloid in the brain is believed to occur 10 years or more before cognitive symptoms present, and therefore lower levels of Aβ42 in (CSF) prior to symptoms of cognitive decline (Buchhave et al., 2012; Jack et al., 2010).

In addition to reduced levels of Aβ42 in CSF, levels of total tau (T-tau) and of phosphorylated tau at threonine 181 (P-tau) have been shown to be elevated in CSF of people with AD pathology (Brys et al., 2009; Hampel et al., 2004; Hansson et al., 2006; Herukka et al., 2005; Mattsson et al., 2009; Riemenschneider et al., 2002). While the presence of Aβ42, occurs early in the disease process, tau is detectable in the CFS later than β-amyloid levels. Studies have found the Aβ42 levels change early and reach a plateau, while T-tau and P-tau levels in the CSF increase slowly over the course of the disease and more correspond with the dementia process (Bouwman et al., 2007b; Buchhave et al., 2012; Buchhave et al., 2009; Kanai et al., 1998). Given that these two biomarkers show up at different stages of the disease, they each provide unique information regarding the stage of the disease process. Where tau is a good indicator of injury to cells and atrophy, Aβ42 is a strong pre-dementia marker, allowing for early identification (Menéndez-González, 2014).

Neuroimaging

In addition to CSF biomarkers, neuroimaging procedures have been shown to be effective biomarkers. Commonly used neuroimaging techniques include structural and magnetic resonance imaging (MRI) and positron emission tomography (PET). These techniques allow for structural, functional, and molecular imaging. Structural imaging techniques (i.e. MRI) reflect changes or atrophy in the neuroanatomical structure (Frankó, Joly, & Alzheimer's, 2013; Holland et al., 2009). These structural changes can be evaluated using qualitative or quantitative techniques. Using quantitative techniques involves creating a three-dimensional representation of brain structures known to be affected in AD (i.e. hippocampus) is created by tracing the border on sequential MRI slices. This allows for quantification of the volumetric and morphometric characteristics of the region examined (Hämäläinen et al., 2007; Jack et al., 1997; Karas et al., 2008).

While structural techniques are frequently used in clinical settings, as they provide details about changes in neuroanatomical structures, they do not allow for direct examination of brain functioning. Often presumptions are made regarding the relationships between structure and function, however this has been repeatedly shown to be a very complex relationship. Functional imaging techniques, such as fMRI, uniquely allow for direct measurement of brain activity. The principal outcome measure utilized in fMRI is the blood-oxygenation level-dependent (BOLD) signal. BOLD provides a measure of regional brain activity by measuring fluctuations in local blood flow and oxygenation. Using this approach, fMRI provides an indication of brain physiology and cellular level activation (Mosconi et al., 2010; Protas et al., 2013). To provide even more detail about how these changes relate to the Alzheimer's disease process, task-related fMRI has been used. In task-related fMRI, individuals undergo fMRI scans while performing

cognitive tasks affected in AD (i.e. encoding and storage of new memories or sematic language tasks) (Binder, Desai, Graves, & Conant, 2009; Koenig et al., 2008). Unfortunately, studies using task-related fMRI in AD populations have yielded conflicting results, with some studies finding decreased activation (Rémy, Mirrashed, Campbell, & Richter, 2005; Yetkin, Rosenberg, Weiner, Purdy, & Cullum, 2006), while others have found higher levels of activation in affected regions (Kircher et al., 2007a; O'Brien et al., 2010). The reasons for these seemingly contradictory findings are not completely clear, although researchers have posited that disease severity may have an impact. Specifically, increased activation is observed in patients who have minimal impairments, due to a compensatory mechanism initiated for successful task completion. However, brain regions with more advanced atrophy are no longer able perform increased or compensatory neuronal activity, resulting in decreased activation, rather than increased, during tasks (Kircher et al., 2007b).

Lastly, using targeted radiotracers, molecular imaging (i.e. PET) measures chemical and cellular level changes in the brain. Recently, there has been significant progress in using PET for diagnosis and staging of AD and PET has even been proposed for use in staging of preclinical AD (Sperling et al., 2011). The advances in this area are due in large part to development and identification of new and more well validated radiotracers. Among the well validated amyloid radiotracers are, N-methyl-[11C]2-(4′-methylaminophenyl)-6-hydroxybezothiazole or Pittsburgh Compound-B (PiB) (Mathis et al., 2003; Matsuda, Shigemoto, & Sato, 2019), flutemetamol (Nelissen et al., 2009), florbetapir (Wong et al., 2010), florbetaben (Barthel et al., 2011), and [^{18}F]NAV4694 (Seibyl, Barret, Marek, & Reininger, 2013).

Radiotracers designed to target amyloid alone, are not sufficient for diagnosis of AD. Postmortem histopathological studies consistently show that NFTs better indicate the severity of

the disease progression, as compared to Aβ. Furthermore, PET studies have found there is little association between amyloid burden and the severity of cognitive decline (Rabinovici & Jagust, 2009). Conversely, the relationship between tau pathology and the severity of cognitive decline is much closer (Villemagne, Doré, Burnham, Masters, & Rowe, 2018), therefore radiotracers that target tau are needed. There have been a number of tau specific radiotracers developed and studied including, [^{18}F]Flortaucipir (AV1451) (Schonhaut et al., 2017), [^{18}F]T808(Declercq et al., 2016), [^{18}F] THK5117(5317) (Okamura et al., 2013), [^{18}F]THK5351 (Harada et al., 2016), [^{11}C] PBB3 (Hashimoto et al., 2015), [^{18}F]PM-PBB3 (Shimada et al., 2018), [^{18}F]GTP1(Sanabria Bohórquez et al., 2019), [^{18}F]MK6240 (Betthauser et al., 2019), [^{18}F]PI2620 (Kroth et al., 2019). Each of these has strengths and weaknesses, and as a result have not been fully adopted for clinical use. Specifically, problems with off-target binding of tau tracers to non-tau protein deposits and other molecular structures is common (Leuzy et al., 2019; Okamura et al., 2018). The research in this area is rapidly growing and focuses on use of PET for identification of AD pathology and responsiveness to treatment. Taken together, PET and the other neuroimaging techniques allow for the assessment of changes in brain structures and or processes that have been implicated in AD (Menéndez González, 2014).

Biomarker Neuropsychological Contributions

Neuropsychological test scores have also been identified as biomarkers. Typically, tests that reflect memory and language abilities (Albert, Moss Tanzi, & Jones, 2001; Chapuis et al., 2016; Ho, & Nation, for the Alzheimer's Neuroimaging Initiative, 2018) are the strongest predictors of AD pathology, although deficits on tests of executive function (Clark et al., 2012; Harrington et al., 2013) and visuospatial abilities also have a predictive role (Alladi et al., 2007; Hof, Vogt, Bouras, & Morrison, 1997; Mendez, Ghajarania, & Perryman, 2002). When used in

combination with other biomarkers such as neuroimaging, laboratory tests and genetic studies, neuropsychological tests have been shown to contribute significantly to the prediction of AD diagnosis above and beyond what is accounted for by these other classes of biomarkers (Ho et al., 2018). This suggests a unique role for neuropsychological test scores in early detection efforts for AD. It is also of interest that neuropsychological test scores are useful in predicting functioning and ADLs (Ashendorf et al., 2018; de Paula et al., 2015; Jefferson et al., 2006; Mlinac and Feng, 2016; Razani et al., 2011) more so than biological or genetic findings, underscoring the unique clinical contribution test results have in the treatment of affected individuals.

Early Identification of Alzheimer's Disease

Based on what is known about the neuropathological process underlying AD and that the disease process begins as many as 20 - 30 years prior to formal diagnosis (Pengas et al., 2010), research has turned towards finding ways of detecting AD in the prodromal phase (Bondi et al., 2008). This work is predicated on the understanding that early neural dysfunction and associated cell death occurs during the period of time prior to onset of clinically significant symptoms. This cell death, once occurred, is irreversible and therefore incurable. It is only after this process is rather far along that we are currently able to make a diagnosis of AD. The advantages of developing early detection techniques, is that this would allow for early intervention and potentially the ability to stop or reverse the disease process (Friedrich, 2013; Petersen, Smith, Ivnik, Kokmen & Tangalos, 1994). The disadvantages or caution associated with early detection is the inherent risk of incorrectly identifying an individual as having AD. In other words, the rate of making a false positive error increases when the level of impairment required for identification is lower (Salmon et al., 2002). A variety of methods have been examined in

attempts to identify individuals who will go on to develop AD, either before any cognitive changes are present or when mild changes have begun, although do not rise to the level of clinical significance. These early detection methods include, neuropsychological testing and the biomarkers previously discussed (i.e. CFS, MRI, PET, etc) (Menéndez González, 2014).

Network Analysis

A recently developed method of examining the covariance of symptoms has been developed called Network Analysis. Network Analysis is a mathematical approach in which symptoms are represented as a system and the way those symptoms change in relation to one another can be examined (Borsboom & Cramer, 2013). This approach allows the disease to be conceptualized not as a collection of symptoms arising from one cause, or as a system, but rather something in the middle (Borsboom & Cramer, 2013). Network analysis also allows for the identification of symptoms that are highly central. Centrality is a measure of how connected a specific symptom is to the other symptoms. Psychological networks are based on the partial correlation network that are estimated using regularization techniques. These regularization techniques, that allow for the removal of spurious edges, have been developed out of methods used in machine learning (Foygel, Mathias, 2010; Meinshausen & Bühlmann, 2006). The networks are made up of nodes that are connected to one another by edges. The nodes represent observed variables, while the edges represent a statistical relationship between the nodes. In recent years, the methodology of network analysis has gained acceptance and has been used across the field of psychology, including clinical psychology (Boschloo et al., 2015; Forbush, Siew, & Vitevitch, 2016; McNally et al., 2015), psychiatry (Isvoranu, Borsboom, van Os, & Guloksuz, 2016; Isvoranu et al., 2017), social psychology (Dalege et al., 2016), and quality of life research (Kossakowski et al., 2016). The theoretical foundation of the network approach is

that symptoms should be thought of as mutually interactive and reciprocal elements of a complex network, rather than symptoms of a disease (Cramer, Waldorp, van der Maas, & Borsboom, 2010; Schmittmann et al., 2013). For this reason, the term element is often used rather than the more commonly used term symptom. While this distinction is subtle, the use of the word element conveys that within these complex networks, the symptoms are thought to be part of a causal system (Borsboom, 2008). In other words, changes in one symptom or element may cause changes in another. To date, this approach has been used to better understand symptoms and psychological disorders, including Major Depressive Disorder, Generalized Anxiety Disorder and Schizophrenia (Zamani Esfahlani, Visser, Strauss, & Sayama, 2018).

Network Analysis has not yet been applied with Alzheimer's Dementia and the associated cognitive symptoms. While there has been substantial research to date on the typical pattern and course of decline, there are individuals differences and some individuals present with atypical symptoms. Research using Network Analysis to investigate these differences and if there is a systematic pattern has yet to been done. Network Analysis is well suited for investigating the relationship between cognitive symptoms and the progression of cognitive decline, as it allows for the examining how the symptoms change in relation to one another. This would allow for a better understanding of the disease progression, allowing for better treatment planning.

Research Aims and Study Hypotheses

The aging population and the high prevalence of AD, alongside the exorbitant costs associated with this disease, has created a great need to develop a better understanding of the course of AD progression. Specifically, how individual differences, such as impact the progression and patterns of impairment seen in AD. While this area has been researched

extensively, there are still many unanswered questions regarding individual differences observed in AD. While there has been extensive research into changes that occur in neurocognitive functioning, there is also little know about how the cognitive domains change in relation to one another as the AD progresses. Based on these needs, the current study was designed with four main goals: (1) characterize the network structure of cognitive abilities affected in AD in normal aging, (2) characterize the AD symptoms network structure in a clinical sample, (3) evaluate the stability of the network structure, and (4) examine if and how the network structure changes over time as the disease progresses. A statistical approach known as Network Analysis was used to examine the inter-connectedness of individual cognitive domains with the aim of determining if some cognitive domains affected in AD are more central than others. The study also examined how the network structure of cognitive domains known to be impacted by AD changes overtime in individuals diagnosed with AD. Lastly, the current study aimed to examine the effect of individual factors, such as sex on the structure of the network. Understanding if there is a particular symptom domain that is more central or if one symptoms domain drives global increases in the other domains will contribute to the overall understand of how AD progresses in different individuals. This understanding has significant implications to better understanding the progression of AD and treatment planning. This will expand upon the current understanding of AD course and further aide in treatment planning for individuals with AD. Based on the above review of the literature it is hypothesized that:

1) The overall network structure of cognitive domains affected in AD will differ for those individuals with normal cognition as compared to individuals with MCI or Dementia due to AD, at time one, prior to meeting criteria for diagnosis.

2) The overall network structure of cognitive domains affected in AD will differ for those individuals with normal cognition as compared to individuals with MCI or Dementia due to AD after diagnosis of MCI or Dementia due to AD is made.

3) The overall network structure for cognitive domains affected in AD will differ for men with MCI or Dementia due to AD as compared to women with MCI or Dementia due to AD.

4) The Temporal Stability of the network will differ for those with normal cognition who remain normal over a four year period, from those individuals who are normal at the initial visit, then go on to develop MCI or Dementia due to AD.

Chapter 3: Methods

Participants

The current study included 864 participants. This included a clinical sample consisting of 432 individuals with Mild Neurocognitive Impairment (MCI) or Major Neurocognitive Impairment (Dementia) due to AD and a healthy control sample of 432 individuals who were individually matched to the clinical sample on age, education and sex. Demographic information for the groups are presented in Table 1. All participants were selected from the National Alzheimer's Coordinating Center (NACC) Database, which was created in 1999 in the United States for the purpose of supporting collaborative research in AD. The NACC is considered one of the largest and most comprehensive databases of its type (more detail about the NACC is provided in the procedures section). All participants selected from the database for the current study were between the ages of 60-90 years old (at the time of their initial evaluation), spoke English as a primary language, and did not have significant hearing or vision impairment that would interfere with testing procedures. Only individuals with at least four consecutive study visits with complete neuropsychological assessment data were included. Study visits were typically completed once a year on average.

Individuals were selected for the clinical sample based on the NACC variable NACCUDSD, which indicates the level of cognitive impairment. Individuals were selected if, at the time of the initial visit, they did not meet criteria for a cognitive diagnosis and, if by the time of the fourth visit, they had been diagnosed (by the study physicians) with either MCI (Mild Neurocognitive Disorder; NACCUDSD[1]=3) or dementia (Major Neurocognitive Disorder;

[1] The subject's cognitive status is determined at every visit. Subjects with a clinical diagnosis of normal cognition have naccudsd = 1. Subjects with either amnestic or non-amnestic MCI have naccudsd = 3 and those with a

(NACCUDSD[2]=4) due to probable AD (NACCALZD[3]=1). The criteria used for determining probably AD for the NACCALZD variable has changed from the UDSD 1.0 and 2.0 to the UDSD 3.0. For the UDSD 1.0 and 2.0 the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA Alzheimer's Criteria; now known as the Alzheimer's Association). This criteria was then changed for the UDSD 3.0 and the National Institute on Aging and Alzheimer's Association (NIA-AA) criteria is now used.

We refer to this sample as the Converter group because they converted to a diagnosis over the course of the study evaluations. Participants were excluded from the Converter group if they had a history of traumatic brain injury or another neurological disorder (e.g., seizure disorder). Additional exclusion criteria included: 1) current or past medical condition or neurological condition known to significantly affect the central nervous system 2) or were taking

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diagnosis of dementia have naccudsd = 4. Subjects who are cognitively impaired but who do not meet the criteria for MCI have naccudsd = 2.

[2] The subject's cognitive status is determined at every visit. Subjects with a clinical diagnosis of normal cognition have naccudsd = 1. Subjects with either amnestic or non-amnestic MCI have naccudsd = 3 and those with a diagnosis of dementia have naccudsd = 4. Subjects who are cognitively impaired but who do not meet the criteria for MCI have naccudsd = 2.

[3] Subjects with normal cognition have naccalzd = 8. Subjects with any cognitive impairment (dementia, MCI, or impaired, not MCI) and Alzheimer's disease indicated as the etiologic diagnosis have naccalzd=1. Subjects with cognitive impairment and no Alzheimer's disease etiologic diagnosis have naccalzd=0. To determine whether the subject was cognitively impaired, not MCI, or had MCI or dementia, refer to the naccudsd variable. It is important to note that the criteria for an etiologic diagnosis of Alzheimer's disease is different in versions 1-2 and 3: in v1.2 and v2, the NINCDS/ADRDA criteria were applied and in v3 the NIA-AA criteria for AD dementia are applied. While these criteria are quite similar, they do have subtle differences.

medication at the time of the evaluation that may affect central nervous system function, with the exception of medication that is specified for the treatment of dementia and its symptoms and 3) diagnosis of substance abuse or dependence at any of the data collection time points. Of the over 38,000 subjects in the database, 433 individuals were selected, based on the above process. One of these individuals was excluded because five years had elapsed between the first and second assessment time point, resulting in a final Converter group of 432 participants. The demographic characteristics of the dataset are included in Table 1.

Individuals in the Control group were selected if they did not at any time over the course of the selection period (initial visit through fourth visit) meet criteria for cognitive impairment (i.e. clinical diagnosis of normal cognition; NACCUDSD[1]=1). Participants were excluded if they had a history of traumatic brain injury or another neurological disorder (e.g., seizure disorder). Additional exclusion criteria included: 1) current or past medical condition or neurological condition known to significantly affect the central nervous system 2) or were taking medication at the time of the evaluation that may affect central nervous system function 3) diagnosis of substance abuse or dependence at any data collection time point.

The Control group was selected by individually matching participants to those in the clinical group on the three key demographic variables of sex, age, and education at the first evaluation. These variables were selected because of differences between men and women reported in the AD literature and because of the well documented strong associations between age and education with neurocognition. Since it was often the case that there were multiple individuals in the dataset who could be matched to a clinical sample participant on sex, age, and education, random selection was used to determine with individual was ultimately included in the Control group. In the less common event where an exact match was not available, the closest

possible match was selected. For example, if there was no control in the data set that could be matched to a Converter group participant who was 80-year-old, male, with 21 years of education, then a control was selected who was 80 years old, male, with 20 years of education. In this case, education was the non-matching variable and the decision to select an individual with more or less education was determined by a "coin flip" selection technique. If there were multiple individuals who had 20 years of education instead of 21, then random selection was used to determine which individual would be included in the Control group. Details of selection process are illustrated in Figure 1.

Figure 1. *Selection process decision tree.*

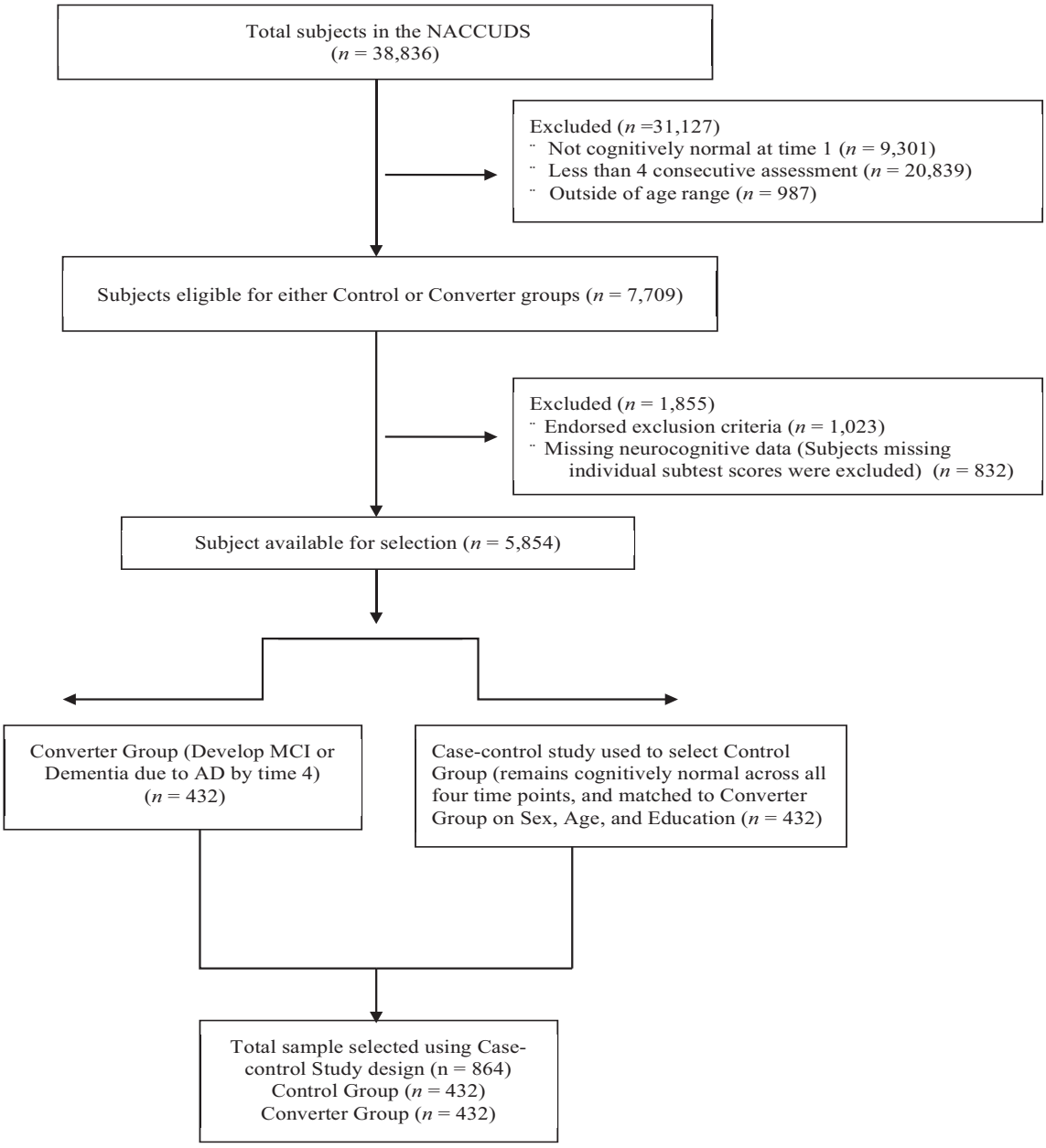


Table 1. *Demographic and Clinical Characteristics of the Sample.*

Variable	**Control**		**Converter**	
	Mean	***SD***	***Mean***	***SD***
Education (time 1)	15.7	2.8	15.7	2.9
Age (time 1)	76.4	7.0	76.4	7.0
	N		***N***	
Sex				
Male	180		180	
Female	252		252	
Race				
Caucasian	371		360	
African American	51		65	
American Indian	1		0	
Pacific Islander	0		0	
Asian	8		5	
Other	1		2	
Handedness				
Left	27		29	
Right	388		388	
Ambidextrous	17		11	
Unknown	0		4	
Cognitive Diagnosis at Assessment 4				
No Cognitive Diagnosis	432		0	
MCI/Mild NCD	0		355	
Dementia/Major NCD	0		77	

Measures

Participants were evaluated using neuropsychological measures of cognitive functioning, including measures sensitive to cognitive decline associated with AD (Ivnik et al., 1992b; Ivnik, Malec, Tangalos, Petersen, & et, 1990; Ivnik et al., 1992c; Ivnik et al., 1992a; Ivnik et al., 1992c; Lucas et al., 1998; Petersen, Smith, Kokmen, Ivnik, & Tangalos, 1992; Petersen, Smith, Ivnik, Kokmen, & Tangalos, 1994; Steinberg, Bieliauskas, Smith, Ivnik, & Malec, 2005; Steinberg, Bieliauskas, Smith, & Ivnik, 2005). When the UDSNB was developed initially, the measures

included brief measures of attention, processing speed, executive function, episodic memory, and language. The battery used has been changed over the course of the NACC project to update the battery based on advances in test development, so some of the cognitive measures have been changed over the years. The reasons for these substitutions are discussed below. Research has been done to equate the measures used in the different versions of the UDS (UDSNB 1.0, UDSNB 2.0, and UDSNB 3.0) and conversion tables are available to equate scores from the various tests. Tables available on the NACC website allow researchers to convert scores from UDSNB 1.0 and UDSNB 2.0 to the measures used on UDSNB 3.0, allowing for direct comparisons in the event subjects selected received the updated battery. The tests used for the UDSNB 1.0 and UDSNB 2.0 included the MMSE, Logical Memory IA- Immediate and Delayed, digit span test forward and backward, category fluency and letter fluency, Boston Naming, and the trail making test (A and B) (Weintraub et al., 2009). The UDSNB 1.0 and UDSNB 2.0 battery consisted of the same tests, with the only differences being clarification of instructions for administration and scoring, and one modification to the instructions of the delayed story recall (Logical Memory A Delayed).

After several years, limitations of the battery were identified and a work group was created to address these limitations. The first limitation of the battery was that healthy controls showed practice effects on longitudinal follow-up, particularly on measures of memory. Second, the UDSNB 1.0 and 2.0 used published tests. Use of published tests increased the likelihood of multiple exposures to the test content, both through clinical practice or through participation in research conducted at the ADCs. Additionally, use of published tests involves licensing costs and restrictions on sharing the materials. Third, early detection requires tests that are sensitive to the early stages of decline and even “preclinical” states. Finally, UDSNB 2.0 did not include tests

that measure visuospatial functions and nonverbal memory, which has now been shown to be affected in some cases of AD (Alladi et al., 2007; Hof, Vogt, Bouras, & Morrison, 1997; Mendez, Ghajarania, & Perryman, 2002;). Furthermore, visuospatial symptoms have been shown to arise later in AD, and the pattern of performance differs on these visuospatial construction and memory tasks between individuals with frontal and parietal cortical atrophy (Possin, Laluz, Alcantar, Miller, & Kramer, 2011a).

The work group was tasked to select tests that would be comparable in many ways to the previous version of the USDNB, while addressing these limitations. The following battery selected to accomplish these goals included the following tests: 1) the Montreal-Cognitive Assessment (MoCA), which replaced the The Mini-Mental State Examination (MMSE); 2) the Craft Story 21 Recall Immediate and Delayed, which replaced the WMS Logical Memory; 3) the Benson Complex Figure Copy Immediate and Delayed which was new to the battery; 4) the Number Span Test forward and backward which replaced forward and backward Digit Span; 5) the Trail Making test (A and B) which was retained from UDSNB 1.0 and 2.0; 6) the Multilingual Naming Test (MINT), which replaced the Boston Naming Test; 7) and Category Fluency (Animal and Vegetable) which was retained from UDSNB 1.0 and 2.0.

Once the UDSNB 3.0 battery was created, research was conducted to establish the equivalence of the new tests to the previously used measures and develop tables that allow researchers using the NACC database to calculate an equivalence score for the tests on the UDSNB 1.0 and 2.0 to scores on the UDSNB 3.0 (Monsell et al., 2016). These conversions allow for direct comparison of test scores from the different iterations of the UDSNB, making longitudinal comparisons possible. Tables are also available to produce standardized scores corrected for age, age and education, or age, education and sex. For the purposes of the current

study, most participants were administered UDSNB 1.0 or 2.0, so for those who completed UDSNB 3.0, raw scores were converted using the conversion tables provided on the NACC website (https://www.alz.washington.edu/ WEB/npsych_means.html) so they would be equivalent across UDSNB versions. Demographic corrections were not used in the current study because the control and Converter groups were matched on sex, age, and education. Raw scores were standardized using the mean and standard deviation of the current sample (N=864) This conversion procedure is discussed in the Analysis section. Below is a description of each measure used in the UDSNB versions.

Cognitive Screener

The Mini-Mental State Examination (MMSE; Folstein, Robins, & Helzer, 1983) and the Montreal-Cognitive Assessment (MoCA; Nasreddine et al., 2005) are cognitive screeners that aim to provide a snap shot of cognitive functioning. These screeners are not particularly sensitive to signs of early dementia, particularly when the individual has above average (or higher) cognitive abilities (Tombaugh & McIntyre, 1992). These cognitive screeners are however useful for identifying dementia when it is present and distinguishing between mild, moderate and severe stages of dementia (Galasko, Gould, Abramson, & Salmon, 2000). Based on this, MMSE and then eventually the MoCA were selected to aid in staging clinical milestones once dementia is diagnosed.

Episodic Memory

Logical Memory IA- Immediate and Delayed (Wechsler, 1987b) from the WMS-R and Craft Story 21 Recall Immediate, and delayed are measures of auditory verbal learning and memory. These tasks require participants to listen to and retell a narrative story. They are then

asked to recount the story after a delay of 20-30 minutes. The use of a delay allows for assessment of encoding, storage, and recall of structured verbal memory.

Visuospatial Construction and Memory

The Benson Complex Figure Copy Immediate and delayed is a measure of the ability to perceive and construct visual stimuli (copy) and to then recall that information after a delay (Possin, Laluz, Alcantar, Miller, & Kramer, 2011b; Possin, 2010). Constructional abilities (Copy condition) are assessed by evaluating the presence and placement of figural elements. Then after a delay, visual memory is assess by asking the participant to reproduce the figure from memory. Once again, the figure is score based on the presence and placement of figural elements. Unfortunately, this measure was not available for most participants in the current study because it was not added until UDSNB 3.0, so we did not include this measure in our analyses.

Simple Attention and Working Memory

Digit Span test from the WMS-R (Wechsler, 1987b) or the Number span test forward and backward were used to measure simple attention and working memory. Digit Span test from the WMS-R was administered in its standard format, which included scores for total trials and the longest correctly recited digit sequence. The UDSNB 3.0 uses the Number span test forward and backward, instead of the WMS-R Digit Span. The Number span test helps to reduce practice effects, by using randomly generated number series. The number span score is based on the longest list recalled.

Verbal Fluency

Both semantic and phonemic fluency are measured. Word fluency is measured by asking participants to generate a list of words based on a provided semantic category. Scores are based on the time of correct words generated in 60 seconds. While the score is not negative impacted

by errors, note is made of errors and rule violations. UDSNB 1.0 and 2.0 included one semantic category (animals), and a second category (vegetables) was added for the UDSNB 3.0). For phonemic fluency or letter fluency participants are asked to generate words that start with a given letter. Again, scores are based on the number of correct words generate in 60 seconds and note is made of errors and rule violations. Phonemic fluency was not included in the UDSNB 2.0, although was added to the UDSNB 3.0. A letter generation tasks was added ("F" and "L") for UDSNB 3.0. Unfortunately, this measure was not added until the UDSNB 3.0 and the majority of the subjects of the current study received the UDSNB 1.0 and 2.0, which did not include a measure of phonemic fluency.

Confrontation Naming

The Boston Naming Test (BNT) was used in the UDSNB 1.0 and 2.0 (Kaplan, Goodglass, & Weintraub, 1983), while the MINT (Multilingual Naming Test) (Gollan, Runnqvist, Montoya, Cera, 2012; Ivanova, Salmon, & Gollan, 2013) replaced the BNT for the UDSNB 3.0. The BNT and the MINT were used to test confrontation naming, a measure of semantic language skills. Participants are asked to name simple line drawing of objects that are individually presented for 20 seconds. In an attempt to save time, a short version of the BNT (the 30-odd numbered items) was constructed. The administration of this short version BNT adheres to the standard full BNT in all ways, aside from the 6 consecutive failures discontinue rule. The score consists of the total number of line drawings that are named correctly, plus the number of items named correctly with a semantic cue. The MINT consists of 32 items, and was developed to be used with individuals who are multilingual or monolingual in several languages including English, Spanish, Hebrew, and Mandarin Chinese. The use of the MINT in an improvement, as the BNT was developed for

monolingual English speakers and was not designed to asses naming skills in monolinguals of other languages or multilinguals.

Processing Speed

The trail making tests were retained from the UDSNB 2.0 to measure processing speed (part A) and executive function (part B) (Reitan & Wolfson, 1993). Part A of the Trail making test requires the participants to draw a line connecting numbers in sequence, as quickly as possible. Trail making test part A is used to measure processing speed, and is scored by recording the time it takes the participant to complete the task. Errors are corrected in real time, and as a result, when errors are committed, the completion time is inherently prolonged, resulting in a lower score, i.e., increased time to complete the test. Additionally, the number and type of errors are recorded, but are not used as a separate score to judge performance (Reitan & Wolfson, 1995). The UDSNB 1.0 and 2.0 also included the Digit Symbol Coding from the WAIS-R as an additional measure of processing speed. Digit Symbol Coding was administered in accordance with the instructions contained in the WAIS-R administration manual and scored by totaling the number of items completed correctly in 90 seconds (Wechsler, 1987a). This test was removed from the UDSNB for the 3rd version and not substituted or replaced with another measure of processing speed. As a result, the WAIS-R was not included in the current study, due to high levels of missing data at assessment time point 4, with no alternative test available for substitution.

Executive Functioning

Part B of the Trail Making Test is a more complex task that requires set shifting, an aspect of executive functioning. In part B, participants much sequence both numbers and letters, alternating back and forth between numbers and letters (i.e. 1-A-2-B-3-C…) (Reitan & Wolfson,

1995). Scoring and administration procedures are similar to those described for Trail Making Test part A.

Procedures

NACC Database

The National Alzheimer's Coordinating Center (NACC) database was created in 1999 in the United States for the purpose of supporting collaborative research in AD and is considered one of the largest and most comprehensive databases of its type. There have been several iterations of the database since its creation, but in its most recent form, the Uniform Data Set (UDS) was implemented in 2005 as a way of collecting standardized, longitudinal data on individuals with AD and other degenerative diseases. The newest version of the UDS 3.0 (version 3) was implemented in March of 2015 and includes prospective and longitudinal clinical data for over 39,400 subjects (as of December 2018). The data is available to both Alzheimer's Disease Center (ADC) and non-ADC researchers and has resulted in more than 600 publications to date (as of December 2018). The dataset also includes neuropathology data for more than 16,600 subjects, which contains autopsy data for 5,500 subjects that had been followed longitudinally in the UDS. The NACC UDS is able to offer such a large sample size due to the collaboration between centers. However, each center determines the methods used to enroll subjects. Some common ways in which subjects come to be involved include clinician referral, self-referral by patients or family members, active recruitment through community organizations, and volunteers who wish to contribute to research on various types of dementia. Volunteers, with normal cognition, are also enrolled at most centers and these individuals tend to be highly educated. As a result, NACC subjects are not a statistically based sample of the U.S. population with or without dementia and are therefore the database is not well suited for making

determinations regarding prevalence or incidence of AD. Instead, they are considered a referral-based or volunteer case series. By whichever means the subjects come to the study, they are enrolled on a volunteer basis and written informed consent is obtained from all participants and their co-participant (usually a spouse, close friend or family member who provides informant or collateral reporting on the status of the participant). The cognitive status of participants ranges from normal to demented and may change over the course of their participation in the study.

The UDS dataset of the NACC database consists of longitudinal data that is collected annually (on average) using a standardized evaluation for subjects enrolled in the ADC. Data is collected from subjects and their co-participants by trained clinicians and/or clinic personnel. Diagnoses are made one of two ways, either by a consensus team or by the physician who conducted the examination. The primary focus of the ADC's is Alzheimer's disease, however, data collection includes a variety of other degenerative disorders, such as vascular dementia, Lewy body dementia, and frontotemporal lobar degeneration. Data is collected during in-person office visits for some tests like the neuropsychological tests, but home visits and telephone calls are also used for collection of other data. Subject death and drop-out are documented using milestone forms. The topics included in the Uniform Data Set include socio-demographics on subject and co-participant, family history, dementia history, neurological exam findings, functional status, neuropsychological test results, clinical diagnosis, neuroimaging when available, and APOE genotyping.

Database

Participants were selected for the current study from the NACC database based on specific inclusion and exclusion criteria previously described. Once selection criteria were applied, the participants data was examined for completeness. In some instances, individuals

received different versions of the UDSND over the course of their participation in the study (i.e. visits 1, 2, and 3 they received UDSND 2.0 and visit 4 they received UDSNB 3.0). In these cases, the NACC conversion tables were used to convert the scores of the UDSNB 3.0 to be comparable to the UDSNB 2.0 (Monsell et al., 2016). Once this process was completed, cases with incomplete data were removed. Raw scores were then transformed to standardized scores (z-scores) using the means and standard deviation at each time point for the entire sample (controls and converters). The z-score means and standard deviations for both groups on each test and at each time point are presented in Table 2 and Table 3. The raw scores means and standard deviations for both groups on each test and at each time point also presented in Table 4 and Table 5.

Table 2. *Z-score overall mean and standard deviations (SD) at each time point of the 9 cognitive domains included in the network analysis for Both Control and Converter Group.*

Variable	Time 1		Time 2		Time 3		Time 4		Time C	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
MMSE - Control	0.25	0.77	0.16	0.87	0.13	0.89	0.16	0.93	0.14	0.89
MMSE- Converter	-0.27	1.12	-0.31	1.13	-0.84	1.15	-0.84	1.15	-0.56	1.16
LMI - Controls	0.06	0.97	0.13	0.95	0.26	0.98	0.35	1.01	0.26	0.96
LMI - Converter	-0.27	0.97	-0.59	1.07	-0.69	1.11	-0.69	1.11	-0.82	1.12
LMII- Controls	0.13	0.93	0.21	0.92	0.33	0.99	0.44	1.02	0.33	0.99
LMII - Converter	-0.34	0.96	-0.39	0.99	-1.06	0.93	-1.06	0.93	-0.73	0.98
DF- Controls	0.10	0.94	0.09	0.91	0.18	0.92	0.11	0.91	0.14	0.89
DF - Converter	-0.09	1.01	-0.08	1.03	-0.69	1.01	-0.69	1.01	-0.29	1.04
DB- Controls	0.13	0.97	0.12	1.01	0.17	0.99	0.24	0.97	0.21	0.98
DB - Converter	-0.16	0.99	-0.14	0.96	-0.78	0.94	-0.78	0.94	-0.39	0.99
Cat Fluency- Controls	0.23	1.16	0.32	1.19	0.24	1.20	0.21	1.19	0.26	1.09
Cat Fluency - Converter	-0.26	0.92	-0.80	1.60	-0.80	0.84	-0.80	0.84	-0.72	1.11
Trails A- Controls	0.17	0.94	0.27	0.86	0.35	0.84	0.28	0.96	0.27	0.94
Trails A - Converter	0.14	1.09	0.18	1.12	0.85	1.14	0.85	1.14	0.39	1.20
Trails B- Controls	0.19	0.90	0.26	0.93	0.30	0.84	0.27	1.01	0.28	0.93
Trails B - Converter	0.20	1.08	0.24	1.08	1.02	1.14	1.02	1.14	0.59	1.24
Boston Naming- Controls	0.20	0.88	0.30	0.87	0.34	0.91	0.31	0.97	0.31	0.92
Boston Naming - Converter	-0.22	1.12	-0.26	1.11	-0.87	1.13	-0.87	1.13	-0.47	1.18

Table 3. *Raw Score overall mean and standard deviations (SD) at each time point of the 9 cognitive domains included in the network analysis for Control Group.*

Variable	Time 1		Time 2		Time 3		Time 4		Time C	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
MMSE - Control	29.24	1.03	29.09	1.16	29.02	1.19	29.03	1.25	29.03	1.18
MMSE- Converter	28.51	1.48	28.09	1.83	27.74	2.10	27.25	2.40	27.60	2.02
LMI - Controls	14.02	3.79	14.25	3.74	14.70	3.87	15.04	3.96	14.71	3.78
LMI - Converter	11.88	3.86	11.44	4.17	10.98	4.32	10.30	4.59	10.50	4.37
LMII- Controls	12.97	3.95	13.34	3.93	13.85	4.27	14.28	4.36	13.84	4.22
LMII - Converter	10.10	4.10	9.71	4.57	9.06	4.74	8.25	5.10	8.55	4.74
DF- Controls	8.73	1.95	8.69	1.88	8.85	1.89	8.68	1.86	8.76	1.84
DF - Converter	8.38	1.98	8.38	1.99	8.15	1.99	8.10	1.99	8.17	1.98
DB- Controls	7.09	2.12	7.04	2.21	7.11	2.16	7.25	2.13	7.20	2.14
DB - Converter	6.41	2.13	6.42	2.09	6.19	2.00	6.04	2.03	6.16	2.02
Cat Fluency- Controls	17.54	4.30	17.81	4.39	17.58	4.51	17.45	4.29	17.54	4.06
Cat Fluency - Converter	15.48	3.91	14.88	3.96	14.26	3.75	13.41	3.79	13.95	3.67
Trails A- Controls	34.33	13.94	33.53	12.89	33.02	12.75	34.63	14.91	34.26	14.34
Trails A - Converter	38.89	17.29	39.21	17.48	41.02	19.03	43.46	23.25	41.14	19.09
Trails B- Controls	87.86	43.49	86.63	45.23	86.74	41.84	89.82	49.24	88.06	45.89
Trails B - Converter	107.71	53.40	112.62	57.80	126.93	69.37	141.34	79.47	132.04	71.85
Boston Naming- Controls	27.60	2.83	27.86	2.79	27.90	2.95	27.77	3.13	27.79	2.97
Boston Naming - Converter	26.09	3.91	26.08	3.86	25.77	4.34	25.26	4.61	25.57	4.33

Data Analysis

The cognitive domains were represented by the neurocognitve test scores known to assess specific cognitive domains affected by Alzheimer's Disease. Cross sectional analyses were conducted to examine the network structures of neurocognitve test scores for both the healthy Control group and the clinical group at the time one, when both were still considered cognitively

normal. In other words, before the clinical group met criteria for a cognitive diagnosis. The networks were then estimated at each time point (Time 1- Time 4) as well as the time point at which the members of the Converter group first met criteria for a cognitive diagnosis (i.e. MCI or Dementia). Finally, the Converter group was subdivided by sex and the networks for men and women were estimated.

Network Estimation

Network analyses of the cognitive domains affected by AD were conducted using the R-Package *qgraph* in Rstudio. *Qgraph* allows for the estimation and visualization of the networks examined. Gaussian Graphical Model (GGM) was used to estimate the regularized partial correlation networks for each group at each time point. The graphical lasso (GLASSO) algorithm was used to control for spurious correlations, which can occur with multiple testing (Friedman Hastie, & Tibshirani, 2008). This procedure produces a sparse network structure with nodes connected by edges that represent conditional dependence relations. In other words, the edges between nodes represent the nodes that remain associated, after controlling for all other nodes in the network. The results of these procedures are visualized as a graph with nodes connected by edges. The edges are shown in green if the association between nodes is positive and red if the associations between nodes are negative. The overall strength of each network was used to calculate the Global Strength of the network. The global strength is the sum of the absolute value of all edges in the network (van Borkulo et al., 2015).

The following networks analyses were performed for the converter and Control groups: 1) Networks were estimated for the initial assessment (Time 1) for both the converters and the Control groups; 2) The networks for each of the four time points were also estimated to examine temporal stability of the network; 3) The network was also estimated for the time point at which

individuals in the Converter group first met criteria for a cognitive diagnosis (MCI or Dementia). Because each participant in the Converter group was demographically matched to a participant in the Control group, the corresponding time point for the matched control participant was also selected and the network was estimated for this matched group of controls. In other words, if an individual in the Converter group met criteria for MCI at time 3, then assessment results for their matched control at time point 3 were included in the Control group database for this network analysis.

In addition to comparing the converter and Control groups, the individuals in the Converter group were subdivided by sex and the networks were estimated for men and women at each time point (Time 1- Time 4 and Time C). Thus, a total of 5 networks analyses were performed for the men from the Converter group and 5 networks analyses were performed for the women from the Converter group that included: 1) Networks were estimated for the initial assessment (Time 1) for both the men from the Converter group and the women from the Converter group; 2) Networks were estimated for each follow-up time point (Time 2- Time 4) for both the men from the Converter group and the women from the Converter group; and 3) The network time at which the participants first met criteria for a cognitive diagnosis was also estimated for both the men from the Converter group and the women from the Converter group.

Network Inference

To provide more insight into the impact of items on the network structures, several centrality analyses were performed. Based on the methods used by previous studies employing Network Analysis, the centrality indices calculated included, strength, betweenness, closeness, and expected influence (Opsahl, Agneessens, & Skvoretz, 2010; Robinaugh, Millner, & McNally, 2016). Strength (*r*) is a measure of node strength and provides information about each

node's relative strength and indicates which of the nodes has the strongest connections with all other nodes. This is calculated by summing the absolute values of all of the edge weights that are connected to the node in question. Betweenness indicates the frequency of a node being on the shortest path between all pairs of nodes in a network. Closeness is a measure of the average length between all other nodes. Closeness is calculated by summing the inverse of the distance between one node and all other nodes. Very commonly, researchers use only these three centrality indices when examining their networks, however strength, betweenness, and closeness do not distinguish between positive and negative edges, and therefore may not adequately account for the nature and strength of the influence a specific node has within the network. For this reason, we chose to include the less commonly used measure of expected influence. Expected influence provides information about the nature and strength of the node's cumulative influence within the network, taking into account positive and negative relationships. This provides insight into the role each node is expected to play in the activation, persistence, and remission of the network (Robinaugh et al., 2016).

Next, analyses were performed to estimate the accuracy of the centrality indices. The R package *bootnet* was used for this process. *Bootnet* utilizes a case-dropping subset bootstrapping approach that outputs the number of participants from the dataset or cases that could potentially be dropped from the dataset before causing the network to become unstable. *Bootnet* also estimates the correlation stability coefficient which ranges from 0-1. Values of 0.25 - .49 indicate moderate stability, while values above 0.5 indicate strong stability. We then used *bootnet* to estimate the accuracy of edge-weights. This is done by calculating bootstrapped 95% confidence intervals (CIs) around each of edge weights. Smaller CIs indicate the estimation of the edges is more accurate. We then tested for significant differences between all edge-weights and all

centrality indices. Each time drawing 1000 bootstraps. It is important to consider, however, that the edge weights difference test and centrality difference test do not control for multiple testing. To date, there is unfortunately no method available for examining these aspects of the network that does control for multiple testing.

Network Comparison Test

To date, a method for comparing the stability of more than two networks is not available. As a result, comparisons were performed to assess the difference in stability of the network structures between the groups at different stages of the disease process. Converters and Controls were compared at times 1, 2, 3, 4, and C. Also, men from the Converter group were compared to women from the Converter group at times 1, 2, 3, 4, and C. The temporal stability of the network structures of the Converters group was assessed by comparing each time point to all other time-points (i.e. Converters time 1 vs. Converters time 2, and Converters time 1 vs. Converters time 3, etc.). To make these comparisons the R package *NetworkComparisonTest* was used (van Borkulo, 2016; van Borkulo et al., 2017). Specifically, the global strength invariance test was used, which assess if the overall level of connectivity is equal across networks. The overall connectivity is the weighted absolute sum of all edges in the network (Opsahl et al., 2010). The results of the network comparison tests are presented as a *p*-value, with alpha level of < 0.05 indicating significant difference in global strength invariance between the networks (van Borkulo et al., 2017). When the global strength invariance test is significant, it suggests that the networks being compared are different from each other. We also calculated maximum difference in edge weights which is a measure of difference in the overall structure of the networks. Finally, a Centrality Difference Test was performed. Centrality Difference Test was performed to evaluate the differences between the various centrality indices for the networks being compared.

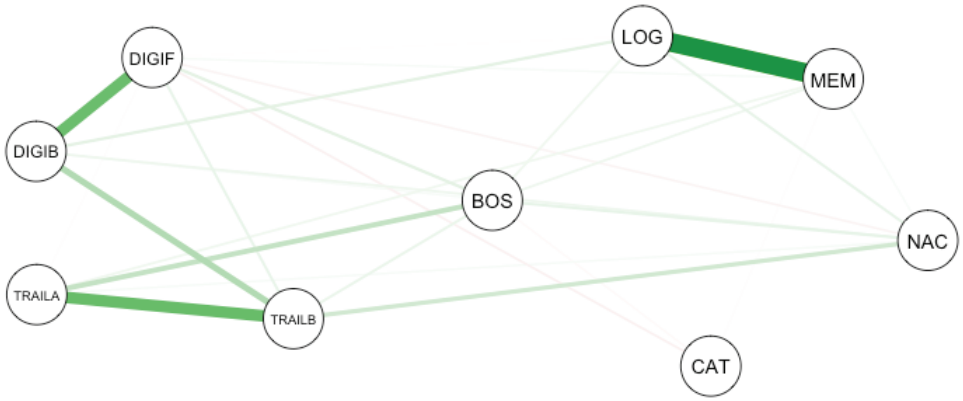
Chapter 4: Results

Network Structure

The control and Converter group estimated networks for the 9 cognitive tests are presented in Figures 1 - 10. Figures 1 – 4 represent the estimated networks for the Control group at each time point (Time 1-4). Figure 5 represents the estimated network for Control group participants who were selected to match the Converter group at Time C (the time point at which each converter first met criteria for a cognitive diagnosis of either MCI or Dementia due to Alzheimer's disease). Figures 6 – 9 represent the estimated networks for the Converter group at each time point and Figure 10 presents the network for the time point at which each participant in the Converter group first met criteria for a cognitive diagnosis of either MCI or Dementia due to Alzheimer's disease.

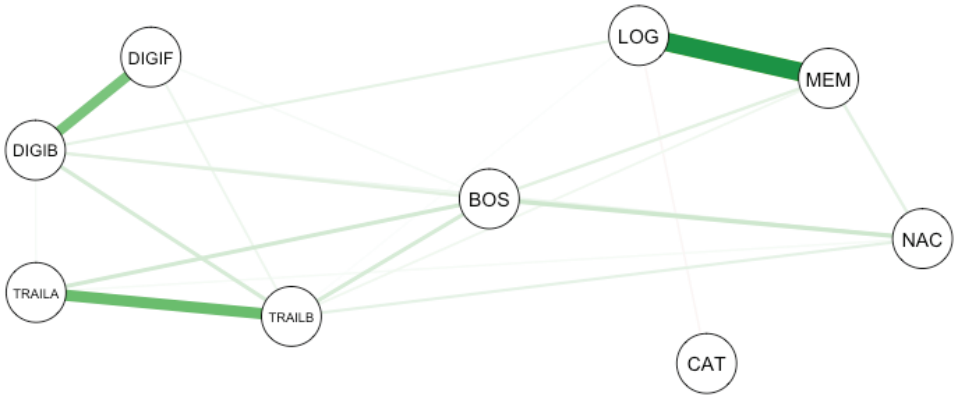
As can be seen from the Figures 1 – 10, across all the time points both the Control and Converter groups evidence strong positive connections (an edge weight > 0.4, is "Strong", > 0.1 is "Moderate", and < 0.1 is "Weak") between Logical Memory I (LOG) and Logical Memory II (MEM) at all time points (Controls: T1 = 0.80, T2 = 0.82, T3 = 0.83, T4 = 0.83, TC = 0.81; Converter: T1 = 0.78, T2 = 0.80, T3 = 0.84, T4 = 0.81, TC = 0.76). There were also strong positive connections between Trails A and Trails B, both the Control and Converter groups, at all time points (Controls: T1 = 0.47, T2 = 0.47, T3 = 0.56, T4 = 0.43, TC = 0.43; Converter: T1 = 0.54, T2 = 0.51, T3 = 0.53, T4 = 0.46, TC = 0.49). At several time points, strong positive connections were present between Digits Span Forward (DIGIF) and Digits Span Backward (DIGIB) (Controls: T1 = 0.45, T2 = 0.41, T3 = 0.50, T4 = 0.45; Converters: T3 = 0.47, T4 = 0.43).

Figure 2. *Network Analysis for Controls Time 1*



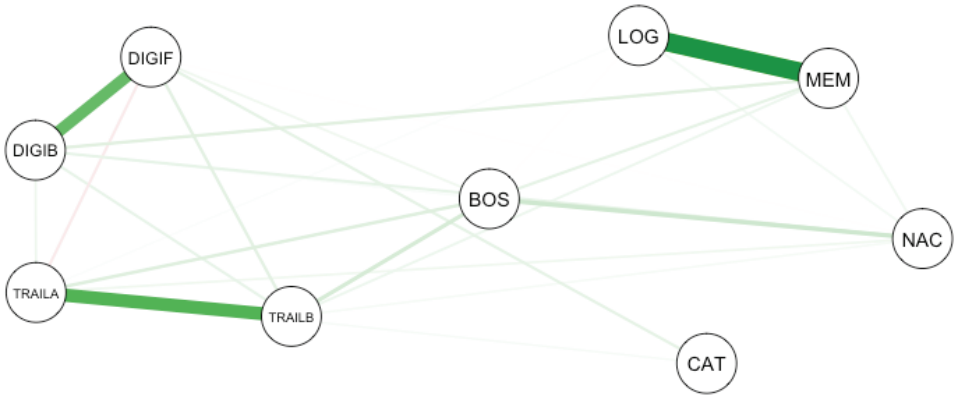
Note: BOS = Boston Naming Test, CAT = Category Fluency, DIGIF = Digit Span Forward, DIGIB = Digit Span Backward, LOG = Logical Memory I, MEM = Logical Memory II, NAC = Mini Mental Status Exam, TRAILA = Trails A, TRAILB = Trails B

Figure 3. *Network Analysis for Controls Time 2*



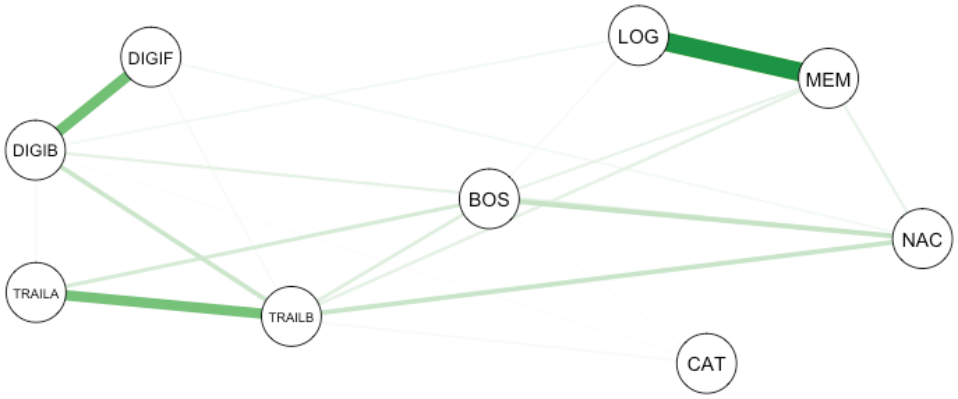
Note: BOS = Boston Naming Test, CAT = Category Fluency, DIGIF = Digit Span Forward, DIGIB = Digit Span Backward, LOG = Logical Memory I, MEM = Logical Memory II, NAC = Mini Mental Status Exam, TRAILA = Trails A, TRAILB = Trails B

Figure 4. *Network Analysis for Controls Time 3*



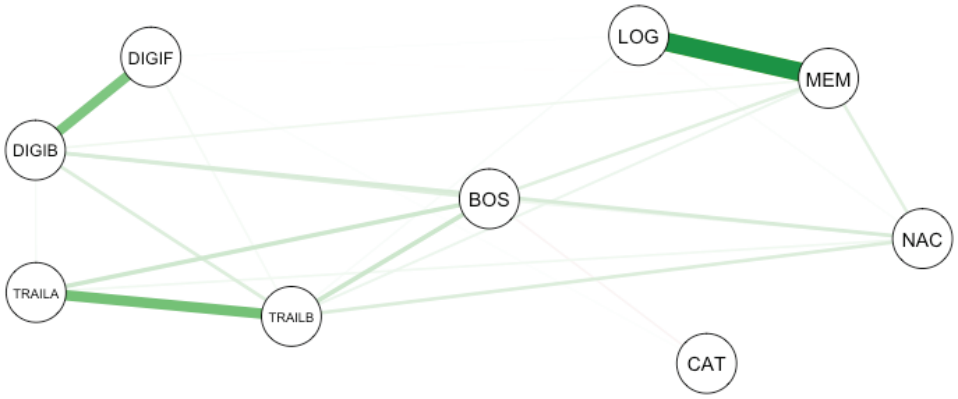
Note: BOS = Boston Naming Test, CAT = Category Fluency, DIGIF = Digit Span Forward, DIGIB = Digit Span Backward, LOG = Logical Memory I, MEM = Logical Memory II, NAC = Mini Mental Status Exam, TRAILA = Trails A, TRAILB = Trails B

Figure 5. *Network Analysis for Controls Time 4*



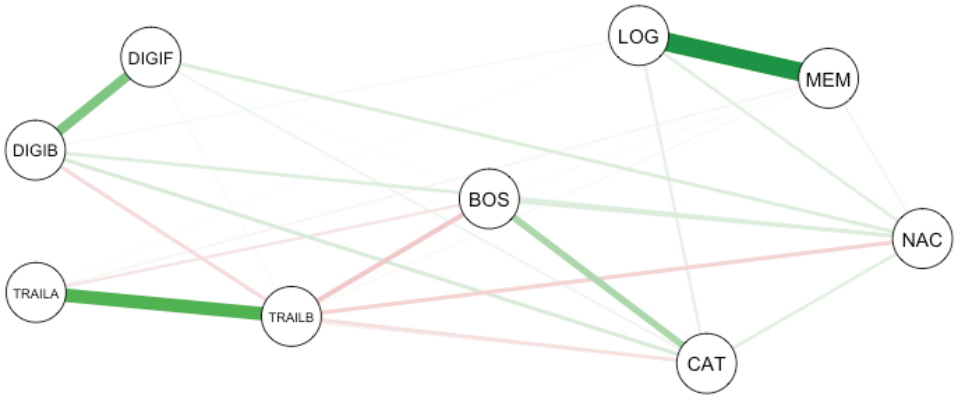
Note: BOS = Boston Naming Test, CAT = Category Fluency, DIGIF = Digit Span Forward, DIGIB = Digit Span Backward, LOG = Logical Memory I, MEM = Logical Memory II, NAC = Mini Mental Status Exam, TRAILA = Trails A, TRAILB = Trails B

Figure 6. *Network Analysis for Controls at the Time of Conversion to MCI or Dementia for matched converters.*



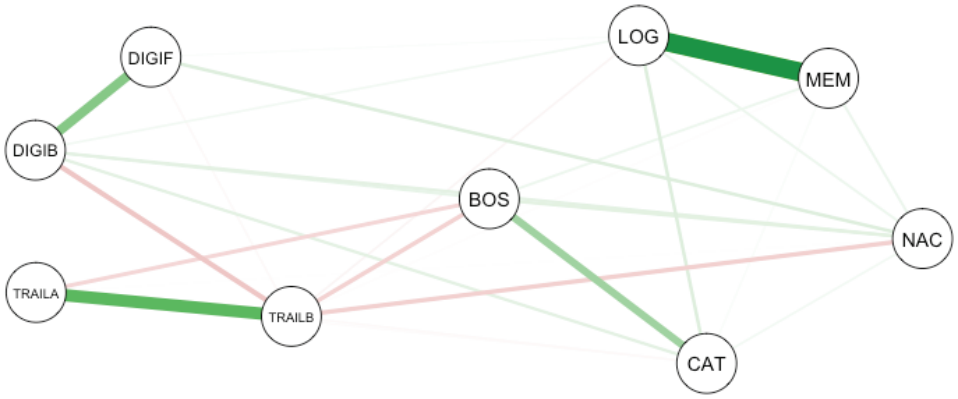
Note: BOS = Boston Naming Test, CAT = Category Fluency, DIGIF = Digit Span Forward, DIGIB = Digit Span Backward, LOG = Logical Memory I, MEM = Logical Memory II, NAC = Mini Mental Status Exam, TRAILA = Trails A, TRAILB = Trails B

Figure 7. *Network Analysis for Converters Time 1*



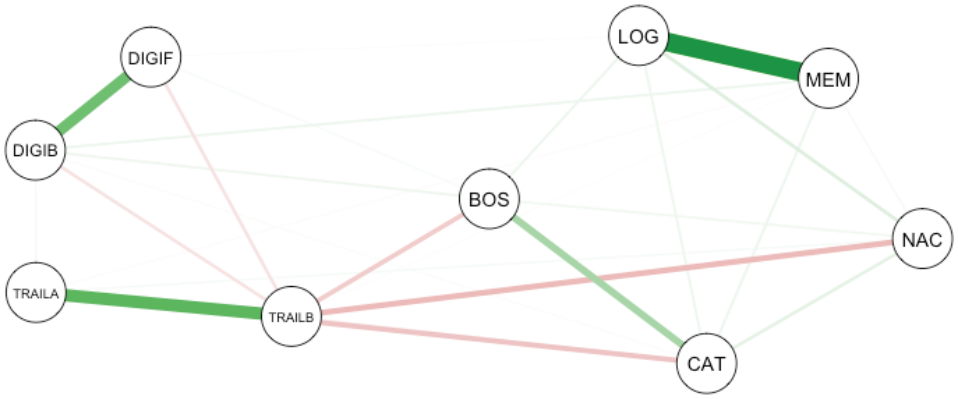
Note: BOS = Boston Naming Test, CAT = Category Fluency, DIGIF = Digit Span Forward, DIGIB = Digit Span Backward, LOG = Logical Memory I, MEM = Logical Memory II, NAC = Mini Mental Status Exam, TRAILA = Trails A, TRAILB = Trails B

Figure 8. *Network Analysis for Converters Time 2*



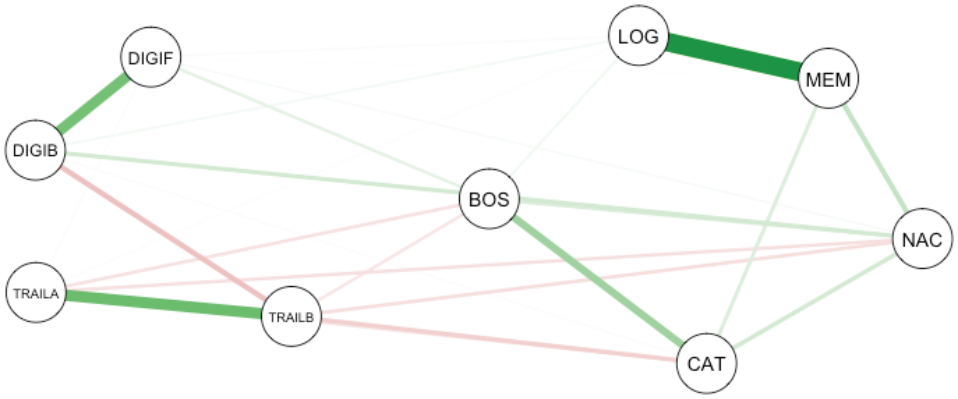
Note: BOS = Boston Naming Test, CAT = Category Fluency, DIGIF = Digit Span Forward, DIGIB = Digit Span Backward, LOG = Logical Memory I, MEM = Logical Memory II, NAC = Mini Mental Status Exam, TRAILA = Trails A, TRAILB = Trails B

Figure 9. *Network Analysis for Converters Time 3*



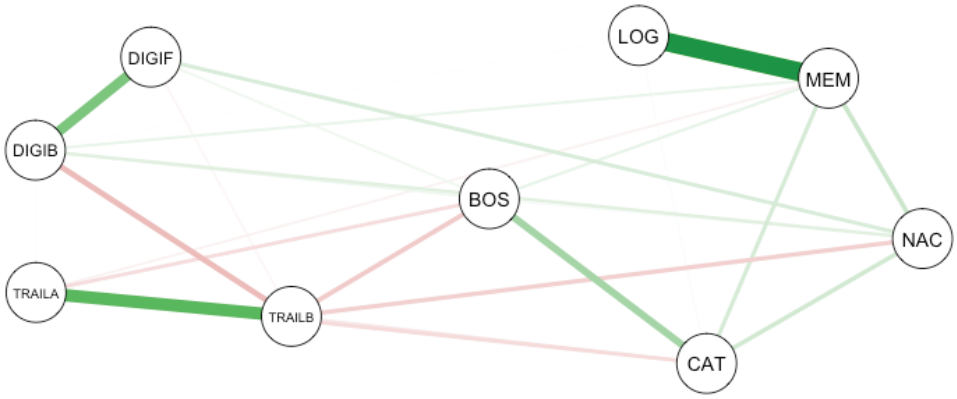
Note: BOS = Boston Naming Test, CAT = Category Fluency, DIGIF = Digit Span Forward, DIGIB = Digit Span Backward, LOG = Logical Memory I, MEM = Logical Memory II, NAC = Mini Mental Status Exam, TRAILA = Trails A, TRAILB = Trails B

Figure 10. *Network Analysis for Converters Time 4*



Note: BOS = Boston Naming Test, CAT = Category Fluency, DIGIF = Digit Span Forward, DIGIB = Digit Span Backward, LOG = Logical Memory I, MEM = Logical Memory II, NAC = Mini Mental Status Exam, TRAILA = Trails A, TRAILB = Trails B

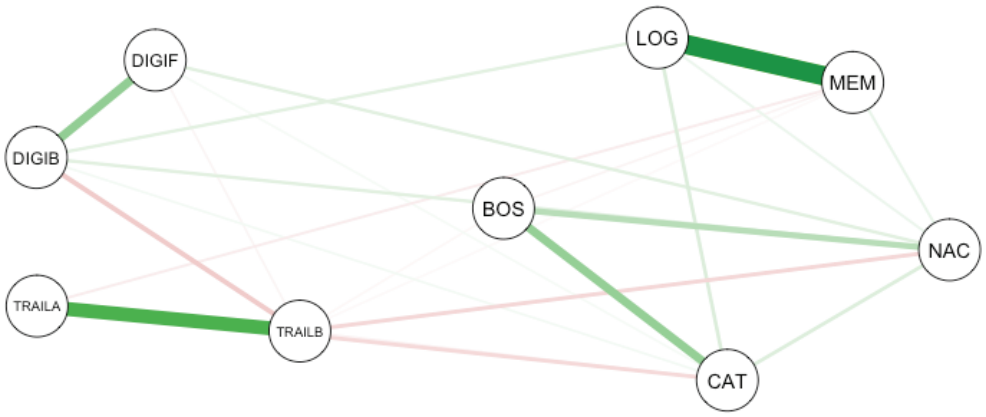
Figure 11. *Network Analysis for Converters at the Time of Conversion to MCI or Dementia.*



Note: BOS = Boston Naming Test, CAT = Category Fluency, DIGIF = Digit Span Forward, DIGIB = Digit Span Backward, LOG = Logical Memory I, MEM = Logical Memory II, NAC = Mini Mental Status Exam, TRAILA = Trails A, TRAILB = Trails B

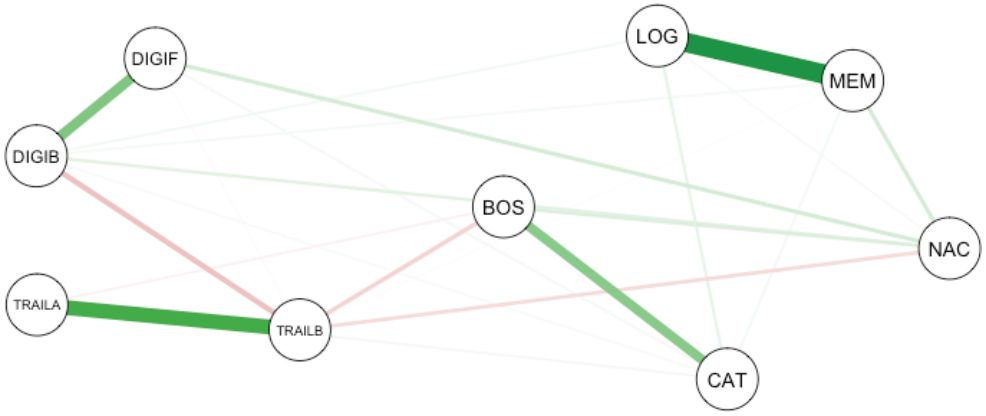
Figures 11 – 20 present the estimated networks for the Converter group when subdivided into male and female groups. Figures 11 – 15 are for males and 16 – 20 are for females. When the Converter group was subdivided by sex, similar trends were observed. For both men and women, there were strong positive connections between Logical Memory I (LOG) and Logical Memory II (MEM) at all time points (Men: T1 = 0.75, T2 = 0.78, T3 = 0.82, T4 = 0.78, TC = 0.76; Women: T1 = 0.80, T2 = 0.80, T3 = 0.82, T4 = 0.77, TC = 0.73). There are also strong positive connections between Trails A and Trails B, groups from the Converter group, at all time points (Men: T1 = 0.53, T2 = 0.58, T3 = 0.53, T4 = 0.46, TC = 0.47; Women: T1 = 0.52, T2 = 0.43, T3 = 0.53, T4 = 0.43, TC = 0.48). Strong positive connections were also present between Digits Span Forward (DIGIF) and Digits Span Backward (DIGIB) at several time points (Men: T3 = 0.42; Women: T1 = 0.42, T4 = 0.42, T = 0.40).

Figure 12. *Network Analysis for Men in the Converters Group at the Time 1*



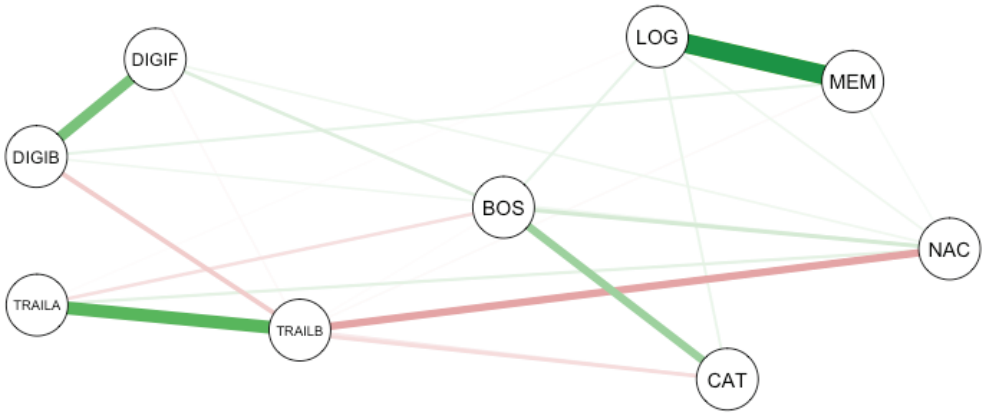
Note: BOS = Boston Naming Test, CAT = Category Fluency, DIGIF = Digit Span Forward, DIGIB = Digit Span Backward, LOG = Logical Memory I, MEM = Logical Memory II, NAC = Mini Mental Status Exam, TRAILA = Trails A, TRAILB = Trails B

Figure 13. *Network Analysis for Men in the Converters Group at the Time 2*



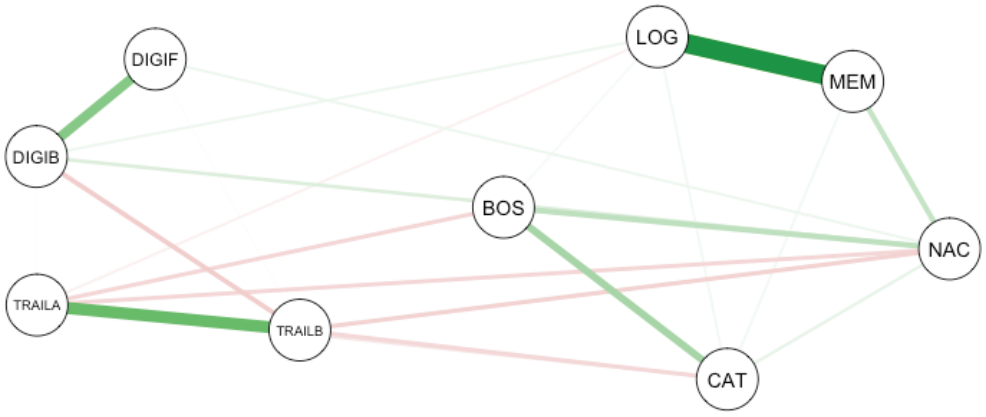
Note: BOS = Boston Naming Test, CAT = Category Fluency, DIGIF = Digit Span Forward, DIGIB = Digit Span Backward, LOG = Logical Memory I, MEM = Logical Memory II, NAC = Mini Mental Status Exam, TRAILA = Trails A, TRAILB = Trails B

Figure 14. *Network Analysis for Men in the Converters Group at the Time 3*



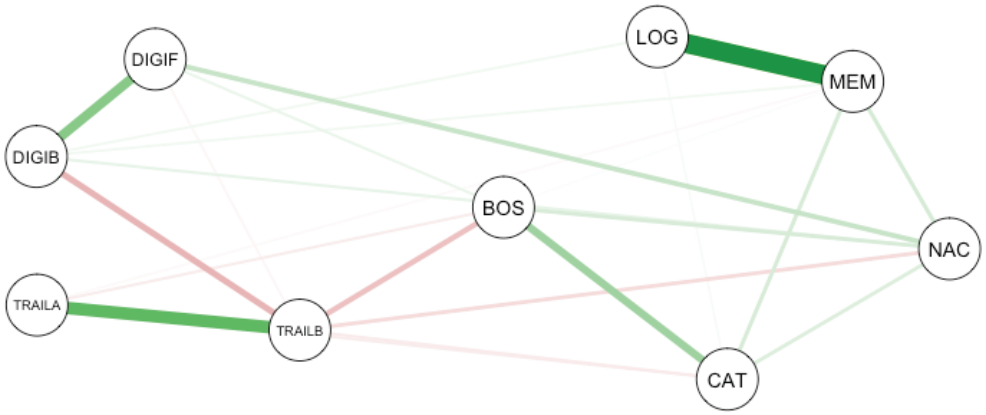
Note: BOS = Boston Naming Test, CAT = Category Fluency, DIGIF = Digit Span Forward, DIGIB = Digit Span Backward, LOG = Logical Memory I, MEM = Logical Memory II, NAC = Mini Mental Status Exam, TRAILA = Trails A, TRAILB = Trails B

Figure 15. *Network Analysis for Men in the Converters Group at the Time 4*



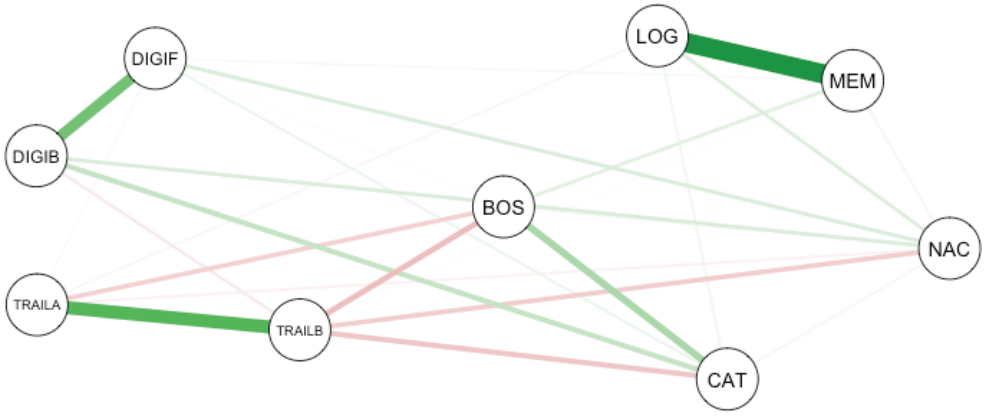
Note: BOS = Boston Naming Test, CAT = Category Fluency, DIGIF = Digit Span Forward, DIGIB = Digit Span Backward, LOG = Logical Memory I, MEM = Logical Memory II, NAC = Mini Mental Status Exam, TRAILA = Trails A, TRAILB = Trails B

Figure 16. . *Network Analysis for Men in the Converters Group at the Time of conversion to MCI or Dementia (Time C).*



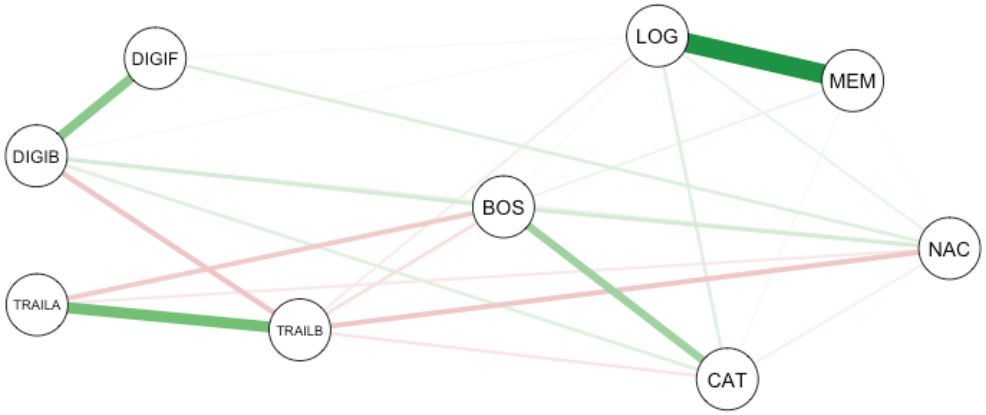
Note: BOS = Boston Naming Test, CAT = Category Fluency, DIGIF = Digit Span Forward, DIGIB = Digit Span Backward, LOG = Logical Memory I, MEM = Logical Memory II, NAC = Mini Mental Status Exam, TRAILA = Trails A, TRAILB = Trails B

Figure 17. *Network Analysis for Women in the Converters Group at the Time 1*



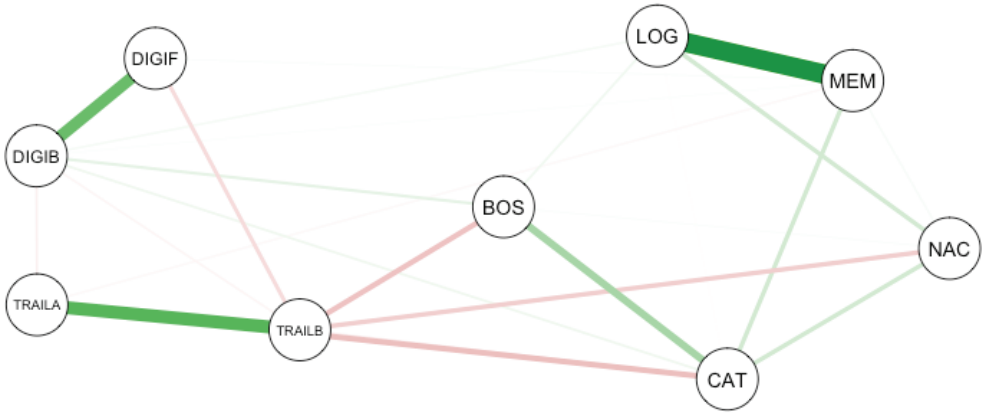
Note: BOS = Boston Naming Test, CAT = Category Fluency, DIGIF = Digit Span Forward, DIGIB = Digit Span Backward, LOG = Logical Memory I, MEM = Logical Memory II, NAC = Mini Mental Status Exam, TRAILA = Trails A, TRAILB = Trails B

Figure 18. *Network Analysis for Women in the Converters Group at the Time 2*



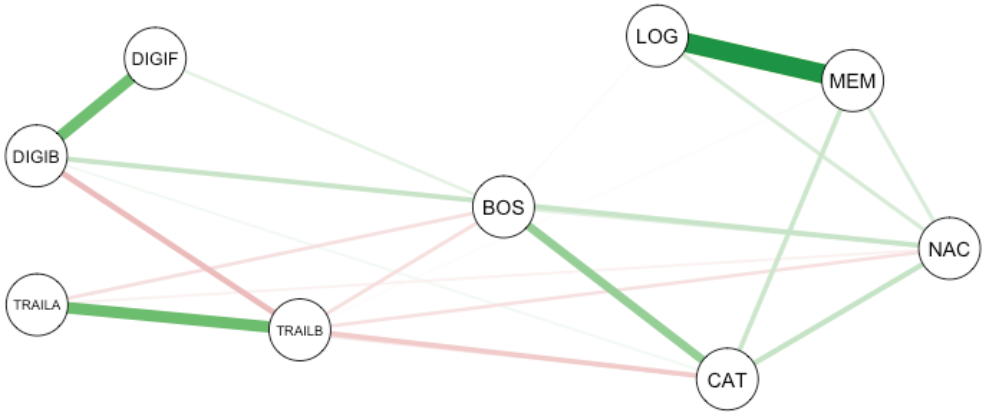
Note: BOS = Boston Naming Test, CAT = Category Fluency, DIGIF = Digit Span Forward, DIGIB = Digit Span Backward, LOG = Logical Memory I, MEM = Logical Memory II, NAC = Mini Mental Status Exam, TRAILA = Trails A, TRAILB = Trails B

Figure 19. *Network Analysis for Women in the Converters Group at the Time 3*



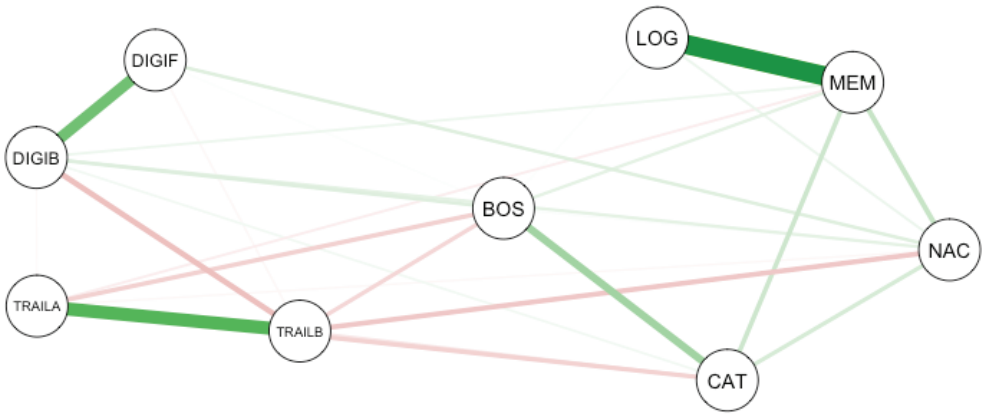
Note: BOS = Boston Naming Test, CAT = Category Fluency, DIGIF = Digit Span Forward, DIGIB = Digit Span Backward, LOG = Logical Memory I, MEM = Logical Memory II, NAC = Mini Mental Status Exam, TRAILA = Trails A, TRAILB = Trails B

Figure 20. *Network Analysis for Women in the Converters Group at the Time 4*



Note: BOS = Boston Naming Test, CAT = Category Fluency, DIGIF = Digit Span Forward, DIGIB = Digit Span Backward, LOG = Logical Memory I, MEM = Logical Memory II, NAC = Mini Mental Status Exam, TRAILA = Trails A, TRAILB = Trails B

Figure 21. *Network Analysis for Women in the Converters Group at the time of conversion to MCI or Dementia (Time C)*



Note: BOS = Boston Naming Test, CAT = Category Fluency, DIGIF = Digit Span Forward, DIGIB = Digit Span Backward, LOG = Logical Memory I, MEM = Logical Memory II, NAC = Mini Mental Status Exam, TRAILA = Trails A, TRAILB = Trails B

Accuracy of the networks was then examine using bootstrapping and the results of these analyses are presented in Figures 21 - 25. Figure 21 contains boot strapping results the correspond to network estimations presented in Figures 1 – 4. Figure 22 contains boot strapping results the correspond to network estimations presented in Figures 6 – 9. Figure 23 contains boot strapping results the correspond to network estimations presented in Figures 11 – 14. Figure 24 contains boot strapping results the correspond to network estimations presented in Figures 15 – 19. Figure 25 contains boot strapping results the correspond to network estimations at the time point C (Figures 5, 10, 15, and 20). In these figures, the sample edge-weights of each edge are indicated with a solid red line, bootstrapped values are indicated by a solid black line, and the 95% confidence intervals around these edge-weights are indicated by gray bars. In these figures,

the X axis represents sample edge weight value of each edge in the network and the y Axis represents each edge in the network (e.g., the first edge listed is the edge between the DIGIFZSCORE and CATFLUENCYZSCORE nodes). Edges are listed in order of edgeweight from lowest to highest. While there is some variability in confidence intervals around the nodes, the bootstrapping results support the accuracy of the networks. As can be seen from the Figure, the gray bars indicate narrow confidence intervals around most nodes. The accuracy of these networks was supported by the bootstrapping graphs shown in Figure 21 – Figure 25.

Figure 22. *Accuracy of the edge-weights (solid red line), bootstrapped value (solid black line) and the 95% confidence intervals around these edge-weights (gray bars) of the networks for Controls at Time 1-4*

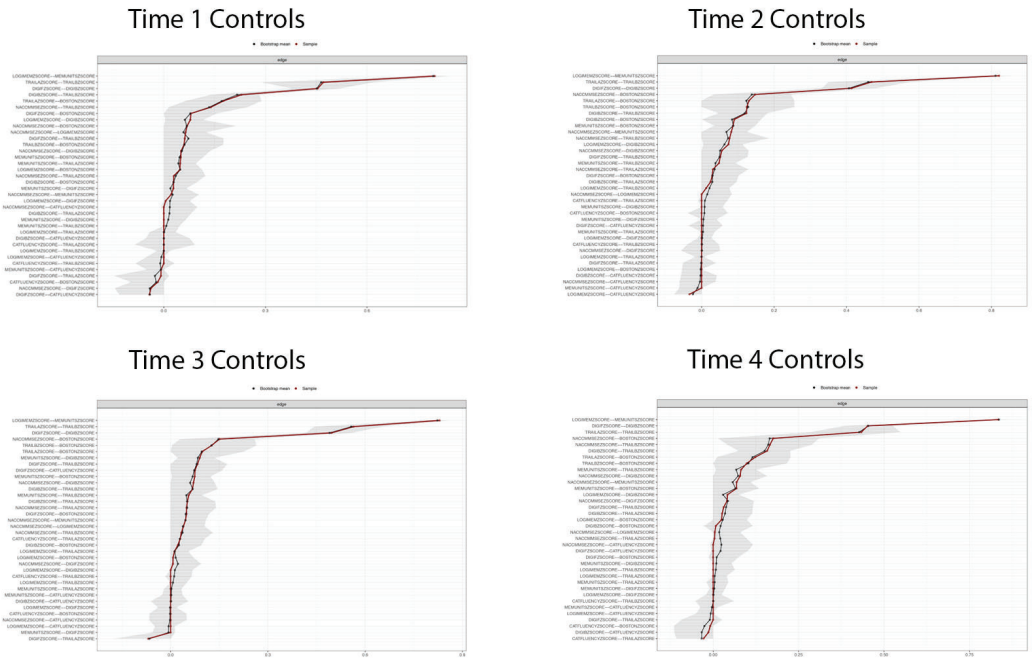


Figure 23. *Accuracy of the edge-weights (solid red line), bootstrapped value (solid black line) and the 95% confidence intervals around these edge-weights (gray bars) of the networks for Converters at Time 1- 4*

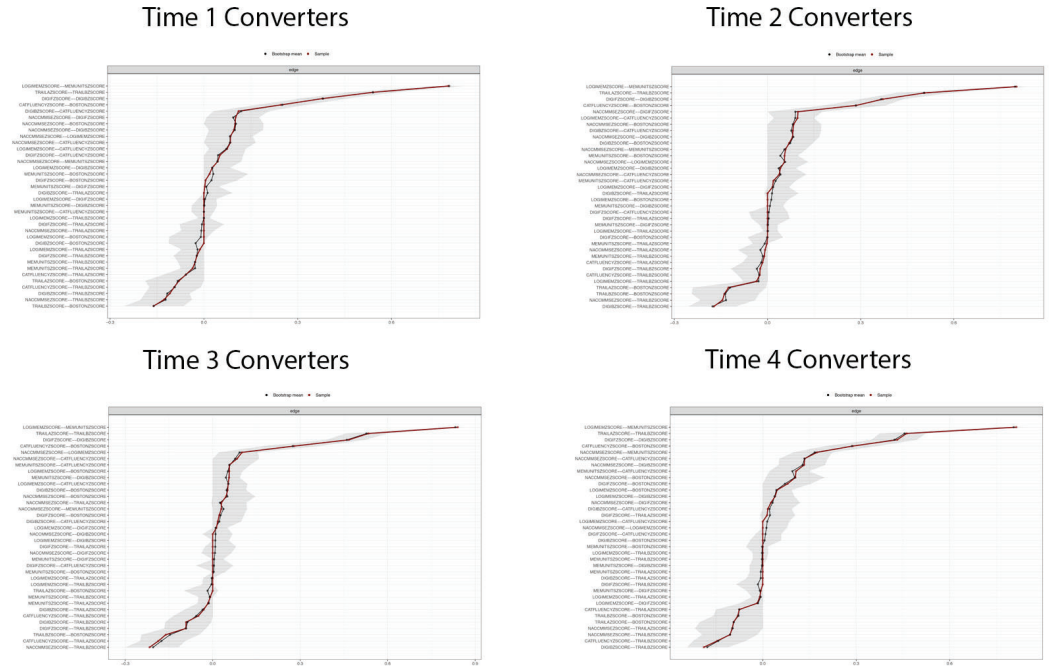


Figure 24. *Accuracy of the edge-weights (solid red line), bootstrapped value (solid black line) and the 95% confidence intervals around these edge-weights (gray bars) of the networks for Men in the Converters group.*

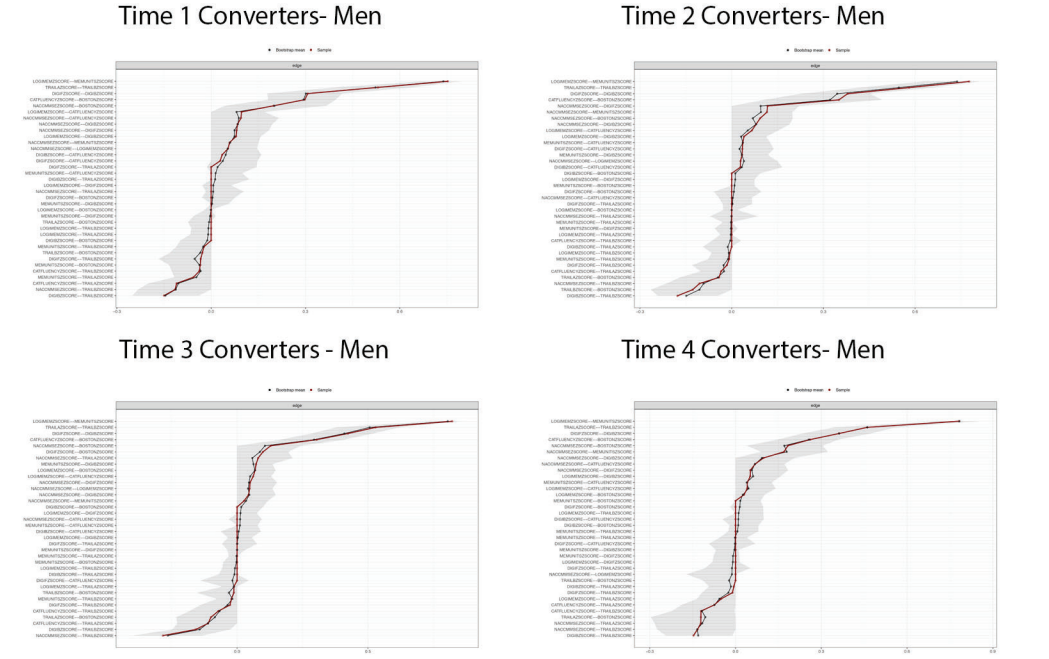


Figure 25. *Accuracy of the edge-weights (solid red line), bootstrapped value (solid black line) and the 95% confidence intervals around these edge-weights (gray bars) of the networks for Women in the Converters group.*

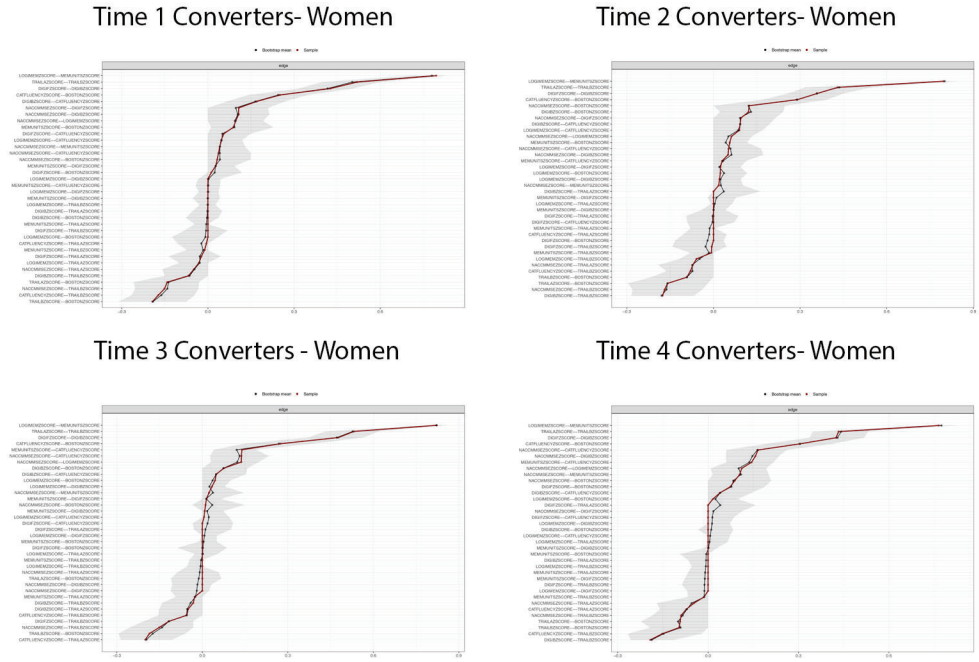
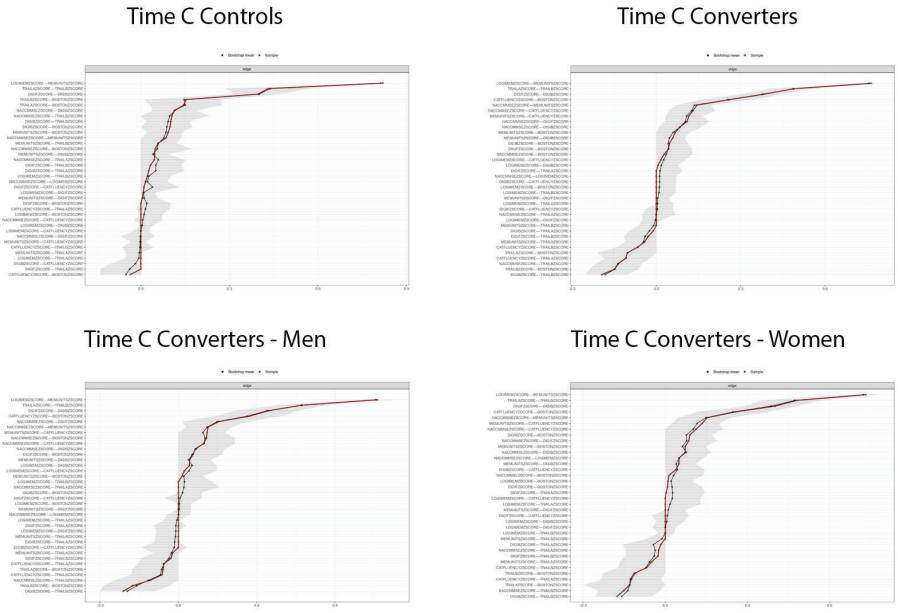
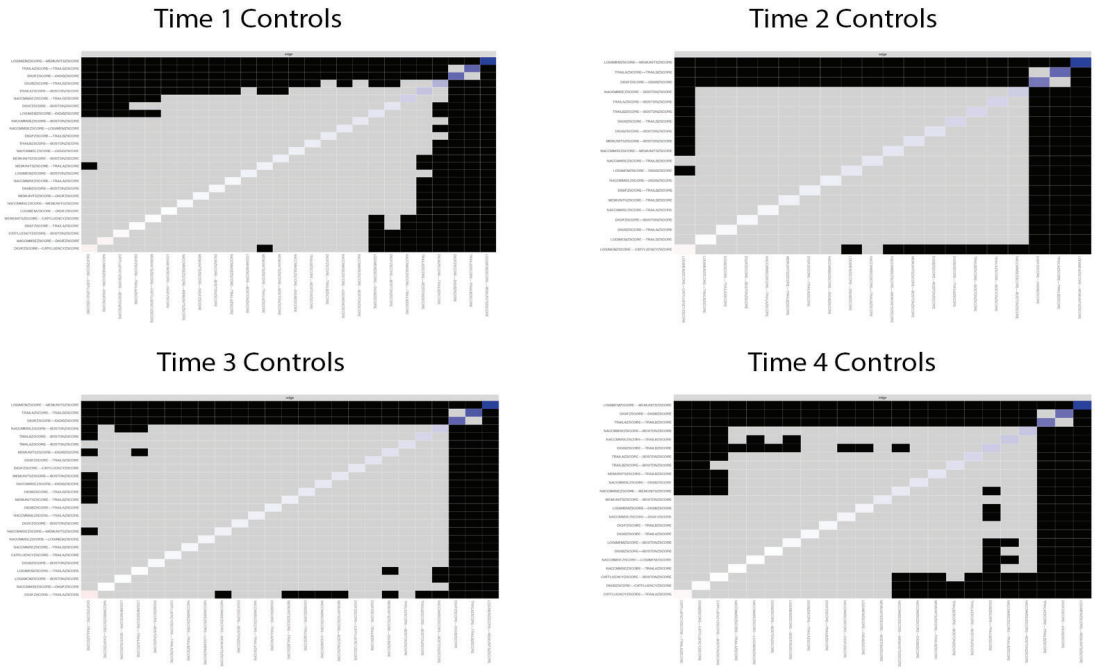


Figure 26. *Accuracy of the edge-weights (solid red line), bootstrapped value (solid black line) and the 95% confidence intervals around these edge-weights (gray bars) of the networks for Time C*



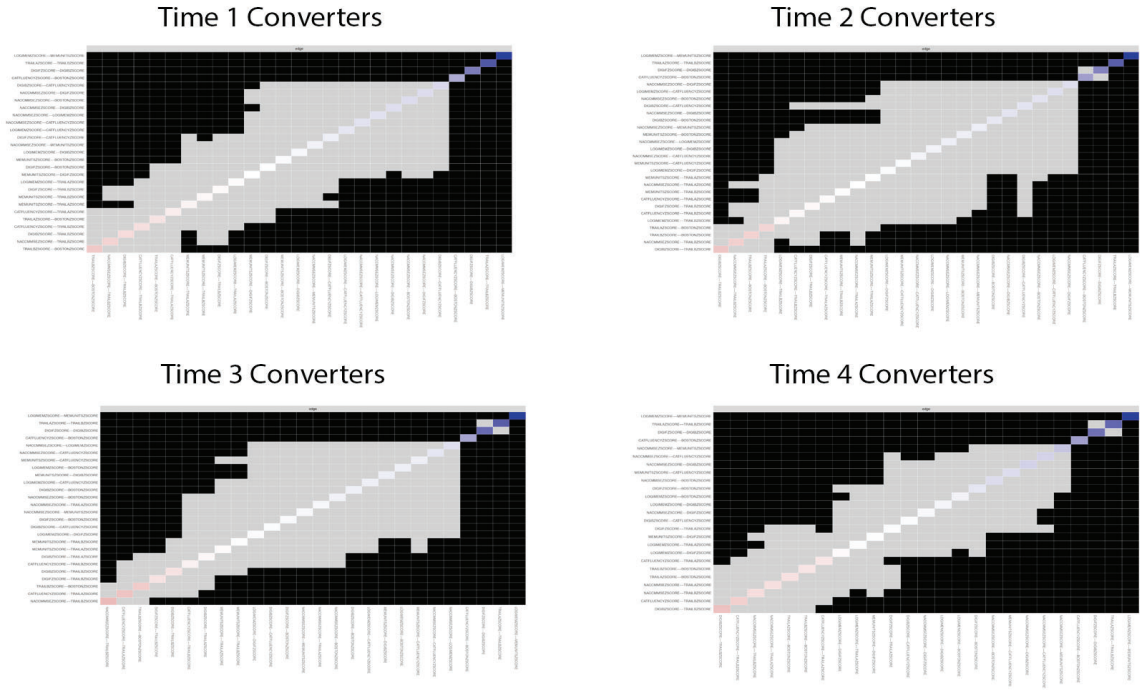
Figures 26 – 28 present the bootstrapped difference tests ($\alpha = 0.05$) between edgeweights that were non-zero in the estimated networks and node strength of the nine cognitive tests. In these figures, gray boxes indicate nodes or edges that do not differ significantly from one-another. Black boxes represent nodes or edges that do differ significantly from one another. Colored boxes (shades of blue for positive connects and red for negative connections) in the edge-weight plot correspond to the strength of the edge in the corresponding network. In these figures, the X axis and the Y Axis represents each edge in the network (i.e. the first edge listed is the edge between the DIGIFZSCORE and CATFLUENCYZSCORE nodes). When examining these tables there are more edges that differ significantly from each other for the networks for the Converter group that Control group networks. This difference is particularly notable when comparing the Bootstrapped difference tests between edgeweights for the Converter group and the Control group at time C, seen in Figure 28. These results suggest that the neurocognitive tests scores for the Converter group are less tightly connected when compared to the Control group.

Figure 27. *Edge-weights difference test for the network estimated for Controls from time point 1 to 4. Bootstrapped Difference Test (α = 0.05) between edges-weights that were non-zero in the estimated networks.*



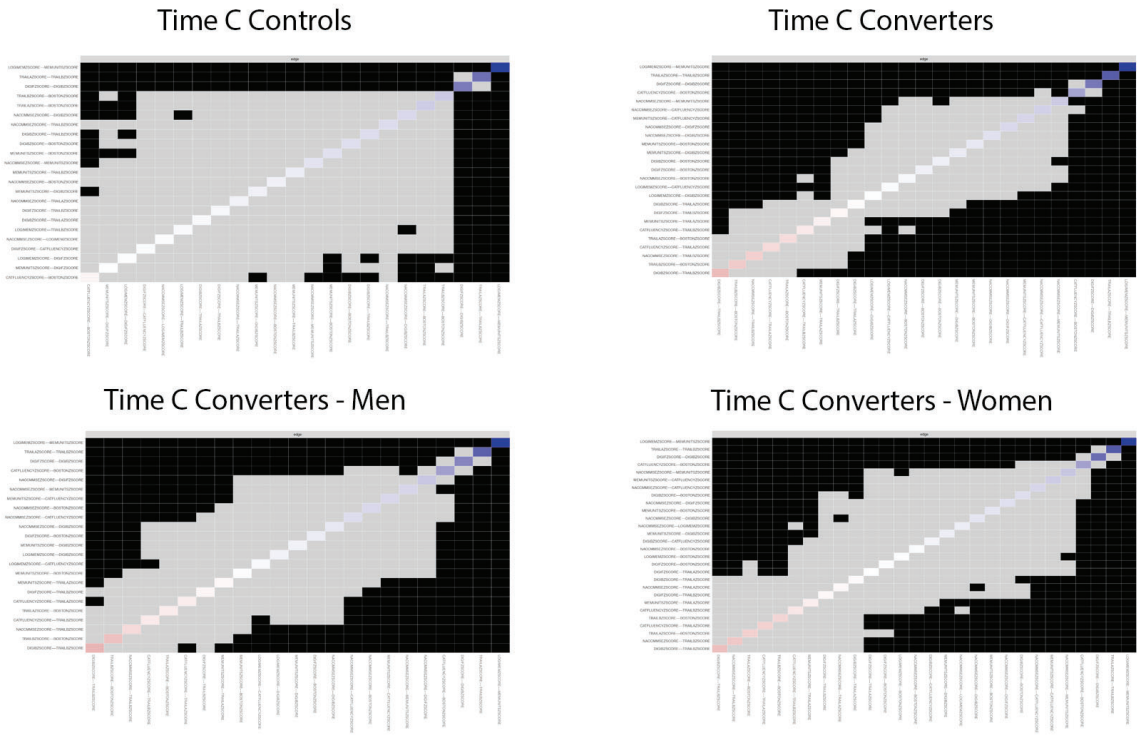
Note. Black boxes represent edges that differ significantly from one-another, and gray boxes indicate edges that do not differ significantly from one-another. Colored boxes in the edge-weight plot represent the strength of the edge in the networks (Shades of blues represent positive values and shades of red represent negative values).

Figure 28. *Edge-weights difference test for the network estimated for Converters from time point 1 to 4. Bootstrapped Difference Test (α = 0.05) between edges-weights that were non-zero in the estimated networks.*



Note. Black boxes represent edges that differ significantly from one-another, and gray boxes indicate edges that do not differ significantly from one-another. Colored boxes in the edge-weight plot represent the strength of the edge in the networks (Shades of blues represent positive values and shades of red represent negative values).

Figure 29. *Edge-weights difference test for the network estimated for Controls and Converters at Time C. Bootstrapped Difference Test (α = 0.05) between edges-weights that were non-zero in the estimated networks.*



Note. Black boxes represent edges that differ significantly from one-another, and gray boxes indicate edges that do not differ significantly from one-another. Colored boxes in the edge-weight plot represent the strength of the edge in the networks (Shades of blues represent positive values and shades of red represent negative values).

Network Inference

As can be seen in Tables 4 – 5 and Figures 32 - 33, over the four time points (Time 1 – 4) and at the time of conversion (Time C) the cognitive tests that had the highest standardized strength for the Control group are Logical Memory I (LOG), Logical Memory II (MEM), and Trails B (TRAILB). For example, standardized strengths for Logical Memory I (LOG) for controls were: T1 = 1.00, T2 = 0.92, T3 = 0.58, T4 = 0.80, TC = 0.69 (see Table 4 and Figure 32). Overall, the strength is relatively consistent for all of the cognitive test over the course of the four visits for the controls group, however there is more fluctuation in the strength over time for the Converter group (see Table 5 and Figure 33). This is particularly noticeable at C time point for LOG. More generally, there is greater variability seen across assessment time points for tests strongly associated with the dementia process, such as learning and memory (LOG and MEM), and sematic fluency (CAT). When the Converter group is subdivided by sex, the highest standardized strength for both sexes are again for LOG, MEM, and TRAILB (see Table 6 and 7 and Figures 34 and 35). These results indicate that LOG, MEM and TRAILB consistently have the strongest connections with all other nodes and therefore the greatest influence on the overall network structure for all groups. However there appears to be more variability in the strength of these nodes for the Converter group over time, suggesting as the dementia process progresses the strength of those cognitive tests strongly associated with the dementia process, such as learning and memory (LOG and MEM), and sematic fluency (CAT) fluctuates more than is observed in the Control group. These results also suggest that there does not appear to be a significant difference between men and women with AD in terms of node strength.

Table 4. *Strength Centrality for the Control group at each time point.*

Node	T1	T2	T3	T4	TC
BOS	-0.53	-0.13	-0.59	-0.50	-0.22
CAT	-2.03	-1.96	-1.96	-1.99	-1.89
DIGIB	0.49	0.42	0.28	0.39	0.45
DIGIF	0.09	-0.50	0.22	-0.44	-0.60
LOG	1.00	0.92	0.58	0.80	0.69
MEM	0.87	1.23	1.24	1.28	1.46
NAC	-0.91	-0.82	-1.02	-0.39	-0.73
TRAILA	0.14	0.02	0.53	-0.15	0.02
TRAILB	0.88	0.82	0.71	1.00	0.83

Note: BOS = Boston Naming Test, CAT = Category Fluency, DIGIF = Digit Span Forward, DIGIB = Digit Span Backward, LOG = Logical Memory I, MEM = Logical Memory II, NAC = Mini Mental Status Exam, TRAILA = Trails A, TRAILB = Trails B

Table 5. *Strength Centrality for the Converter group at each time point.*

Node	T1	T2	T3	T4	TC
BOS	-0.91	-0.05	-0.80	-0.80	-0.50
CAT	-0.30	-0.98	-0.32	-0.33	-0.49
DIGIB	-0.29	0.23	-0.37	-0.07	-0.06
DIGIF	-1.18	-1.23	-0.89	-1.54	-1.14
LOG	1.16	1.31	1.17	0.67	-0.04
MEM	0.77	0.84	0.93	1.77	1.95
NAC	-0.75	-0.96	-1.28	-0.28	-0.81
TRAILA	-0.25	-0.53	0.00	-0.43	-0.22
TRAILB	1.74	1.36	1.56	1.02	1.31

Note: BOS = Boston Naming Test, CAT = Category Fluency, DIGIF = Digit Span Forward, DIGIB = Digit Span Backward, LOG = Logical Memory I, MEM = Logical Memory II, NAC = Mini Mental Status Exam, TRAILA = Trails A, TRAILB = Trails B

Table 6. *Strength Centrality for the Men from the Converter group at each time point.*

Node	T1	T2	T3	T4	TC
BOS	-0.96	-0.60	-0.40	-0.83	-0.39
CAT	-0.17	-0.92	-1.25	-0.77	-0.72
DIGIB	-0.42	0.05	-0.47	-0.46	-0.26
DIGIF	-1.57	-0.94	-0.99	-1.73	-0.91
LOG	1.42	0.98	1.15	1.07	0.38
MEM	1.09	1.25	0.79	1.27	1.65
NAC	-0.25	-0.98	-0.67	0.39	-0.59
TRAILA	-0.19	-0.37	0.22	0.43	-0.78
TRAILB	1.05	1.51	1.62	0.64	1.61

Note: BOS = Boston Naming Test, CAT = Category Fluency, DIGIF = Digit Span Forward, DIGIB = Digit Span Backward, LOG = Logical Memory I, MEM = Logical Memory II, NAC = Mini Mental Status Exam, TRAILA = Trails A, TRAILB = Trails B

Table 7. *Strength Centrality for the Women from the Converter group at each time point.*

Node	T1	T2	T3	T4	TC
BOS	-0.57	0.39	-0.94	-0.74	-0.59
CAT	-0.46	-0.79	0.27	0.48	-0.38
DIGIB	-0.25	0.15	-0.34	0.10	0.17
DIGIF	-0.98	-1.55	-0.86	-1.75	-1.45
LOG	0.94	1.45	1.09	0.57	-0.09
MEM	0.91	0.60	1.05	1.37	1.93
NAC	-1.15	-0.75	-1.54	-0.19	-0.74
TRAILA	-0.26	-0.66	0.04	-0.89	0.11
TRAILB	1.82	1.16	1.23	1.06	1.04

Note: BOS = Boston Naming Test, CAT = Category Fluency, DIGIF = Digit Span Forward, DIGIB = Digit Span Backward, LOG = Logical Memory I, MEM = Logical Memory II, NAC = Mini Mental Status Exam, TRAILA = Trails A, TRAILB = Trails B

Figure 30. *Strength Centrality analysis of the 9 cognitive domains at each time point for the Control group.*

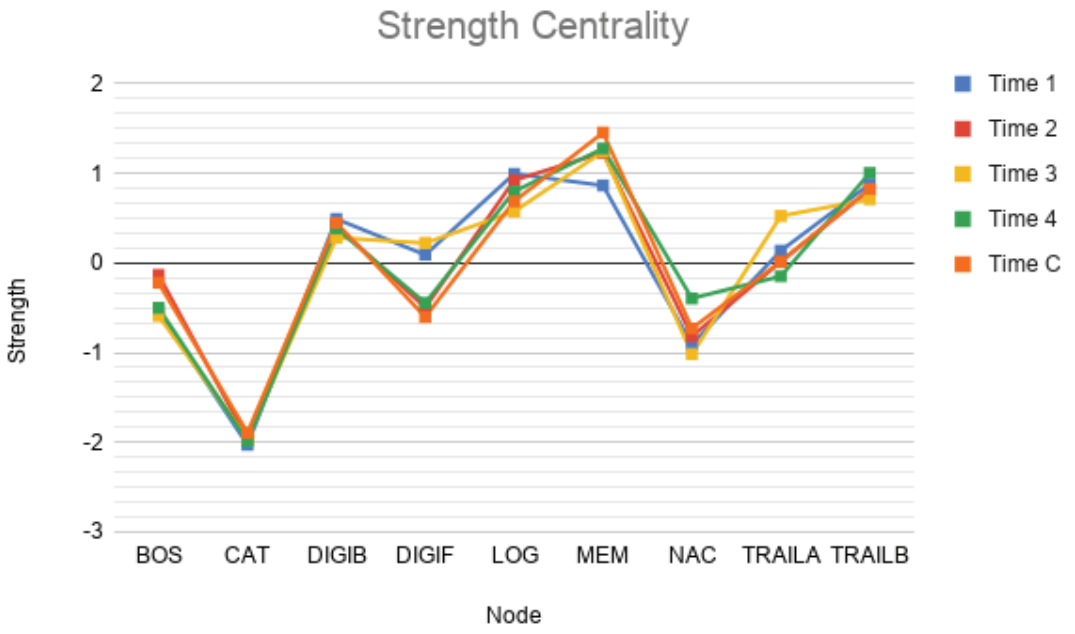


Figure 31. *Strength Centrality analysis of the 9 cognitive domains at each time point for the Converter group.*

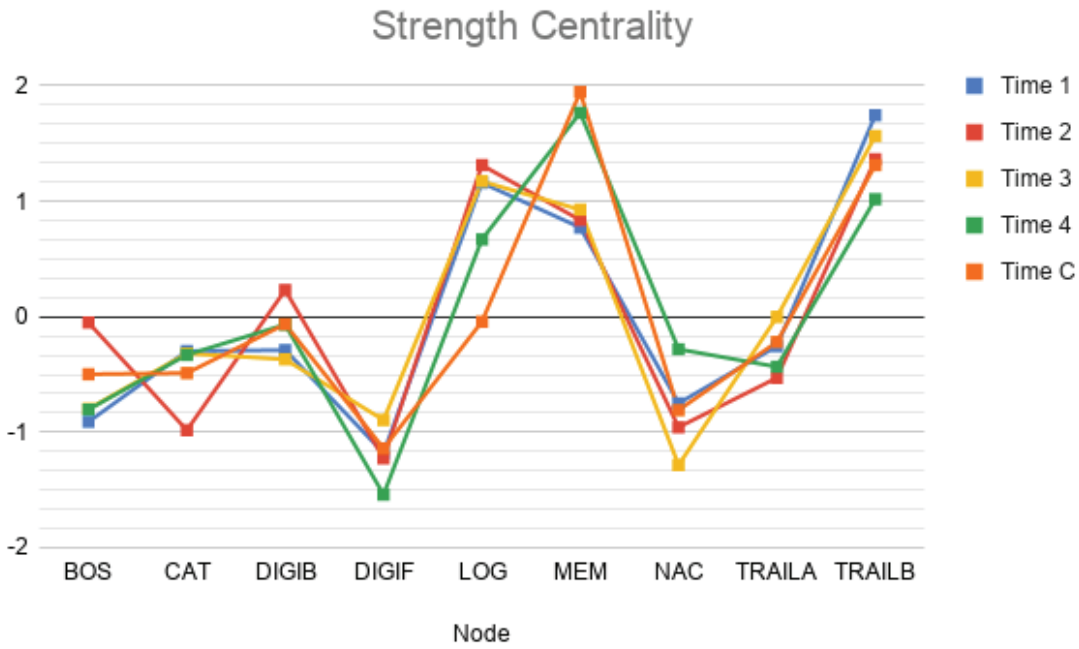


Figure 32. *Strength Centrality analysis of the 9 cognitive domains at each time point for the men in the Converter group.*

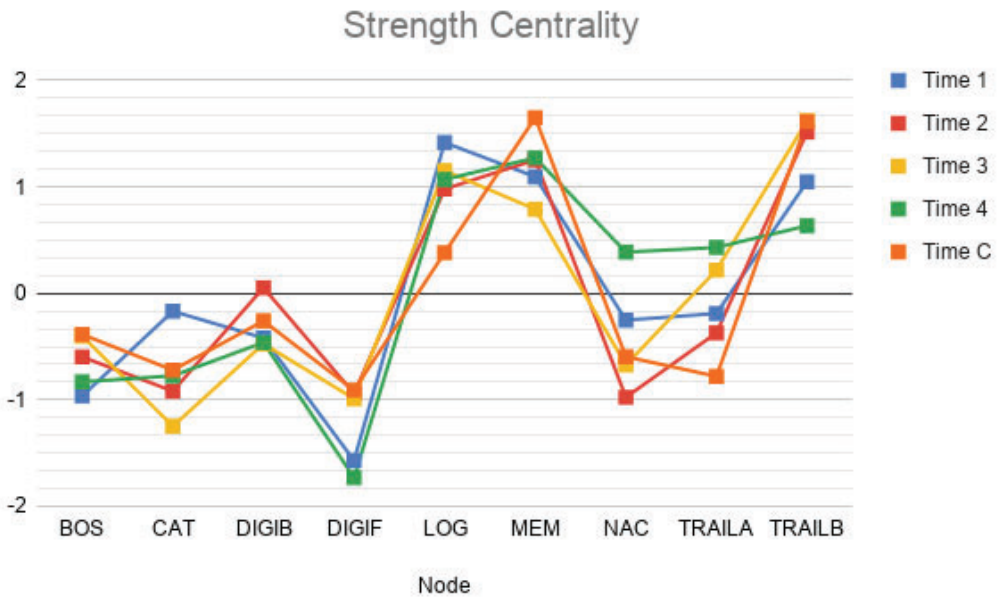
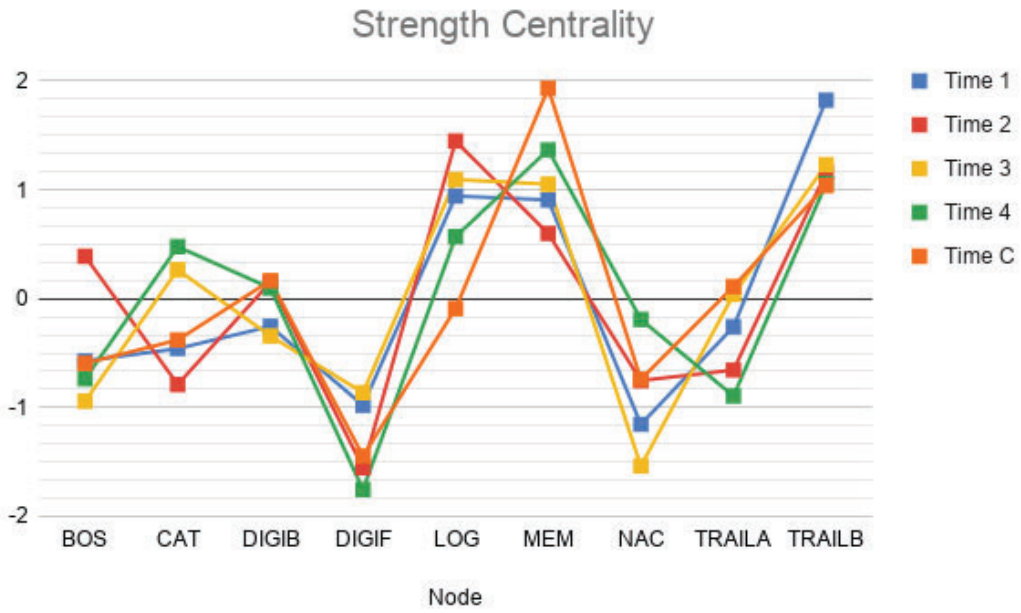


Figure 33. *Strength Centrality analysis of the 9 cognitive domains at each time point for the women in the Converter group.*



Plot significant differences of the node strength was also performed and the results of this test are presented in Figures 33 – 36. Figure 33 shows the significant differences of the node strength for the Control group at Time 1 – 4. In Figures 33-36, boxes shaded black represent nodes that differ significantly from one another ($p < 0.05$), while grey boxes represent those nodes that do not differ significantly from one another. White boxes contain the specific node strength for that node. These figures show that there are more nodes that differ from one another in terms of strength for the Control group than the Converter groups.

Figure 34. *Plot significant differences of node strength (α = 0.05) for controls from Time 1-Time 4*

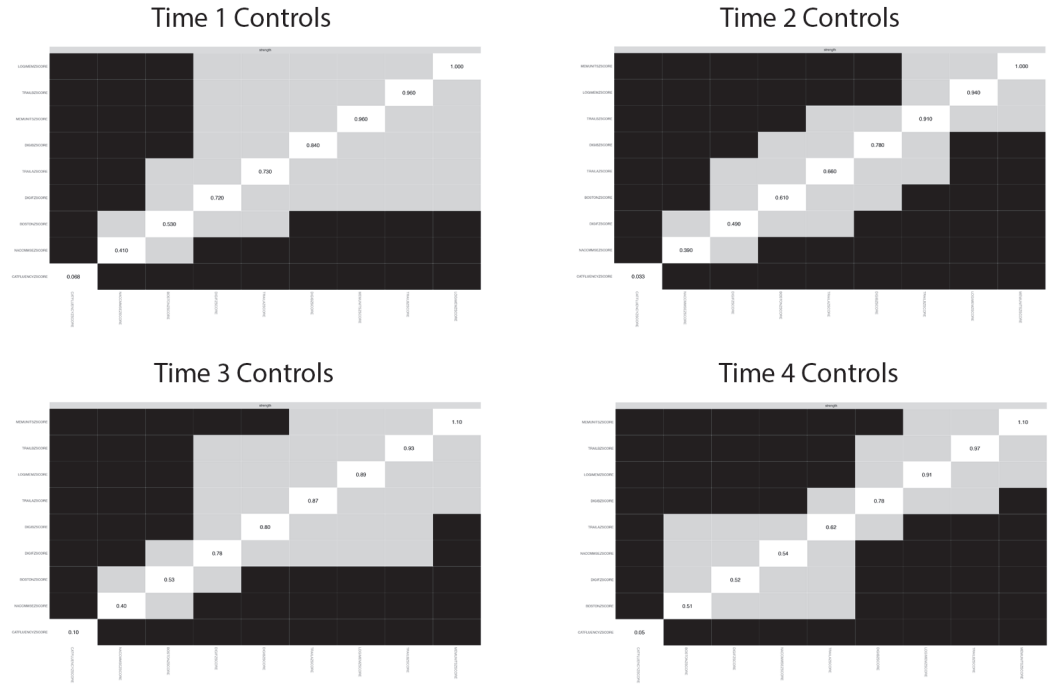


Figure 35. *Plot significant differences of node strength (α = 0.05) for converters from Time 1-Time 4*

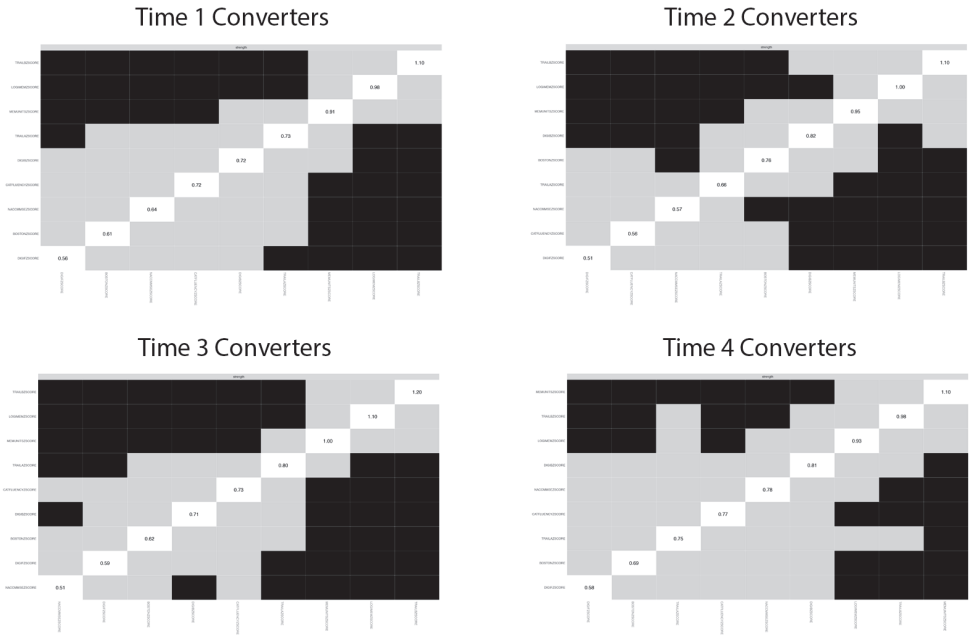
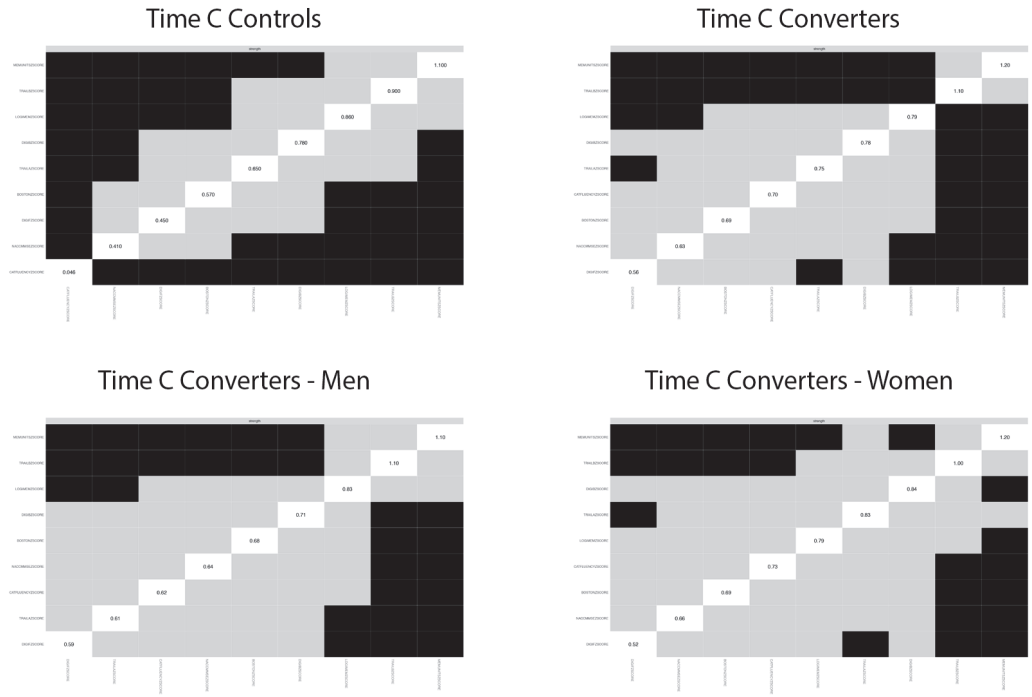


Figure 36. *Plot significant differences of node strength (α = 0.05) for controls and converters from Time C*



The correlation stability coefficient for strength centrality for Time 1- Time 4 and Time C for the Control group was 0.75, 0.75, 0.75, 0.75 and 0.67 (Fig. 36); thus, all time points (Time 1 – Time 4 and Time C) exceeded the recommended threshold for stable estimation of 0.5 (Epskamp, Borsboom, & Fried 2018). For the Converter group, the stability coefficient for strength centrality for Time 1- Time 4 and Time C for the Control group was 0.67, 0.75, 0.75, 0.67 and 0.67 (Fig. 37); thus, all time points (Time 1 – Time 4 and Time C) exceeded the recommended threshold for stable estimation of 0.5, (Epskamp et al., 2018). When the correlation remains high after dropping a substantial number of participants from the sample, it

means the centrality estimates in the original network can be considered stable. These results indicate the maximum proportion of cases that can be dropped from the sample while maintaining a 95 % probability the correlation between original centrality indices and centrality of networks based on sample subset. While this parameter can be determined by the research based on theoretical factors, it is typically accepted that CS-Coefficient = 0.7 indicates a very large effect in the behavioral sciences (Cohen, 1977), while CS-coefficient should not be below 0.25, and CS-coefficient above 0.5 are preferable. The CS-coefficients for the current study exceeded the 0.5 benchmark for all time points, and therefore the strength centrality estimates in the original network can be considered stable.

Figure 37. *Stability of strength centrality index representing the average correlation of the strength centrality index in the networks for the Control Group from T1 to T4.*

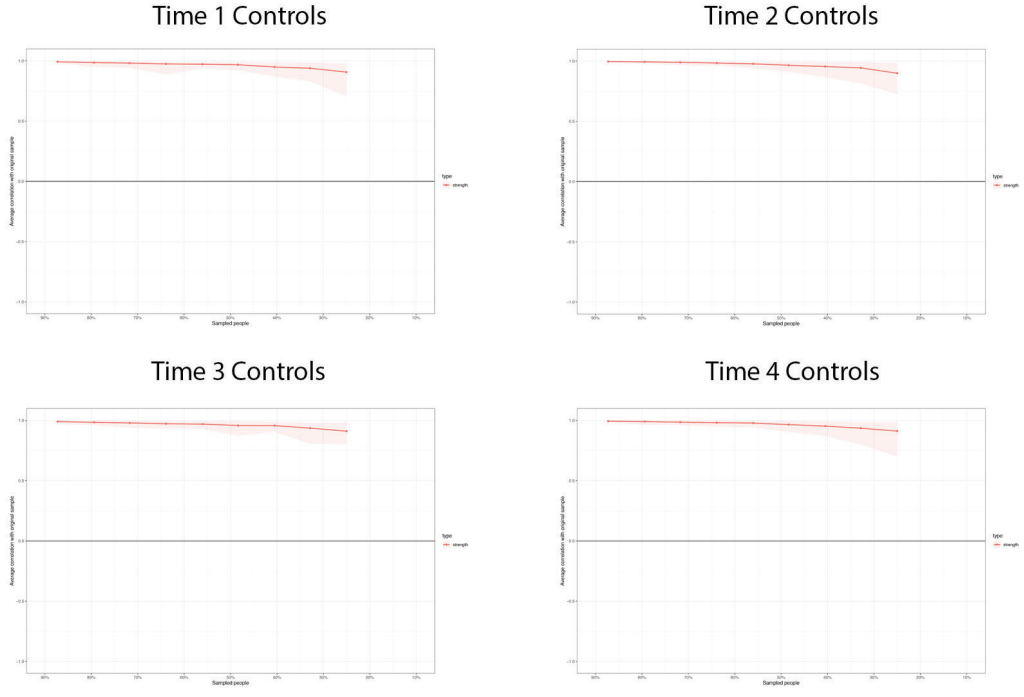


Figure 38. *Stability of strength centrality index representing the average correlation of the strength centrality index in the networks for the Converter Group from T1 to T4.*

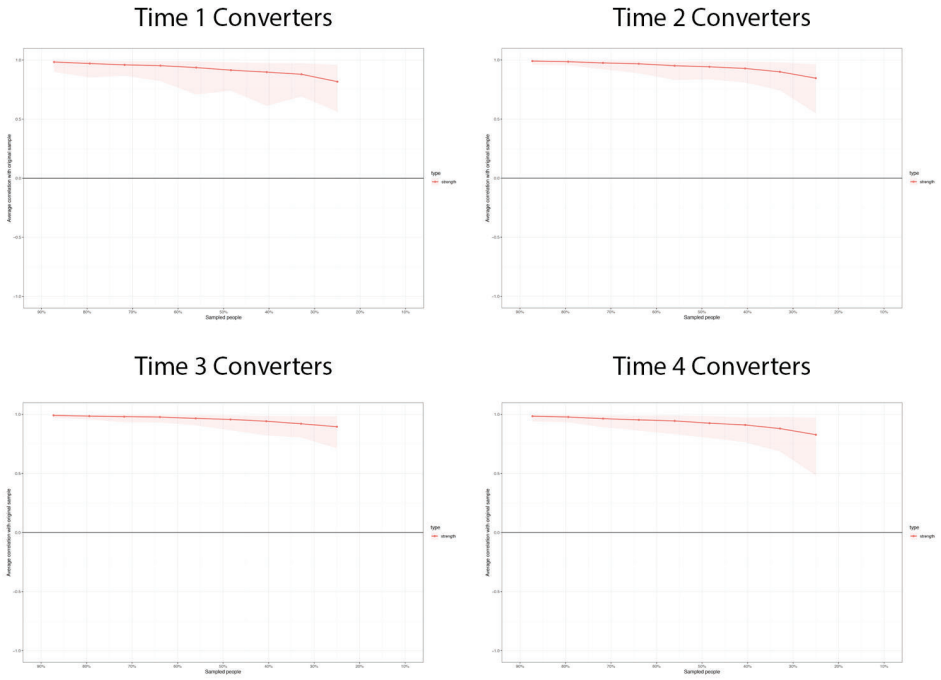


Figure 39. *Stability of strength centrality index representing the average correlation of the strength centrality index in the networks for the Men in the Converter Group from T1 to T4.*

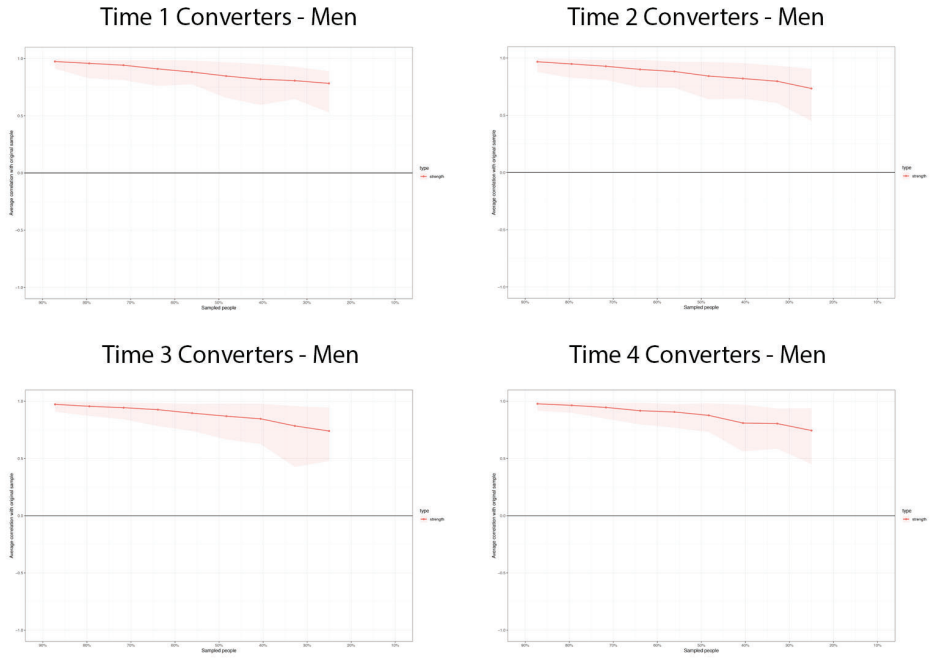


Figure 40. *Stability of strength centrality index representing the average correlation of the strength centrality index in the networks for the Women in the Converter Group from T1 to T4.*

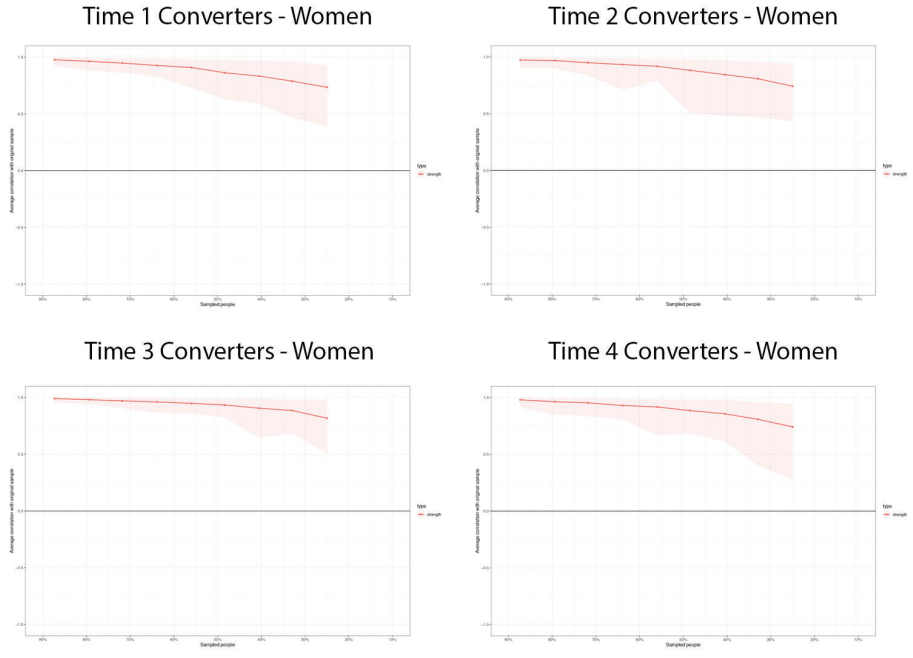
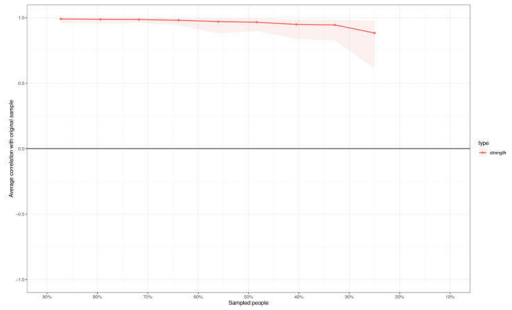
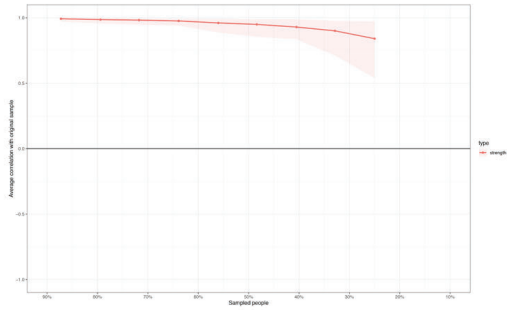


Figure 41. *Stability of strength centrality index representing the average correlation of the strength centrality index in the networks for all groups at Time C.*

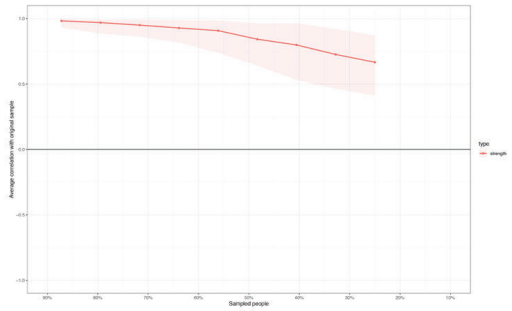
Time C - Controls



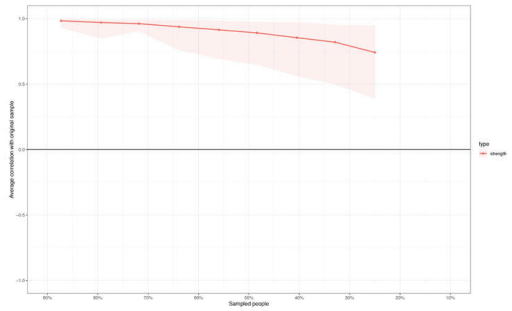
Time C Converters



Time C Converters - Men



Time C Converters - Women



Expected influence is another measure of centrality that provides information about the nature and strength of each node's cumulative influence within the network, while taking into account positive and negative relationships. As can be seen in Tables 8 – 12 and Figures 41- 44 , over the four time points (Time 1 – Time 4) and at the time of conversion (Time C) the cognitive tests that had the highest expected influence for both the Control group and the Converter group are Logical Memory I (LOG), and Logical Memory II (MEM). Trails B (TRAILB) also had a high expected influence for the Control Group, at all time points, but not for the Converter group. When the Converter group is subdivided by sex, Logical Memory I (LOGI) and Logical Memory II (MEM) continued to have the highest expected influence for both the men and the women from the Converter group (Table 10 & 11, and Figure 43 & Figure 44). These results

indicate that LOG and MEM consistently have the highest expected influence on all other nodes and therefore the most influence on the overall network structure for all groups, when both positive and negative relationships are considered. These results also indicate that TRAILB has a high expected influence on all other nodes, for the Control group, although the expected influence of this node was not high in the Converter group. As was seen with the strength centrality, there appears to be more variability in the strength of these nodes for the Converter group over time, suggesting as the dementia process progresses the expected influence on the network of those cognitive tests strongly associated with the dementia process, such as learning and memory (LOG and MEM) fluctuates more than is observed in the Control group. These results also suggest that there does not appear to be a significant difference between men and women with AD in terms of the expected influence of the nodes.

Table 8. *Expected Influence Centrality for the Control group at each time point.*

Node	T1	T2	T3	T4	TC
BOS	-0.42	-0.08	-0.50	-0.44	-0.37
CAT	-2.01	-2.06	-1.90	-2.06	-1.95
DIGIB	0.57	0.45	0.39	0.34	0.47
DIGIF	-0.28	-0.43	-0.13	-0.34	-0.52
LOG	1.01	0.74	0.69	0.80	0.70
MEM	0.85	1.24	1.37	1.24	1.42
NAC	-0.86	-0.75	-0.94	-0.30	-0.64
TRAILA	0.22	0.06	0.18	-0.24	0.06
TRAILB	0.91	0.84	0.83	0.99	0.83

Note: BOS = Boston Naming Test, CAT = Category Fluency, DIGIF = Digit Span Forward, DIGIB = Digit Span Backward, LOG = Logical Memory I, MEM = Logical Memory II, NAC = Mini Mental Status Exam, TRAILA = Trails A, TRAILB = Trails B

Table 9. *Expected Influence Centrality for the Converter group at each time point.*

Node	T1	T2	T3	T4	TC
BOS	-1.08	-0.70	-0.33	-0.32	-0.66
CAT	-0.12	0.07	-0.44	-0.38	-0.23
DIGIB	0.19	0.05	0.14	-0.07	-0.14
DIGIF	0.23	0.02	-0.02	0.21	0.24
LOG	1.72	1.60	1.71	1.21	1.04
MEM	1.13	1.43	1.43	1.84	1.96
NAC	-0.22	-0.61	-0.92	-0.25	-0.18
TRAILA	-0.32	-0.31	-0.24	-0.74	-0.57
TRAILB	-1.53	-1.55	-1.34	-1.50	-1.46

Note: BOS = Boston Naming Test, CAT = Category Fluency, DIGIF = Digit Span Forward, DIGIB = Digit Span Backward, LOG = Logical Memory I, MEM = Logical Memory II, NAC = Mini Mental Status Exam, TRAILA = Trails A, TRAILB = Trails B

Table 10. *Expected Influence Centrality for the Men from the Converter group at each time point.*

Node	T1	T2	T3	T4	TC
BOS	-0.15	-0.82	0.15	-0.16	-0.66
CAT	-0.27	-0.06	-0.73	-0.58	-0.15
DIGIB	-0.47	-0.42	-0.16	-0.14	-0.45
DIGIF	-0.36	0.06	0.32	0.00	0.28
LOG	2.14	1.49	1.60	1.41	1.18
MEM	0.96	1.67	1.34	1.84	1.76
NAC	-0.06	-0.62	-0.99	-0.27	-0.02
TRAILA	-0.44	0.02	-0.14	-0.98	-0.30
TRAILB	-1.36	-1.32	-1.39	-1.10	-1.64

Note: BOS = Boston Naming Test, CAT = Category Fluency, DIGIF = Digit Span Forward, DIGIB = Digit Span Backward, LOG = Logical Memory I, MEM = Logical Memory II, NAC = Mini Mental Status Exam, TRAILA = Trails A, TRAILB = Trails B

Table 11. *Expected Influence Centrality for the Women from the Converter group at each time point.*

Node	T1	T2	T3	T4	TC
BOS	-1.08	-0.18	-0.60	-0.50	-0.61
CAT	-0.16	0.14	-0.24	-0.09	-0.21
DIGIB	0.55	0.12	0.34	-0.09	0.12
DIGIF	0.47	0.13	-0.17	0.11	0.16
LOG	1.31	1.53	1.68	1.29	1.08
MEM	1.40	1.34	1.50	1.62	1.94
NAC	-0.60	-0.76	-0.77	0.09	-0.31
TRAILA	-0.47	-0.65	-0.50	-0.72	-0.81
TRAILB	-1.43	-1.67	-1.23	-1.71	-1.36

Note: BOS = Boston Naming Test, CAT = Category Fluency, DIGIF = Digit Span Forward, DIGIB = Digit Span Backward, LOG = Logical Memory I, MEM = Logical Memory II, NAC = Mini Mental Status Exam, TRAILA = Trails A, TRAILB = Trails B

Figure 42. *Expected Influence Centrality analysis of the 9 cognitive domains at each time point for Control group.*

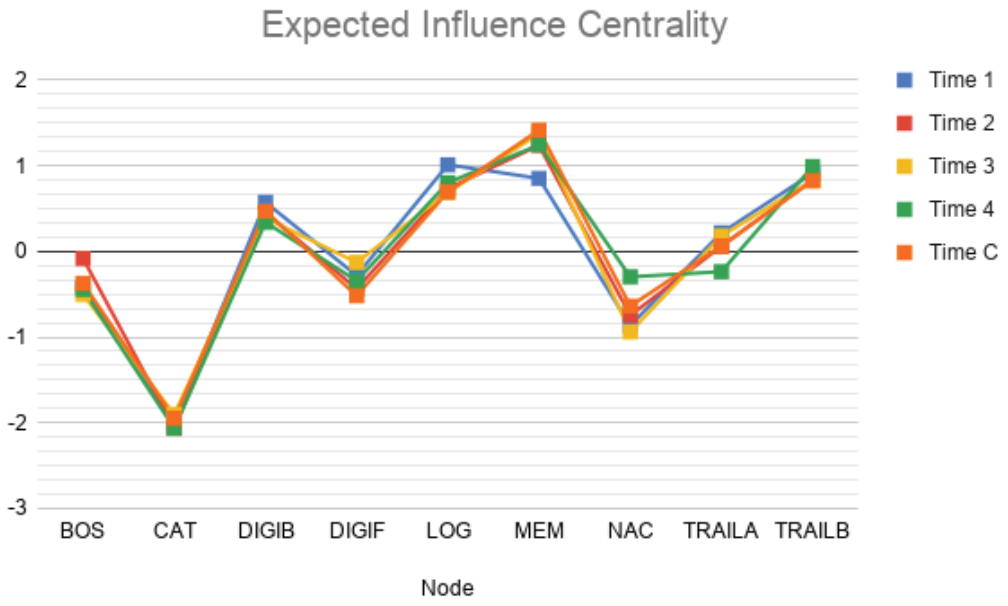


Figure 43. *Expected Influence Centrality analysis of the 9 cognitive domains at each time point for the Converter group.*

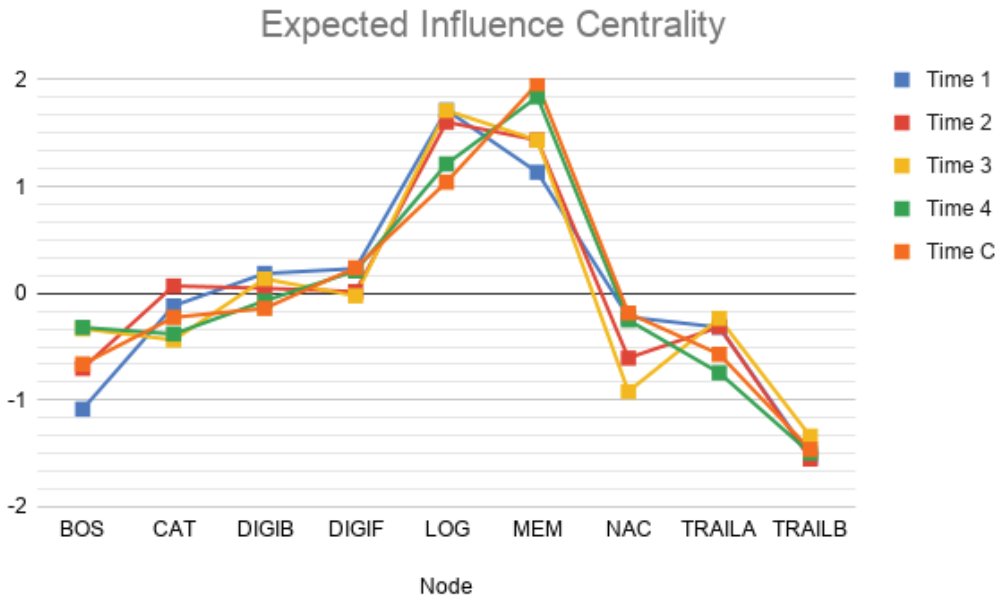


Figure 44. *Expected Influence Centrality analysis of the 9 cognitive domains at each time point for the Men in the Converter group.*

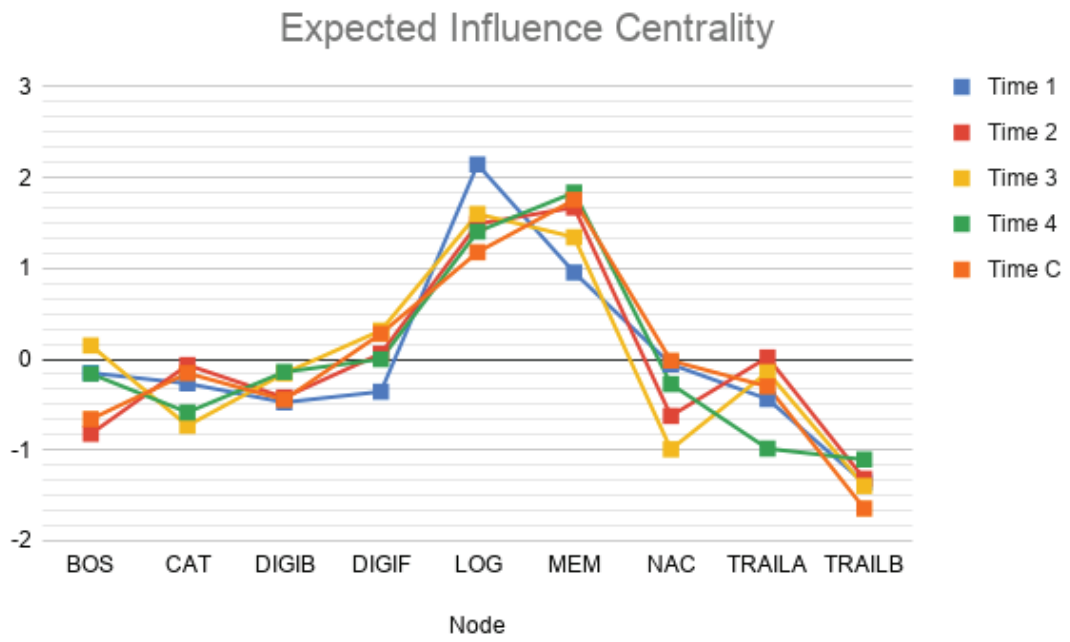
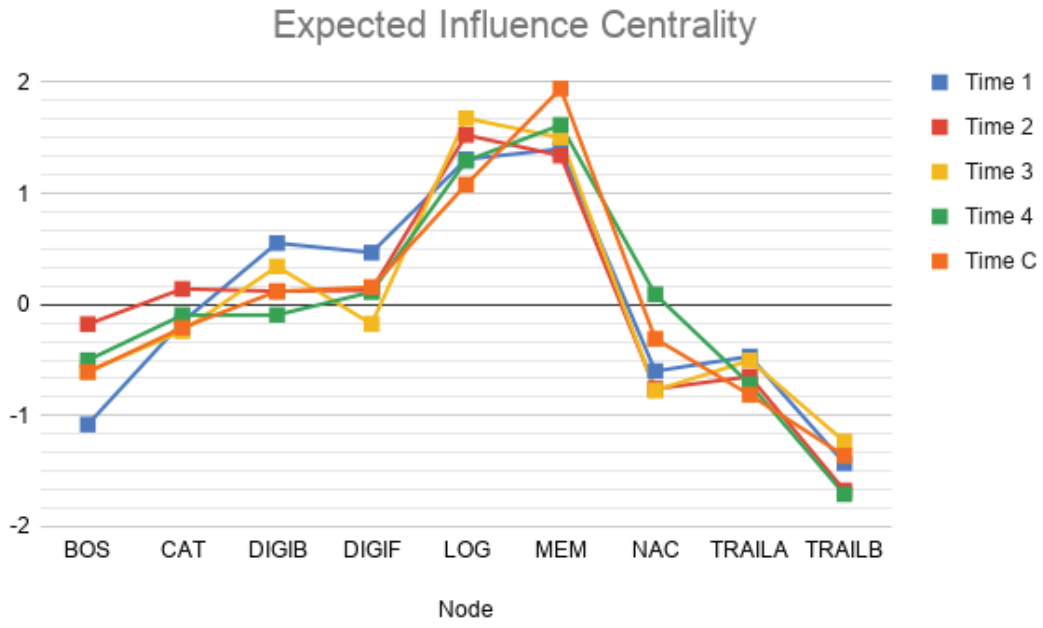


Figure 45. *Expected Influence Centrality analysis of the 9 cognitive domains at each time point for the Women in the Converter group.*



Temporal Stability of the Network

The temporal stability of the network structure was evaluated using the network comparison test. Global strength invariance and maximum difference in edge weights was examined to determine if and to what degree the Control and Converter groups differed from one another at each time point on overall strength of the network and the total difference in edge weights. A centrality difference test was also used to determine if there were significant differences in the strength centrality and the expected influence. The results of these analyses are presented in Table 12. The findings can be summarized as follows: There was a statistically significant difference ($p < .05$) between the Control and Converter groups for the maximum difference in edge weights test at all time points. There was also a statistically significant difference ($p < .05$) between the Control and Converter groups for the global strength test (the overall connectivity or density of the network) at Time 2, Time 3, Time 4, and Time C. The overall global strength of the networks was not significantly different at Time 1 ($p = 0.25$). When these comparison tests were used to compare the men and women from the Converter group, they did not differ significantly on either the global strength test or the maximum difference in edge weights test at any of the time points. When the global strength invariance and maximum difference in edge weights was examined to determine if and to what degree the Converter group differed from one time point to another, they did not differ significantly on either the global strength test or the maximum difference in edge weights test at any of the time points compared. These results suggest, that there are significant differences in the overall network structures between the Control and Converter groups at each time point, except for the initial assessment (time 1), when they only differed in terms of the maximum difference in edge weights test. However, the Converter groups network structure does not change significantly

from one time point to another. With regard to the centrality difference tests, there were statistically significant difference between the groups in terms of strength and expected influence centrality measures on for several of the connections.

Table 12. *Results of the network comparison test based on global strength and network invariance*

Group/Time point	Global Strength *p*-value	Maximum difference in edge weights *p*-value
Controls T1 vs Converter T1	0.25	< 0.001
Controls T2 vs Converter T2	0.04	< 0.001
Controls T3 vs Converter T3	0.01	< 0.001
Controls T4 vs Converter T4	0.001	< 0.001
Controls TC vs Converter TC	0.005	< 0.001
Converter (Men) T1 vs Converter (Women) T1	0.19	0.55
Converter (Men) T2 vs Converter (Women) T2	0.73	0.26
Converter (Men) T3 vs Converter (Women) T3	0.82	0.33
Converter (Men) T4 vs Converter (Women) T4	0.41	0.96
Converter (Men) TC vs Converter (Women) TC	0.23	0.99
Converter T1 vs Converter T2	0.91	0.99
Converter T1 vs Converter T3	0.37	0.41
Converter T1 vs Converter T4	0.17	0.45
Converter T1 vs Converter TC	0.43	0.62
Converter T2 vs Converter T3	0.32	0.08
Converter T2 vs Converter T4	0.16	0.60
Converter T2 vs Converter TC	0.36	0.86
Converter T3 vs Converter T4	0.51	0.21
Converter T3 vs Converter TC	0.97	0.61
Converter T4 vs Converter TC	0.51	0.86

note. T1-T4 = Time 1 through Time 4. Time C = Time of Conversion to MCI or Dementia.

Chapter 5: Discussion

Early detection of individuals who will go on to develop Alzheimer's disease has been the focus of great research interest over the last 30 years for a number of reasons. For example, Petersen and colleagues (1994) have long argued that early detection is important because it can guide early invention efforts that will allow for preservation of neuronal tissue before significant tissue death and atrophy can occur. Early identification is feasible because it has been well established that there is a 20-30 year latency between when neuropathological changes first begin and when cognitive and functional decline are apparent (Nestor, Fryer, Smielewski, & Hodges, 2003; Pengas, Hodges, Watson, & Nestor, 2010). Unfortunately, once cognitive and functional declines are apparent and a diagnosis of MCI or Dementia due to AD can be made, the amount of cell death and atrophy in the brain is quite advanced and, with today's treatments, irreversible and therefore incurable. As such, finding ways to detect the presence of AD pathology early and stop the progression has been a goal for researchers and clinicians for some time now.

Current work in the early detection focuses on combining results from several different bio-behavioral markers to identify individuals who will go on to develop dementia due to Alzheimer's disease at some later point in time. Cognitive tests that are sensitive to the cognitive domains affected in AD, such as memory and language abilities (Albert, Moss Tanzi, & Jones, 2001; Chapuis et al., 2016; Ho, & Nation, for the Alzheimer's Neuroimaging Initiative, 2018), have been used in this effort. Pattern and level of performance on these tests are often combined with other early detection methods, such as neuroimaging techniques and genetic testing and other bio behavioral markers to identify those individuals that are likely to develop AD (Bondi et al., 2008). While the current methods of early detection have shown promise, additional

methods, that can be used in combination with those already developed are still needed to improve the efficiency and accuracy of early detection. The current study attempted to further these efforts by using a novel approach, network analysis, to examine the multivariate structural dependencies among cognitive domains known to be affected in Alzheimer's disease across four serial cognitive assessments, each conducted approximately one year apart, in two groups of individuals who were both cognitively normal at baseline assessment. One remained cognitively normal over the four-year assessment period and the other demonstrated cognitive decline consistent with a diagnosis of mild cognitive impairment or dementia. The use of network analysis in this context allows for understanding how associations between tests that are sensitive to the neuropathology of AD change within the context of AD pathology in those individuals that will go on to be diagnosed with AD, as compared to individuals with normal cognition. The addition of network analysis results to other early detection techniques including neuroimaging, genetic testing, and other biomarkers may provide even greater power in identifying individuals early on in the disease process and allow for earlier interventions which may slow the progress of the disease or delay development of cognitive disorder.

The results of the study suggest that while global differences in network strengths are not particularly useful in differentiating individuals at baseline assessment, similar to what might be observed when using cognitive screener such as the Mini Mental Status Examination or MoCA, differences between strength of associations of individual tasks within the networks were able to distinguish individuals who have normal cognitive function at baseline and maintain normal function over the four your time period, from those who were normal baseline but went on to convert to having a cognitive diagnosis due to AD over the course of 4 years. They build on prior research that has demonstrated the usefulness of neuropsychological test as part of the early

identification process (Ashendorf et al., 2018; Chapuis et al., 2016; de Paula et al., 2015; Ho et al., 2018; Jefferson et al., 2006; Mlinac and Feng, 2016; Razani et al., 2011) by demonstrating that not only are absolute scores important as prior studies have shown (Albert et al., 2001; Alladi et al., 2007; Chapuis et al., 2016; Clark et al., 2012; Harrington et al., 2013; Ho, & Nation, for the Alzheimer's Neuroimaging Initiative, 2018; Hof et al., 1997; Mendez et al., 2002), but the associations between scores in a battery of tests with demonstrated sensitivity to Alzheimer's disease can be informative in identifying those who will develop Alzheimer's disease as much as four years after initial testing when cognition was identified as normal. Furthermore, these results may also help explain some of the inconsistent findings reported for cognitive tests when used to predict individuals who are at risk for developing Alzheimer's disease, by suggesting that many of the important changes occurring in cognition may not be reflected in overall global indicators of cognition or even changes at the test level. Instead, the current results suggest the associations between various test scores can aid in distinguishing those that will go on to develop AD from those who will not.

Study Aims and Hypotheses

With regard to study aims, the first major aim of the study was to compare individuals that are normal at the initial assessment (Time 1) who then go on to develop either Mild Neurocognitive Impairment (MCI) or Major Neurocognitive Impairment (Dementia) due to AD at one of the subsequent assessments, to individuals who are normal at baseline and remain free of a cognitive diagnosis across all four assessment time points. The second major aim was to investigate differences in the network structures of men and women with MCI or dementia due to AD over time. Based on these aims, the following hypothesis were made: 1) The overall network structure of cognitive domains affected in AD will differ for those individuals with

normal cognition as compared to individuals with MCI or Dementia due to AD, at time one, prior to meeting criteria for diagnosis; 2) The overall network structure of cognitive domains affected in AD will differ for those individuals with normal cognition as compared to individuals with MCI or Dementia due to AD after diagnosis of MCI or Dementia due to AD is made; 3) The overall network structure for cognitive domains affected in AD will differ for men with MCI or Dementia due to AD as compared to women with MCI or Dementia due to AD. 4) The Temporal Stability of the network will differ for those with normal cognition who remain normal over a four year period, from those individuals who are normal at the initial visit, then go on to develop MCI or Dementia due to AD.

With regard to the first hypothesis, there were notable differences between the Control and Converter groups in the overall level of connectivity of the networks, as measured by the global strength test, and the maximum difference in edge weights test at all of the time points, except for time 1, where only the maximum difference in edge weights differed, which provides support for the hypothesis. The significant difference between groups in the maximum difference in edge weights indicate subtle difference between those individuals that will go on to be diagnosed with MCI or Dementia due to AD and those that remain normal across all four evaluations. While these differences do not affect the overall connectedness of the cognitive tests and in turn the network structure as measured by the global strength test, there are differences in the connections between each node, even before a cognitive diagnosis is warranted. These findings suggest that while the overall relationship between the cognitive abilities is not significantly different prior to AD diagnosis, there are differences that can be observed, even before full diagnostic criteria is met. Previous longitudinal research has reported the expected pattern of more pronounced cognitive differences between individuals who go on to develop

Alzheimer's disease when compared to those who do not as the diagnosis of dementia becomes imminent (Bondi et al., 2008; Menéndez González, 2014). The current study extends these results by finding that the differences in network structure between the Control and Converter groups became more apparent over the assessment time points, with the greatest difference between groups in global network strength occurring at time 4. Future research examining additional time points after conversion to a cognitive diagnosis would likely find that these differences become even more pronounced as the disease progresses.

In addition to the difference at time 1 for edgeweight strength, there also were significant differences between the groups at all subsequent time points, including the time of conversion, both in terms of the overall level of connectivity of the networks, as measured by the global strength test, and the maximum difference in edge weights test. These results support the second hypothesis, that the two groups network structures would differ once a cognitive diagnosis was made. The differences observed in the network structures demonstrates that the neurodegenerative process associated with AD gives rise to changes in how various cognitive abilities, as measured by neuropsychological tests, relate to one another. More specifically, when the connection within the networks estimated were compared, there were strong positive relationships between Logical Memory I and Logical Memory II at all time points for both the Control and Converter groups. There were also strong positive connections between Trails A and Trails B for both groups at all time points. Finally, there was strong positive connections between Digits Span Forward (DIGIF) and Digits Span Backward (DIGIB) for the Control group at Time 1, Time 2, Time 3 and Time 4, and for the Converter group at Time 3 and Time 4. Logical Memory I, Logical Memory II, and Trails B were the cognitive tests with consistently high strength centrality. The strength centrality was relatively consistent overtime for the Control

group, although more fluctuations in strength centrality were observed in the Converter group. These findings were supported by the accuracy analysis. The stability coefficient for strength centrality was found exceed the recommended threshold of CS-Coefficient = 0.5 and in some cases exceeded the optimal CS-coefficient of 0.7. There were some time points at which the CS-coefficient was below the optimal threshold of 0.7, including Controls Time C, and Converters Time 1, 4 and C. Therefor the network strength was less stable than is considered to be ideal, for some time points, however it never fall below the recommended threshold of 0.5, therefore the strength centrality estimates in the original network can be considered stable. Increasing the sample size in future studies may help to improve the stability of the strength centrality coefficient to meet the ideal CS-coefficient of 0.7. The weakening of network association in the Converter group as the diagnosis of dementia becomes imminent may correspond to a weakening of neural networks necessary to perform well on the tests due to disease progression and neuronal death, although this possibility could not be examined in the current study. Future research examining associations between neural connectivity using neuroimaging techniques and weakening of associations in global network strength for cognitive tests may shed light on this matter.

The current study also examined the network structure of men and women with MCI or Dementia due to AD, and based on previous research exploring sex differences in AD predicted there would be differences between the network structures of men and women with AD. However, this hypothesis was not supported as there were no notable differences observed between the overall network structures or the stability of the networks between men and women with MCI or dementia due to AD. While substantial research has been conducted examining sex differences in AD and has demonstrated differences between men and women in terms of onset

and progression of dementia (Hebert et al., 2013; Hebert et al., 2001; Plassman et al., 2007; Letenneur et al., 1999; Liu et al., 1998; Kivohara et al., 1996; Mielke et al., 2014; Roberts et al., 2014; Seshadri et al., 1997), the current results suggest that the network structure of cognitive abilities affected by AD does not differ between men and women. These findings are significant in that they help to demonstrate the similarities between men and women in terms of how the neuropsychological tests results for individuals with AD relate to one another and support the use of network analysis in early detection of AD across sex, furthering the generalizability of the current findings.

Structural Importance of Cognitive Tests In the Network

When further examining the networks of the Control and Converter groups and the structural importance of the various cognitive tests within the networks, there were strong positive connections (edge weight > 0.4) observed between Logical Memory I and Logical Memory II were expected given Logical Memory II is a measure of information that was learned in the Logical Memory I task and retained after a delay. While the overall information learned and retained after a delay may decline with the progression of AD (Albert, et al., 2001; Chapuis et al., 2016; Ho, et al., 2018), the connection between these tests in the network remained strong for both Controls and Converter groups across all time points. A similar pattern was observed in the strong positive connections between Trials A and Trails B for both controls and Converter groups at all time points. This relationship was also expected given the similarity between these tasks, with Trails A measuring processing speed, and Trails B measuring processing speed as well as executive functioning. The final strong relationship observed Digits Span Forward, a measure of simple attention, and Digits Span Backward, a measure of working memory. These strong positive connections observed between Logical Memory II and II, Trails A and B, and

Digit Span Forwards and Backwards are indicative of the extra variance explained due to each specific ability in these tasks and the variance these tasks account for in the estimated networks. There was more variability between the Control and Converter groups for these measures, suggesting while a relationship remains between simple attention and working memory in the presence of AD pathology, the relationship is less stable than the other cognitive domains evaluated in the current study. Results are also consistent with factor analytic studies that identify these tests to load on separate factors, and support the distinctions classically drawn between cognitive constructs of long-term memory, executive function and working memory, and the tests used to assess them.

As discussed previously, we found there were significant differences between network structures for the Control and Converter groups. While relationship between several of the cognitive tests remained strong for both groups, there were significant differences between the groups on the network comparison tests for the global strength and maximum difference in edge weights test for Time 2, 3, 4 and C. At time 1, while there was a significant difference between the groups on the maximum difference in edge weights test, there was not a significant difference in the global strength test for the two groups. To better understand these differences, the overall network structures of the Control and Converter groups at each time point were examined. Based on this examination, one striking difference was the number of negative connections present in the networks of the Converter group as compared to the Control group. These negative relationships are primarily centered around the Trails B test and while none rise to the level of being considered strong negative connections (edge weight > - 0.4), there are several considered moderate negative connections (edge weight > - 0.1). This appears to become more prominent in the Converter group as time goes on and the dementia process progresses. The presence of more

negative relationships in the network in the presence of AD pathology represents a change in how the cognitive abilities assessed by the tests relate to one another. Generally, we expect to see positive relationships between cognitive abilities, as the different abilities support or mutually reinforce each other. In the case of a negative partial correlation between Trails B and the other abilities, this suggests performance on Trails B is not mutually reinforcing the other abilities in those that Convert to AD. Trails B is a measure of executive functioning that is most affected later in the progression of AD, although these findings suggest that its role in the network structure changes even before diagnosis is made and impairments in executive functions are apparent. This is likely related to the neuroanatomical changes that occur as the disease progresses and consistent with the greater role of the disease process on neuropsychological test performance as the AD pathology progresses. The influence of other variables, such as age, sex, level of education, etc., which contribute to individual differences among those with normal cognition are progressively diminished as the AD pathology progresses and increasing amount of neural tissue is compromised. As discussed previously, there are specific regions of the brain (i.e. medial temporal lobes and progresses frontally) known to atrophy as AD progresses (Korf, et al., 2004; Nestor et al., 2003; Pengas et al., 2010). This atrophy results in declines in the cognitive abilities mediated by those regions (Hebert et al., 2003). In turn, the nature of the relationship between those affected cognitive abilities would be expected to change. As mentioned, Trails B is considered a measure of executive functioning, and is thought to be a general indicator of the biological status of the brain that declines as the neuropathology load become greater. When taken together the differences between the network structures of Controls and Converters demonstrate an alteration in how the different cognitive domains that are

impacted by AD relate to one another in the presence of a disease process known to negatively impact those cognitive domains.

The final hypothesis, which posited changes over time in the network structure of those with AD, was only partially supported. Although there was a progressive decrease in network strength in the Converter group from time 1 to time 4, these differences were not statistically significant. Comparisons between time 1 and time 2 suggested little if any difference in network strength (p = .91), with larger but still nonsignificant differences present when time 1 was compared to time 3 (p = .37), and to time 4 (p = .17). The trend noted in these results suggest that this hypothesis may not have been fully supported because of the limited duration of the study data. Given this trend, if a fifth assessment was available, it is quite possible that a significant difference in network structure would have been identified from time 1 to time 5. It was also the case that only 17.8% of the Converter group had a cognitive diagnosis of dementia, while the others were diagnosed with mild cognitive impairment. Greater differences in network structure over time may also have been observed if all individuals in the Converter group developed dementia over the 4 year period. AD is a disease that progresses on average over the course of 10 years (Warner & Butler, 2000) and for some individuals, particularly those with high levels of cognitive reserve, significant cognitive declines only occur in the later years of the disease. Given that the current study included individuals who were normal at baseline and followed them for 4 years, it is not surprising that many of the individuals in the Converter group did not progress to full dementia. The 4 year period was selected to ensure there were enough participants for network analyses. However, it seems likely that the duration of the current study, while useful in understanding differences in the networks prior to formal cognitive diagnosis, limited the ability to examine differences between the group later in the disease

process. Future research could examine these same individuals at subsequent time points (if retained in the study) to examine if significant differences in the networks arise within the Control groups network structure as the disease has progressed and the cognitive abilities measured have further declined.

Limitations and Future Directions

Some limitations should be taken into account when interpreting the results of the current study. Firstly, the demographic representation of the participants is limited in terms of diversity, such that the sample is comprised of primarily White individuals with an average education of 15.7 years. Previous research has demonstrated differences in performance on cognitive tests between individuals of different races who are at risk or who have developed Alzheimer's disease (Heaton, Ryan, & Grant, 2009; Kim et al., 2017; Rilling et al., 2005; Smith, Wong, Ivnik & Malec, 1997). These studies examined performance at the test score or global index level, as opposed to the network level as done in the current study. As such, it remains to be seen whether there will be differences in network structure that might be attributable to differences in race or ethnicity. Future research should examine this matter. A number of factor analytic studies indicate that the latent structure of well-validated cognitive tests such as IQ tests typically generalize well across different racial and ethnic groups, even when group differences are present in overall level of performance. Since network analysis focuses on the relationships between tests similar to factor analysis, it is possible that different racial groups would demonstrate similar patterns in network structures despite overall differences in level of performance. If this were the case, then examining cognitive networks as an early detection technique may generalize well across different racial and ethnic groups. In any case, in order for the current results to be generalized to other ethnic and racial groups with different levels of

education, direct comparisons of network structure are needed.

Another limitation of the current study involves the parameter stability of the network. While a sample of 432 controls and 432 converters is relatively large in terms of psychological research studies, in regularized partial correlation models/network analysis a large number of parameters are estimated (Epskamp & Fried, 2018). Therefore, despite the fact that the current study is based on 864 participants (432 per group) and showed at least moderate stability and accuracy, these results should be considered preliminary in nature and should be replicated with other large samples. Future research in this area would benefit from including more participants from more diverse backgrounds.

Finally, since the development of the NACC database, there has been additional cognitive tests found to be helpful in identifying cognitive decline due to AD pathology. As such, the NACC UDSNB has been updated over the years and is now on the third version, UDSNB 3.0. This new version now includes a measure of visuospatial construction and memory, processing speed, and phonemic fluency. These measure were only available for a limited number of our participants at the later time points, and were therefore not able to be included in the current study. Given their sensitivity to AD, the addition of these additional tests could help to provide a network structure that is more useful in understanding the relationship between cognitive abilities within the context of AD. Similarly, because the current tests were selected for their known sensitivity to Alzheimer's disease, the results may vary substantially when other neuropsychological tests are used, i.e., differences between groups may be more or less apparent in network structure depending on the tests include in the assessment. Future studies would benefit from including these additional tests, as available. Despite these limitations, the current study results contribute to the existing body of research in a number of important ways,

providing a clearer understanding the impact of AD on the changes in cognitive functioning to further efforts of early detection, with the goals of improved intervention and prevention.

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Zamani Esfahlani, F., Visser, K., Strauss, G. P., & Sayama, H. (2018). A network-based classification framework for predicting treatment response of schizophrenia patients. *Expert Systems with Applications*, *109*, 152-161. doi:10.1016/j.eswa.2018.05.005

Curriculum Vitae

Abigail R. Baily
(Formerly Abigail R. Mayfield)

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EDUCATION

Doctor of Philosophy Anticipated Graduation: August 2020
University of Nevada, Las Vegas (UNLV) Advisor: Daniel N. Allen, Ph.D.

APA-Accredited Clinical Psychology Program, Neuropsychology Track
Dissertation: Network Analysis of Cognitive Symptom Domains in Alzheimer's Disease (AD)

Masters of Arts in Psychology May, 2017
University of Nevada Las Vegas (UNLV) Advisor: Daniel N. Allen, Ph.D.

APA-Accredited Clinical Psychology Program, Neuropsychology Track
Thesis: Neurocognitive Correlates of the Comprehensive Trail Making Test (CTMT) in Brain Injured Children

Bachelor of Science in Psychology December, 2011
Texas State University- San Marcos Advisor: Reiko Graham, Ph.D.
Magna Cum Laude

CLINICAL INTERNSHIP

VA North Texas Health Care System July 2018 - July 2018
APA-Accredited Clinical Internship, Neuropsychology Track
Primary Supervisor: Barry Ardolf, Psy.D., ABPP-CN

- **Neuropsychology Consult Team** July 2018 - October 2018
  Major Rotation Supervisor: Barry Ardolf, Ph.D., ABPP-CN
  - Outpatient comprehensive neuropsychological assessments, interviewing, and report writing adult and geriatric populations for veterans diagnosed with medical or neurological conditions and/or comorbid psychiatric conditions such as neuropsychiatric disorders, dementias, stroke, traumatic brain injury, chronic pain, PTSD, depression, anxiety, and pre- and post-surgical evaluations for patients undergoing Deep Brain Stimulator implantation.

- **Spinal Cord Injury Center** October 2018 - January 2019
  Major Rotation Supervisor: Emma Shapiro, Ph.D.

    - 30-bed inpatient unit to care for the medical and rehabilitation needs of persons with spinal cord injuries or other neurological dysfunctions (e.g., Multiple Sclerosis, Guillain-Barre Syndrome, and cervical myelopathy) as well as an outpatient clinic for comprehensive care throughout the lifespan. Inpatient and outpatient rehabilitation psychology. Experiences included working within an interdisciplinary team addressing behavioral medicine issues, neuropsychological disorders, behavioral issues, and psychological disorders within a specialized medical unit. Services include bedside assessments, neuropsychological assessments, comprehensive assessments of an individual's coping status and adaptation to chronic illness and disability in the context of personality, cognitive status, as well as family and social systems in order to implement an appropriate treatment plan

- **Mental Health Silver Team** January 2019 - April 2019
  Major Rotation Supervisor: Heejin Kim, Psy.D. ABPP-CN
    - Geriatric Specialty clinic for patients age 62 and older are assigned to this team for their care regardless of their psychiatric diagnosis. Experiences will include cognitive screening, interviewing, neuropsychological assessment, report writing, and provisions of feedback.

- **Community Living Center – Hospice Care** January 2019 - April 2019
  Minor Rotation Supervisor: Mallory Lamb, Psy.D.
    - 120-bed extended care facility which provides interdisciplinary medical rehabilitation, long-term residential care, and hospice care. The CLC includes a CARF-accredited program for acute-intensive rehabilitation for survivors of serious injury or illness. Veterans admitted for rehabilitation often present with orthopedic injuries, amputation, stroke, and other medical and neurological conditions along with adjustment, mood, and behavioral concerns that may impact recovery. Veterans admitted for hospice care have a terminal diagnoses (e.g., cancer, COPD) with typical life-expectancy of less than six months. Experiences include supportive therapy with Veterans and their family.

- **Mental Health Inpatient Unit** April 2019 - July 2019
  Major Rotation Supervisor: Aletha Miller, Ph.D.
    - Inpatient psychiatric unit for acute treatment of severe psychopathology. Services provided include group and individual therapy interventions that contribute to remediation of acute symptoms. Interventions consist primarily of primarily motivational interviewing and CBT.
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PRACTICUM EXPERIENCES

Cleveland Clinic Lou Ruvo Center for Brain Health June 2016 - July 2017
Las Vegas, NV
Supervisors: Sarah Banks, Ph.D. ABPP-CN, Justin B. Miller, Ph.D., ABPP-CN, Jessica Z. Caldwell, Ph.D. ABPP-CN

Pre-Doctoral Practicum Student

- Conducted comprehensive neuropsychological assessments with adult individuals in an outpatient specialized medical clinic.
    - Scoring, interpretation, interviewing (under live supervision), and comprehensive report writing.
- Commonly presented patient diagnoses including individuals suspected of having neurodegenerative disease, particularly dementias, movement disorders, and multiple sclerosis referred from neurology and psychiatry.
- Co-facilitated a weekly support group for caregivers with a psychologist.
- Weekly individual supervision meetings in addition to weekly case conferences and group supervision with neuropsychology supervisors, post-doctoral fellows, and students.
- Weekly case conferences, didactics, or grand rounds with neurology, physical therapy and/or social work.

Neuropsychology Technician July 2017 - June 2018

- After formal practicum training ended, hired to continue conducting neuropsychological assessments, scoring, and report writing on an as-needed basis.

Center for Applied Neuroscience May 2015 - August 2016
Las Vegas, NV
Supervisors: Thomas F. Kinsora, Ph.D., and Sharon Jones-Forrester, Ph.D.

Pre-Doctoral Practicum Student

- Conducted neuropsychological and forensic assessments with children and adults in an outpatient private practice setting or the Clark County Detention center.
- Responsibilities included scoring, interpretation, integrative report writing, participation in intake interviews and feedback sessions, as well as record review.
- Commonly presented patient diagnoses included cognitive disorders of varying etiologies, affective disorders, pervasive developmental disorders, learning disabilities, and TBI.
- Weekly individual supervision and group supervision, as well as didactic training and case conferences.
- Saw Active-duty service member patients referred for neuropsychological evaluation for combat-related injuries including TBI, polytrauma, PTSD, for Medical Evaluation Board, and Aeromedical Waiver evaluations.

Testing Assistant August 2016 - June 2018

- After the formal practicum training ended, hired to continue conducting neuropsychological assessments, scoring, and report writing on an as needed basis.

Disability Resource Center (DRC)/Academic Success Center
May 2016 - August 2017
Supervisor: Michelle Paul, Ph.D.

Graduate Assistant

- Administered, interpreted, and wrote integrated psychoeducational and neuropsychological evaluations for UNLV students presenting with academic difficulties to determine eligibility for accommodations.
- Participated as a consultant to DRC staff in weekly documentation review meetings regarding eligibility for academic accommodations.
- Diagnoses included: Specific Learning Disorders, Attention-Deficit Hyperactivity Disorder, Borderline Intellectual Functioning, Language Disorder, Autism Spectrum Disorder, Unspecified Neurodevelopmental Disorders, Neurocognitive Disorder, Depressive Disorders, Anxiety Disorders, Bipolar I Disorder, Posttraumatic Stress Disorder, Eating Disorders, and Substance Use Disorders.

The Partnership for Research, Assessment, Counseling, Therapy, and Innovative Clinical Education (The PRACTICE) August 2014 - August 2015
May 2017- August 2017
Supervisor: Michelle Paul, Ph.D.

Pre-Doctoral Practicum Student

- Provided individual psychotherapy to a caseload of approximately 4-7 patients per week.
- Conducted clinical intakes.
- Patients included adolescents and adults of diverse cultural backgrounds from the community.
- Diagnoses seen included affective disorders, adjustment disorders, trauma, and severe mental illness, including bipolar disorder and delusional disorder.
- Theoretical approach was integrative, including biopsychosocial, CBT, and interpersonal orientations and aspects of DBT and ACT.

Psychological Assessment and Testing Clinic sAugust 2014 – August 2015
University of Nevada Las Vegas
Supervisor: Michelle Paul, Ph.D.

Pre-Doctoral Practicum Student

- Conducted comprehensive neuropsychological and psychoeducational assessments, used a flexible battery approach, for adult patients referred from the community and the university disability resource center.
- Conducted intake interview and feedback sessions.
- Scoring, interpretation, integrative report writing, and provision of feedback.

PUBLICATIONS AND PRESENTATIONS

Manuscripts Published

Parke, E. M., Becker, M. L., Graves, S. J., **Baily, A. R.,** Paul, M. G., Freeman, A. J., & Allen, D. N. (2018). Social Cognition in Children With ADHD. *Journal of Attention Disorders*.

Mayfield, A. R., Parke, E. M., Barchard, K. A., Zenisek, R. P., Thaler, N. S., Etcoff, L. M., & Allen, D. N. (2016). Equivalence of mother and father ratings of ADHD in children. *Child neuropsychology*, 1-18.

Parke, E. M., **Mayfield, A. R.,** Barchard, K. A., Thaler, N. S., Etcoff, L. M., & Allen, D. N. (2015). Factor structure of symptom dimensions in attention-deficit/hyperactivity disorder (ADHD). *Psychological Assessment,* 27(4), 1427-1437.

Ceballos, N., **Mayfield, A. R.,** & Graham, R.(2015). ERPs to alcohol images among Hispanic and non-Hispanic female college freshmen. *AIMS Neuroscience, 3*(1), 1-21. doi:10.3934/Neuroscience.2016.1.1

Manuscript Submitted

Baily, A. R., Lee, B. G. Donohue, B., Mayfield, J. W., Allen, D. N., (re-submitted with revision) Neurocognitive predictors of executive function deficits in children with brain disorders.

Manuscript in Preparation

Nunez, A., San Miguel, L. **Mayfield A. R.,** Allen, D. N., Donohue, B., Barchard, K. (in preparation). Short form validity of the Spanish and English versions of the Wechsler Intelligence Scales for Children-Fourth Edition (WISC-IV) in a clinical sample.

Presentations

Mayfield, A. R., Lee, B.G., Mayfield, J.W., & Allen, D.N., (2016). *Neurocognitive Correlates of the Comprehensive Trail Making Test (CTMT) in Children with Neurological Disorders.* Poster presented at the National Academy of Neuropsychology 36th Annual Meeting, Seattle, Washington.

Mayfield, A. R., (2016). *Neurocognitive Correlates of the Comprehensive Trail Making Test (CTMT) in Brain Injured Children.* Presentation conducted at the University of Nevada Las Vegas psychology graduate research data blitz symposium.

Mayfield, A.R., Ciobanu. C., Etcoff. L., & Allen, D.N., (2015). *Utility of WISC-IV Short Forms in Attention-Deficit/Hyperactivity Disorder (ADHD).* Poster presented at the National Academy of Neuropsychology 35th Annual Meeting, Austin, Texas.

Mayfield, A.R., Reyes, A., Mayfield, J.W., & Allen, D.N., (2014). *Improvement in Executive Function Following Traumatic Brain Injury (TBI) in Children.* Poster presented at the National Academy of Neuropsychology 34th Annual Meeting, Fajardo, Puerto Rico.

Mayfield, A.R., Reyes, A., Mayfield, J.W., & Allen, D.N., (2014). *Improvement in Executive Function Following Traumatic Brain Injury (TBI) in Children.* Presentation conducted at

the University of Nevada Las Vegas Graduate & Professional Student Association Research conference.

Mayfield, A.R., Ceballos, N.A., & Graham, R. (2013). *Alcohol-related attentional biases in female college freshman: A cross-cultural ERP study. Alcohol-related attentional biases in female college freshman: A cross-cultural ERP study***.** Presented at the Cognitive Neuroscience Society meeting in San Francisco, California.

Dodwell, G., **Mayfield, A.R.**, Ceballos, N.A., & Graham, R. (2013). *Gaze cuing elicited by gazing expressive faces and alcoholic/non-alcoholic targets in social drinkers.* Presented at the Cognitive Neuroscience Society meeting in San Francisco, California.

Ceballos, N.A., **Mayfield, A.R.**, Paz, J.M., Vela-Gude, M.L., Graham, R. (2012). *A cross-cultural study of automatic and controlled processing of alcohol images in female college freshman.* Poster presented at the 52nd annual meeting of the Society for Psychophysiological Research, New Orleans, Louisiana.

Graham, R., **Mayfield, A.R.**,. & Ceballos, N.A. (2012). *A longitudinal cross-cultural study of automatic and controlled processing of alcohol images in female college freshmen*. Paper presented at TM's 1st World Neuroscience Online Conference.

Graham, R., **Mayfield, A.R**., & Ceballos, N.A. (2012). *A longitudinal cross-cultural study of automatic and controlled processing of alcohol images in female college freshmen*. Paper presented at TM's 1st World Neuroscience Online Conference.

Reiter, K., **Mayfield, A.R.**, & Graham, R. (2012). *Event-Related Potentials to Static and Dynamic Expressive Faces.* Health Psychophysiology Lab, Department of Psychology. Poster presented at the Cognitive Neuroscience Society Meeting, Chicago, Illinois.

Abstracts

Mayfield, A. R., Lee, B.G., Mayfield, J.W., & Allen, D.N., (in press). Neurocognitive Correlates of the Comprehensive Trail Making Test (CTMT) in Children with Neurological Disorders. *Archives of Clinical Neuropsychology.*

Mayfield, A.R., Ciobanu. C., Etcoff. L., & Allen, D.N., (in press). Utility of WISC-IV Short Forms in Attention-Deficit/Hyperactivity Disorder (ADHD). *Archives of Clinical Neuropsychology.*

Mayfield, A.R., Reyes, A., Mayfield, J.W., & Allen, D.N., (in press). Improvement in Executive Function Following Traumatic Brain Injury (TBI) in Children. *Archives of Clinical Neuropsychology.*

Ceballos, N. A., **Mayfield, A. R.**, Paz, J. M., Vela-Gude, M. L., & Graham, R. (2012). A Cross-Cultural Study of Automatic and Controlled Processing of Alcohol Images in Female College Freshman. *Psychophysiology* (Vol. 49, pp. S105-S105).

Mayfield, A., Ceballos, N., & Graham, R. (2013). Alcohol-related Attentional Biases in Female College Freshman: A Cross-Cultural ERP Study. In *Journal of Cognitive Neuroscience* (pp. 211-211).

RESEARCH EXPERIENCE

Neuropsychology Research Program August 2013 - July 2018
University of Nevada, Las Vegas Advisor: Daniel N. Allen, Ph.D.

Graduate Research Assistant August 2013 - July 2018

- Collaborated in research related to neuropsychology.
- Conducted research related to cross cultural neuropsychology.
- Conducted literature reviews, write, and review manuscripts.
- Assisted in training of other students with IRB, statistics, etc.
- Conducted psychological assessments.

Relevant Projects

Study (dissertation): Network Analysis of Cognitive Symptom Domains in Alzheimer's Disease (AD)

- Responsibilities include project development, selection of study variables, proposal presentation and database acquisition. Additional responsibilities will include conducting literature review, statistical analysis and interpretation.

Study (thesis): Neurocognitive Correlates of the Comprehensive Trail Making Test (CTMT) in Brain Injured Children

- Responsibilities included project development, database management, selections and completion of statistically analyses, and manuscript preparation.

Study: Standardization of the Wechsler Intelligence Scale for Children, Fifth Edition (WISC-V).

- Responsibilities included recruiting, screening, and assessing children with traumatic brain injury, intellectual disability, and attention-deficit/hyperactivity disorder with the standardization version of the WISC-V to assist Pearson in establishing normative data.

Study: Standardization of Halstead Category Test, Computer Version.

- Responsibilities included training undergraduates and coordinating assessments of individuals from the UNLV Psychology subject pool in a two-part neuropsychological battery. Measures included the Halstead Category Test (computer and original version), and measures of intellectual functioning, executive functioning, motor functioning, and attention.

Study: Social Cognition in children with ADHD

- Screening and assessment of healthy controls and children with ADHD using an

extensive neuropsychological battery to assess social cognitive functioning

Event Related Potential Laboratory 2011-2013
Texas State University- San Marcos Advisor: Reiko Graham, Ph.D.

Event Related Potentials (ERP) Laboratory Coordinator
- EEG capping, administration of study protocol, data collection, data pre-processing, data processing, data plotting.

Salivary Analysis Laboratory Assistant
- Sample collection and handling, sample storage techniques, sample assay techniques.

TEACHING EXPERIENCE

University of Nevada Las Vegas August 2016 - May 2018
Las Vegas, NV

Instructor
- PSY 101 General Psychology
  - Designed and taught two sections of course per semester.
  - Prepared all course material, lecturing, assigning class grades, and advisement of students.

- PSY 451 Introduction to Principals of Psychotherapy
  - Designed and taught two sections of course per semester.
  - Prepared all course material, lecturing, assigning class grades, and advisement of students.

SERVICE

National Academy of Neuropsychology 2015-2017
Awards Committee - Student Member

UNLV Outreach Undergraduate Mentorship Program August 2013 - May 2018
Provided mentorship of undergraduate students from underrepresented populations to prepare them for a career in psychology or a related field.

Chair, Clinical Student Committee August 2016 - May 2017
Responsibilities included attending faculty meetings, assisting with interview weekend activities, organizing student focused events, and serving as a liaison between clinical faculty and graduate students.

The PRACTICE Advisory Board - Student Representative Summer 2017

Served as the student representative on the advisory board for the UNLV Partnership for Research, Assessment, Counseling, Therapy, and Innovative Clinical Education, The PRACTICE, is a community mental health training clinic. The advisory board works on planning and program development for the PRACTICE.

FURTHER TRAINING AND CERTIFICANTION

Nevada Psychological Association Comprehensive Training in Dialectical Behavior Therapy (DBT), Las Vegas, NV Presenter/Instructor: Alan Fruzzetti, Ph.D.

- Completed Part I: Theory, Structure, Targets, and Treatment Strategies, Feb. 5th – 7th, 2015
- Completed Part II: DBT Skills, Skill Training & Skill Coaching, Apr. 16th – 18th, 2015

SCID Training Program Fall 2015-Spring 2016
University of Nevada, Las Vegas Training Supervisor: Daniel N. Allen, Ph.D.

- Completed a 40-hour training program for administration of the Structured Clinical Interview of the DSM-IV-TR Axis I Disorders (SCID-IV).

Symptoms Rating Training Program Fall 2015 – Spring 2016
University of Nevada, Las Vegas Training Supervisor: Daniel N. Allen, Ph.D.

- Completed a 30-hour training program for the administration of several of clinician administered symptom scales associated with symptoms of schizophrenia and bipolar disorder.

The Collaborative IRB Training Initiative (CITI) Program Fall 2013 - Present

- Certified to work with human participants through The Protection of Human Research Subjects online course, sponsored by The Collaborative IRB Training Initiative (CITI) Program.

HONORS AND AWARDS

Barrick Graduate Fellowship 2017-2018
This fellowship is awarded to outstanding doctoral students who have demonstrated excellence in scholarship during their graduate study at UNLV. These fellowship awards provide a $15,000 stipend; full tuition and fees paid up to 9 credits per semester, full health insurance benefits, and a waiver of out-of-state tuition, if applicable.

Graduate & Professional Student Association travel funding 2016
Awarded funding to attend and present at The National Academy of Neuropsychology 36th Annual Convention, Seattle, WA ($700).

Graduate & Professional Student Association travel funding 2015

Awarded funding to attend and present at The National Academy of Neuropsychology 35th Annual Convention, Austin, Texas ($750).

Graduate & Professional Student Association travel funding 2014
Awarded funding to attend The National Academy of Neuropsychology 34th Annual Convention in Fajardo, Puerto Rico ($800).

Graduate Access Grant ($2,000) 2013 - 2017

Member, **Psi Chi** the National Honor Society in Psychology 2008 - 2011

AFFILIATIONS AND ACTIVITIES

Member, American Psychological Association 2013 - present

Member, National Academy of Neuropsychology 2013 - present

Member, Nevada Psychological Association 2013 - present

Member, International Neuropsychological Society 2018 - present

REFERENCES

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