NONVERBAL SPREADING ACTIVATION IN ALZHEIMER'S DISEASE

by

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ABSTRACT

The purpose of this study was to determine the degree of nonverbal spreading activation within a sample of individuals diagnosed with Alzheimer's disease (AD) as compared to a control group. Prior research on spreading activation has typically focused on verbal memory networks. Nonverbal spreading activation is a relatively new topic that has received little research attention to date. This study measured nonverbal spreading activation using the Design Frequency Corpus created by Paul S. Foster. Results indicated that nonverbal spreading activation was roughly equal between the two groups. This finding supports typical AD pathology, which primarily impacts the left hemisphere of the brain and relatively preserves the right hemisphere. Additionally, results indicated that verbal spreading activation was significantly different among the two groups. Clinical and research implications of these findings will be discussed.

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CHAPTER I

INTRODUCTION

Alzheimer's Disease

Leifer (2009) states that Alzheimer's disease (AD) is the most frequently occurring manifestation of the dementias. Blennow, de Leon, and Zetterberg (2006) further report that AD makes up between 50% to 60% of all dementia cases. AD is a progressive neurodegenerative disease that has a slow and gradual onset. The disease affects over 4.5 million people within the United States alone (Leifer, 2009). Globally, Alzheimer's disease has been estimated to affect over 15 million people (Blennow et al., 2006). The earliest signs of AD are often disregarded or mistaken as common symptoms that can be attributed to the natural process of aging. Alzheimer's disease often remains undiagnosed until symptoms escalate to more severe and distinguishing stages of the disease (Blennow et al., 2006). This delay could help describe why less than half of the people who qualify for a diagnosis are currently diagnosed with AD. A recent study has shown physician diagnosis of AD typically occurs an average of one year after the emergence of symptoms occurs (e.g., Leifer, 2009).

Backman, Jones, Berger, Laukka, and Small (2004) report that with pre-clinical AD, individuals typically begin performing worse in episodic memory, executive functioning, verbal ability, visuospatial skills, attention, and perceptual speed compared to those who will not receive a similar diagnosis. This impairment can sometimes be seen years or even several decades before a clinical diagnosis occurs (Backman et al., 2004). Episodic memory tasks (such as facial recognition and word recall) have proven to be of

specific empirical use for detecting individuals whom are at risk for future development of AD. Further, measures of overall cognitive decline have similar accuracy in diagnosing preclinical AD. This includes the aforementioned measures of episodic memory, executive functioning, perceptual speed, verbal ability, visuospatial skills, and attention. However, the first three abilities seem to possess the most accuracy in differentiating between those with preclinical AD and control groups (Backman et al., 2004).

The formation of new memories generally remains intact in typical aging. One distinguishing factor between AD and typical age-related decline is that AD will cause problems with activities in daily living (ADL), such as getting lost in familiar places, forgetting recent events, and a decline in motor functioning. AD is often ignored until problems with overall function, behavior, and cognition worsen and cannot be only attributed to the typical effects of aging. Specific symptoms of AD that cannot be attributed to the normal aging process include: memory loss, difficulties with everyday tasks, language problems, decreased orientation to time and place, decreased judgment, difficulty with abstract thinking, misplacing items, irregular mood/behavior, personality changes, and decreases in initiative and motivation. Clinically, AD may manifest as symptoms such as aphasia, apraxia, agnosia, problems with executive functioning, and gradual changes in personality (Braak & Braak, 1995; Leifer, 2009). Raz et al. (1987) further noted that global skills, such as memory, decline before lateralized cognitive abilities are impacted in patients with AD. Braak and Braak (1995) described that symptom intensification reveals the steady increase of brain atrophy, which spreads in a

predictable fashion across the following brain regions: the hippocampus, the neocortex and a number of subcortical nuclei (Braak & Braak, 1995).

According to Blennow et al. (2006), studies have found various causes and associations linked to AD. Aging appears to be the most prominent risk factor for developing dementias, including AD. Despite only 1% of individuals aged 60 to 64 years old having dementia, the prevalence rate profoundly raises to 24% to 33% in individuals aged 85 years old or above (Blennow et al., 2006). AD rates are predicted to rise due to anticipated increases in life expectancy as medicine and technology continue to advance. Other provisional associations found by studies include reduced brain capacity, low achievement in education and occupation, decreased mental development in early years, along with reduced physical and mental abilities later in life (Blennow et al., 2006).

Braak and Braak (1995) report that the hippocampal formation, the presubiculum, and the entorhinal region play an essential role in the preservation of memory. These regions begin to break down in AD (Braak & Braak, 1995). Furthermore, both structural and functional imaging have shown that the hippocampal complex is impacted long before official diagnosis of AD occurs. According to Backman et al. (2004), the medial-temporal lobe (MTL), anterior cingulate, temporal sulcus, posterior cingulate, neocortical temporoparietal regions, frontal regions, precuneus, and temporal and frontal cortices are often affected before AD is formally diagnosed. Further, Reilly, Antonucci, Peele, and Grossman (2011) report that AD functions as a disconnection syndrome caused by deficiencies in the lexical and/or visual access to intact semantic representations. This disconnect is a result of damage to the perforant pathways, which connects the

hippocampus to the entorhinal cortex. Others argue that there is a decay of core semantic representations, which is supported by naming and error distribution patterns (Reilly et al., 2011). As mentioned by Balthazar, Cendes, and Damasceno (2008), this population commonly complains of naming difficulties. Further, Balthazar et al. (2008) state that some hypothesize that naming difficulties are due to a disruption of concepts and semantic knowledge, while others hypothesize that naming difficulties are caused by difficulty in accessing the intact lexical-semantic field (p. 703).

Braak and Braak (1995) mention that neurodegeneration is initially restricted to the transentorhinal region in the earliest preclinical stages. There is destruction in the entorhinal and transentorhinal regions in the middle stage, which is accompanied by mild changes in the hippocampus. It should be noted that most of the neocortex is not involved in this stage. However, the damaged entorhinal and transentorhinal regions obstruct the ability of the neocortex and hippocampus to convey data to one another. The middle stage represents impending AD, which manifests as cognitive function impairment and subtle personality changes. The late stage is specified by the severe destruction of neocortical association areas and corresponds with clinical criteria for a diagnosis of AD (Braak & Braak, 1995). The later stages also are marked by a significant number of neuritic amyloid plaques (NP) and neurofibrillary tangles (NT) in essentially all parts of the cerebral cortex. According to Delacourte et al. (1999), amyloid plaques and neurofibrillary tangles are the two lesions considered characteristic of AD. The plaques are a product of extracellular accumulations of Aβ peptide and the tangles are made up of intraneuronal groupings of paired helical filaments (PHF). Paired helical filaments are a

product of aggregated pathologic tau proteins, also referred to as PHF-tau. These two lesion types spread gradually throughout the brain, eventually reaching neocortical brain areas during the course of AD.

Backman et al. (2004) state that the anterior cingulate, temporal sulcus, posterior cingulate, neocortical temporoparietal, and frontal regions tend to have noticeable atrophy and reduction of volume. Other areas also are affected: the posterior cingulate and precuneus regions are affected by a reduction in blood circulation, the temporoparietal regions lose efficiency in metabolizing glucose, and the frontal and temporal cortex begin to collect deposits of neuritic amyloid plaques (Blackman et al., 2004). Also, more generalized modifications in preclinical AD brain functions have been noted, such as elevations of white matter hyperintensities and a general whole-brain decrease of the ability to metabolize glucose. This whole-brain decrease in glucose metabolization occurs asymmetrically in AD, which may suggest that the disease affects cerebral hemispheres unequally (Raz et al., 1987).

Scahill, Schott, Stevens, Rosser and Fox (2002) found in three patient groups consisting of pre-symptomatic, mild, and moderate AD that all had bilateral atrophy. However, left hemisphere atrophy occurred more prominently compared to right hemisphere atrophy. Bugiani, Constantinidis, Ghetti, Bouras, and Tagliavini (1991) support this notion in their study, which found that most AD patients have one hemisphere that experiences more negative effects. Their study found that 75% of the experimental group had structural degradation that was more prominent in the associated areas surrounding the left sylvian fissure. All of the patients who showed more left

hemisphere damage complained of memory loss and language deterioration, while those who experienced more right hemisphere damage complained of short-term recall and time orientation issues (Bugiani et al., 1991). Nielsen, Zielinski, Ferguson, Lainhart, and Anderson (2013) report that lateralized brain functions primarily control both language and visuospatial abilities. Devoting attention to language-based stimuli results in greater brain activity in the left hemisphere in the typical human brain. Further, the left hemisphere contains classical language regions including Broca's area and Wernicke's area. Yet, attending to visuospatial-based stimuli results in greater brain activity in the right hemisphere.

Spreading Activation Overview / Nonverbal Spreading Activation

Roediger, Balota, and Watson (2001) summarize that spreading activation can be described as the process in which the brain navigates through an entire network of ideas to retrieve specific information. Current theories and investigations of spreading activation typically focus on semantic memory networks. A theory regarding the functioning of spreading activation in semantic processing was presented by Collins and Loftus in 1975. This theory focused on the notion that specific semantic memories (e.g., rats) are structured as nodes within a semantic network that contains a larger-scale concept (e.g., animals). Therefore, each semantic memory is represented as a node within a conceptual network. Related semantic nodes (e.g., rats and mice) within a semantic conceptual network (e.g., animals) will share stronger connections through associative, bidirectional links than semantic nodes from different conceptual networks will. These associative links within a conceptual network will have varying strengths between nodes

of a network, with some of the connections being stronger (e.g., rats and mice) and others sharing relatively weaker associative connections (e.g., rats and possums).

When a particular node is activated, activation will spread along associative links to other similar nodes within the network. Spreading activation will first take place to the nodes linked to the original node and then branch out towards nodes linked further away, and so forth. Typically, the strength of the connections between conceptual nodes is, in part, determined by production frequency norms or the frequency of use of the links. Foster and Drago (2013) proposed that the connection strength between specific conceptual nodes is likely related to the Hebbian principle, which states that neurons (or neuron assemblies that make up the semantic network) that fire together wire together. According to Foster et al. (2018), the speed of the spreading activation that occurs is influenced by the strength of the associative links between the nodes. The degree of spreading activation that occurs is influenced by the potency of the initial activation of the node, to the extent that greater initial activation will result in a greater spread of activation from that node. Therefore, a stronger initial activation will produce a greater spread of activation from the initial node to other nodes, including those with either weaker direct or even indirect connections to the initially activated node. The spreading activation will then decrease over time or with some intervening activity (Collins & Loftus, 1975). Foster et al. (2018) mentions dopamine's role in constricting spreading activation as an example of an intervening activity.

The Controlled Oral Word Association Test (COWAT) is a measure of verbal fluency that can additionally be used as an instrument to measure verbal spreading

activation (e.g., Foster et al., 2014; Foster, Drago, et al., 2013; Foster, Roosa, et al., 2013; Foster et al., 2012; Foster et al., 2011; Foster et al., 2008). Specifically, this measurement can be done by calculating the average word frequencies for the respondent's generated words. Words that occur more frequently in the English language, should have stronger representations and hence require less spreading activation. Alternatively, infrequently occurring words should require a greater extent of spreading activation. Therefore, increased spreading activation leads to low overall average word frequency, since a greater number of lower frequency words will be included. Alternatively, decreased spreading activation is associated with higher average word frequency due to responses consisting of higher frequency words. Finally, the word frequencies are calculated by how often the response words that are generated on the COWAT are normally used by English speakers/readers (Foster et al., 2018).

The Ruff Figure Fluency Test (RFFT) is a measure of nonverbal fluency that can be used similarly to the COWAT for investigating spreading activation in visuospatial/nonverbal memory networks (Foster et al., 2018). Specifically, this measurement can be done by calculating the frequency of each design produced by respondents on the RFFT. The Design Frequency Corpus developed by Foster is based on normative data from the RFFT and contains 1397 different designs produced by the normative sample on the test. The frequency of each of these different designs is included in the corpus. Hence, similar to obtaining word frequencies based on the COWAT, the Design Frequency Corpus permits investigators to obtain a design frequency and use it as a measure of spreading activation in nonverbal/visuospatial

memory networks. Designs produced less frequently should require a greater extent of spreading activation, whereas more frequent designs should be closer in the network and require less spreading activation. Therefore, increased spreading activation leads to lower overall average design frequency, since a greater number of lower frequency designs will be included. Alternatively, decreased spreading activation is associated with higher average design frequency due to responses consisting of higher frequency designs (Foster et al., 2018).

Numerous other spreading activation and semantic priming models have been presented to date. However, these models all focus on the structure and flow of information within semantic memory. Yi, Moore, and Grossman (2007) explain that semantic memory is a shared collection of knowledge about the world that is common to many, such as long-term representations of objects, actions, ideas and thought processes that allow people to communicate meaningfully with others. These models primarily center their attention on verbal memory networks, despite the fact that research has suggested separate verbal and nonverbal (or visuospatial) memory networks do exist. Studies conducted on the Wechsler Memory Scale - Revised (WMS-R) have found healthy individuals to have separate verbal and visuospatial memory factors (Jurden, Franzen, Callahan, & Ledbetter, 1996; Moore & Baker, 1997). These findings are not isolated to the WMS-R, other studies also have identified separate factors when investigating a variety of tests of verbal and visuospatial memory within a large neuropsychology test battery (Clark et al., 2004; Heilbronner, Buck, & Adams, 1989; Larrabee, Trahan, & Curtiss, 1992; Robinette, Sherer, & Adams, 1993). Therefore, the

findings of these aforementioned studies support the existence of separate verbal and visuospatial memory systems

Variations in the role of the left and right hemispheres in verbal and visuospatial memory have been reported. Specifically, left hippocampal volume has been found to correspond with verbal memory, whereas right hippocampal volume corresponds with visuospatial memory (Baxendale et al., 1998). Coleshill et al. (2004) found that electrical stimulation focused on the left hippocampus hindered word recognition, while electrical stimulation on the right hippocampus hindered facial recognition. Further, encoding words has been linked to triggering left hippocampal activation, whereas encoding faces has been linked to triggering right hippocampal (and amygdala) activation (Powell et al., 2005). Researchers have produced additional evidence in regard to the different hemispheric roles for verbal and visuospatial information. Patients with left temporal lobe epilepsy exhibited relative impairment in verbal memory, while patients with right temporal lobe epilepsy exhibited relative impairment in visuospatial memory (Bohbot et al., 1998; Bornstein, Pakalnis, & Drake, 1988; Jones-Gotman et al., 1993; Kim, Yi, Son, & Kim, 2003; Moscovitch & McAndrews, 2002). Graydon, Nunn, Polkey, and Morris (2001) detected a deteriorated auditory verbal memory following patients whom underwent left unilateral temporal lobectomy and a deteriorated visuospatial memory following patients whom underwent right unilateral lobectomy. Pillon et al. (1999) established additional evidence on lobectomy findings by demonstrating the important concept of double dissociation between left/right temporal lobectomy patients and their performance on verbal versus visuospatial memory tasks.

This study focused on investigating spreading activation within both verbal and nonverbal memory networks in patients with AD versus normal, healthy individuals. Given the relatively greater left hemisphere dysfunction associated with AD, it was predicted that patients with AD will exhibit reduced spreading activation within verbal memory networks, as indicated by higher average word frequencies from the COWAT. Further, patients with AD were predicted to exhibit no significant difference in spreading activation within nonverbal memory networks, as indicated by similar average design frequency scores on the RFFT.

CHAPTER II

METHOD

Participants

This study was retrospective in nature and included an experimental group of patients diagnosed with Alzheimer's disease (AD) and a normal, healthy control group. The patients with AD in the experimental group had been evaluated for memory and cognitive problems at Murfreesboro Medical Clinic (MMC) by a licensed neuropsychologist and on the basis of this evaluation were diagnosed with AD. The criteria to diagnose Alzheimer's disease was based on the diagnostic guidelines provided by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA; McKhann et al., 1984). The AD group consistent of 24 individuals with an age range of 59 to 86 years (M = 71.83, SD = 7.22). Mini-Mental State Examination (MMSE) scores among the patients with AD ranged from 16 to 30 (M = 23.83, SD = 3.56). Most patients with AD were classified as mild, i.e. MMSE score of 20 or above. There were 4 patients with AD whose scores fell below 20. No patients in the AD group were taking acetylcholinesterase inhibitors at the time of their neuropsychological evaluation. Participants within the control group consisted of healthy relatives of patients in the experimental group, individuals who presented at MMC for a memory evaluation and were not found to have any memory or cognitive problems, or individuals who volunteered to participate in a normative study on aging. The control group consisted of 24 participants aged 62 to 86 with a mean age of 72.67 years (SD = 6.38). The

participants in the control group were not found to have memory problems following a comprehensive neuropsychological evaluation and/or had scores of 25 or above on the MMSE to ensure there was no cognitive impairment. The MMSE scores in the control group ranged from 23 to 30 (M = 27.96, SD = 1.90). There were 2 participants in the control group who had MMSE scores below 25. However, since their performance on a comprehensive neuropsychological test battery indicated no problems with memory and cognitive functioning they were included in the present study. Each group consisted of 18 female and 6 male participants. Exclusionary criteria for the full sample include individuals with a reported history of head injury, stroke, or neurological diagnoses other than AD. Table 1 provides a summary of demographic information by group.

Table 1

Demographic Information for Each Group

	Control *M* (*SD*)	AD *M* (*SD*)	*F*	*p*
Age	72.67 (6.38)	71.83 (7.22)	0.180	0.674
Education	13.74 (2.47)	12.33 (3.34)	3.48	0.068
GDS	7.04 (6.96)	7.54 (5.57)	0.07	0.789

Measures

Controlled Oral Word Association Test (COWAT). Strauss, Sherman, and Spreen (2006) state that the purpose of the COWAT (also known as the verbal fluency test) is to assess unprompted word production under specific conditions. Specifically, the COWAT

is a verbal fluency measure that is sensitive to left temporal and left frontal brain dysfunction. F, A, and S are the most commonly used letter sets, but other combinations exist (Strauss et al., 2006). Clients are given the instruction that the examiner will say a letter and the test taker will need to say as many words as possible that begin with that letter. The test taker is instructed not to say proper nouns or the same words with different tenses or endings. The examiner gives the test taker 60 seconds to name words that begin with the stated letter. If the test taker states a word that could be either an ordinary word or a proper noun (e.g., frank), then the examiner recorded the response and inquired about the examinee's use of the word after the allotted time span has concluded for the particular letter. Also, the test taker is allowed to say the same word with different meanings (e.g., to, two, too) and each meaning was considered individually and clarified after administration (Ruff, Light, Parker, & Levin, 1996). The dependent variable of interest is the average word frequency for the words generated on the COWAT. Word frequencies were obtained using the Francis and Kucera corpus (Francis & Kucera, 1982). Words that appeared less commonly in English literature at the time the corpus was constructed were assigned lower scores, down to a minimum of 0 for infrequent words or words not in the corpus. Words that appeared more commonly in English literature (e.g., and) were conversely assigned higher scores.

Strauss et al. (2006) assessed the COWAT's reliability in two ways. First, they assessed a coefficient alpha by adding the total number of words produced for each separate letter and then totaled the scores to create a measure of internal consistency. The test was found to have a coefficient alpha of $r = .83$ and a test-retest reliability of above

.70 for both letter and semantic fluency. Alternative form reliability was found to be .74. Interrater reliability is significantly high at .99. Regarding validity, the correlation between different versions of the COWAT is high with forms ranging between .85 to .94.

Geriatric Depression Scale (GDS). Yesavage, Brink, Rose, and Lum (1983) developed the GDS. Strauss et al. (2006) state that the purpose of the GDS is to screen the elderly for depression by measuring affective and behavioral symptoms and excluding measures for somatic symptoms and dementia. The format of the GDS includes 30 true or false questions designed to allow for easy self-administration. Administration takes about 5 to 10 minutes. Scores span from 0 (no depression) to 30 (severe depression). The dependent variable of interest for this measure is the total score on the GDS.

Yesavage et al. (1983) report that internal consistency has been shown to be high (r = .94). Split half reliability also has demonstrated high correlations (r = .94) (Yesavage, et al., 1983). When retesting over spans of 1 week to 2 months, test-retest correlations for the GDS were found to be high (r = .80 to .98). When retest periods were increased to 6 months, the correlations were lower (>.70). GDS test scores correlate moderately with related self-report measures, such as the Beck Depression Inventory (r = .73 to .90) and the Hamilton Scale (r = .33 to .83), which provides backing for the convergent validity of the GDS. The GDS also has been compared to cognitive screening tests (e.g., MMSE) and found low correlations, providing support for the divergent validity of this measure (Strauss et al., 2006).

Mini Mental State Examination (MMSE). Strauss et al. (2006) explain that the purpose of the MMSE is to assess for mental impairment, especially in elders. Tombaugh and McIntyre (1992) describe the exam as lasting between 5 to 10 minutes. The questions can be grouped into seven distinct categories: orientation to time, orientation to place, registration of three words, attention and calculation, recall of three words, language, and visual construction. The MMSE is used to classify the severity of impairment in dementia patients. Typically, scores are broken down into the following ranges: 0-17 = severe cognitive impairment, 18-24 = mild cognitive impairment and 25-30 = no cognitive impairment (Folstein, Folstein, & McHugh, 1975). The dependent variable of interest is the total score on the MMSE.

A sample of medical patients showed the highest correlation in internal consistency (r = .96), while three community samples showed lower levels (r = .31, .68, and .77) (Strauss et al., 2006). Interrater reliability has shown to be acceptable (above .65). Test-retest scores of both cognitively impaired and intact groups demonstrated a reliability score between .80 and .95 when remeasured in intervals of less than 2 months (Strauss et al., 2006). The MMSE has been assessed for concurrent validity with various other cognitive functioning tests. The MMSE showed a .78 correlation with the verbal scale and a .66 correlation with the performance scale of the Wechsler Adult Intelligence Scale. When compared to the 26-item Blessed Information-Memory-Concentration test (BIMC) and the shortened Blessed Orientation-Memory-Concentration test (BOMC), there was a correlation of -0.66 and -0.93. Further, the MMSE has demonstrated modest-

to-high correlations to other cognitive tests such as the Trails B, WMS, digit span, story recall, and word list recall (Folstein et al., 1975; Tombaugh & McIntyre, 1992).

Ruff Figural Fluency Test (RFFT). The RFFT was created by Ron M. Ruff (1996) as a measure of nonverbal fluency and executive functioning comparable in nature to letter fluency (verbal fluency) tasks, such as the Controlled Oral Word Association Test. The RFFT is a design fluency measure that is sensitive to right anterior and right frontal brain dysfunction (Strauss et al., 2006). Fluency is defined as the ability for an individual to utilize strategies that maximize response production while at the same time avoiding response repetition (Ruff, Allen, Farrow, Niemann, & Wylie, 1994). Specifically, Strauss et al. (2006) describe that the RFFT serves as a measurement of participants' abilities to produce unique designs under time constraints. The RFFT is used to calculate nonverbal fluency (figural fluency) by the total number of unique designs produced across five trials. The dependent variable of interest is the average design frequency for all designs produced on the RFFT, as obtained by the Design Frequency Corpus (Foster et al., 2018). The Design Frequency Corpus assigned less common designs with a lower point value, down to a minimum of 0 for infrequent or unrecorded designs. Conversely, commonly appearing designs were assigned a higher point value.

The RFFT was found to be a reliable measure (test-retest reliability: $r = .76$), while preservative scores were less established ($r = .36$). Therefore, respondents are more likely to increase their numbers of unique designs when retested. Further, the test was found to have concurrent validity with a similar Design Fluency Measure by Jones-Gotman and Milner (Ruff, 1996). Ross (2014) reported that the RFFT has modest

convergent validity demonstrated by correlations between designs created on the RFFT and other measures of executive functioning. However, there are mixed results for divergent validity as evidenced by the RFFT indices modestly correlating with Block Design performance and nonverbal measures of working memory, while indices were unrelated to measures of verbal fluency, verbal learning, and working memory for verbal material (Ross, 2014).

Procedure

After review and approval from Middle Tennessee State University's Institutional Review Board (Appendix A), participants had their archived data examined by the researcher. This study was retrospective in nature as the data for the patients with AD and the control group existed prior to the onset of this study. The case files were all reviewed and matches were found between the patients with AD and the control participants in regard to their age and gender. The COWAT, RFFT, GDS, and MMSE were all administered following standardized procedures. All tests were administered in a pseudo-random manner for AD patients as these tests were administered in the context of a larger neuropsychological evaluation by a licensed clinician, while controls were administered the tests in a randomized manner by a licensed clinician. The frequency of each word produced on the COWAT was obtained using the Francis and Kucera (1982) corpus. An average word frequency was then calculated for each participant. The frequency of each design produced on the RFFT was obtained by using the Design Frequency Corpus (Foster et al., 2018). An average design frequency was then calculated for each participant.

CHAPTER III

RESULTS

Initial analyses were conducted using a series of oneway ANOVAs to determine group differences in age, education, and GDS score between the two groups. Results indicated no significant differences between the AD and the control group for age, education, and GDS score (see Table 1). However, the differences in education between the groups approached significance (p = .068). Hence, education level was included as a covariate in all subsequent analyses to ensure that this variable was not a confound. Finally, any differences between the groups in regard to the number of words produced on the COWAT or the number of unique designs produced on the RFFT were also evaluated using oneway ANOVAs. The results indicated a significant difference, $F(1, 47) = 4.50$, p = .039, between the AD and control group in the number of words produced on the COWAT, with the AD group producing significantly few words (M = 30.25, SD = 14.51) than the control group (M = 38.33, SD = 11.76). A significant difference, $F(1, 47) = 6.77$, p = .012, was also found between the groups in regard to the number of unique designs produced on the RFFT, with the AD group generating significantly fewer designs (M = 47.46, SD = 19.40) than the control group (M = 61.96, SD = 19.21). Although the number of words and unique designs generated by the two groups significantly differed, this was controlled by using the average word frequency and the average design frequency, as opposed to using the total word and design frequencies.

To examine the first hypothesis that patients with AD would exhibit a higher average word frequency, and hence experience less verbal spreading activation than the

control group, a one-way ANCOVA (α = .05) was conducted on the average word frequency scores from the COWAT. Word frequencies were found to be significantly lower among the AD group (M = 201.99, SD = 226.01) as compared to the control group (M = 537.88, SD = 561.88) when controlling for education, $F(1, 45) = 8.89$, $p = .012$.

To examine the second hypothesis that no significant difference would be found between the AD and the control groups in regard to design frequency, and hence indicate the two groups experienced similar degrees of nonverbal spreading activation, another one-way ANCOVA (α = .05) was conducted on the average design frequencies from the RFFT. Design frequencies were not found to be significantly different between the AD group (M = 88.81, SD = 42.37) and the control group (M = 82.87, SD = 42.03), when controlling for education, $F(1,45) = .18$, $p = .676$.

CHAPTER IV

DISCUSSION

The purpose of this study was to determine the degree of nonverbal spreading activation within a sample of individuals diagnosed with Alzheimer's disease (AD) as compared to a control group. According to current results, the hypothesis predicting average design frequency scores between the two groups would be roughly equal was supported. The two groups responded with an average of similarly common designs on the RFFT as determined by the Design Frequency Corpus. These similar design frequency scores indicate that the two groups exhibited similar degrees of nonverbal spreading activation. This finding is consistent with the finding that AD primarily impacts the left hemisphere of the brain and relatively preserves the right hemisphere, especially in the early (or mild) stages of AD (Bugiani et al., 1991; Scahill et al., 2002). Further, past research has shown that early AD does not significantly affect brain functions associated with the right hemisphere (Nielsen et al., 2013), such as nonverbal spreading activation. The majority of patients tested in the present study were classified as having mild AD, and hence earlier in the disease course. Therefore, due to the aforementioned right hemisphere preservation that occurs in early AD, nonverbal spreading activation was not found to be impacted within our sample. As AD progresses, the right hemisphere also becomes more involved (Braak & Braak, 1995). Hence, the possibility exists that spreading activation within nonverbal memory networks may become affected in later stages of the disease. Further research will need to be conducted to determine if patients with moderate to severe AD exhibit disruption in spreading

activation within nonverbal memory networks, as compared to those with mild (or early) AD.

One implication from this study is that given the relative preservation of nonverbal spreading activation, the possibility exists that patients with mild cognitive impairment or early AD might benefit from mnemonic techniques that utilize visuospatial functions, such as the method of loci. As an example, the method of loci can be used with visuospatial memory by having an individual walk down a street lined with buildings. Later, have that individual recall the buildings from said street by visualizing themselves walking down the street again. Previous research has demonstrated a relationship between episodic memory and the extent of spreading activation (Foster, Roosa, et al., 2013). Hence, there is a possibility that greater spreading activation in nonverbal memory networks may be associated with better visuospatial memory. Research has in fact found that elderly individuals benefit from the method of loci (Gross et al., 2014). Further, Engvig and colleagues (2010) reported that elderly individuals who were trained in the method of loci exhibited regional increases in cortical thickness. However, to date there have been no research projects reported that have examined whether patients with mild cognitive impairment or mild AD may benefit from this mnemonic technique. Given the present findings, it may be important for future research to address this possibility.

The second hypothesis that average word frequency scores would be significantly higher in the AD group was not supported by the data in this study. Rather, the opposite was found, and the AD group recorded lower average word frequency scores on the

COWAT as calculated by the Francis and Kucera corpus. These lower word frequency scores indicate that our AD group exhibited a higher degree of verbal spreading activation compared to healthy controls. This finding is consistent with past research where AD patients produced lower frequency words on the COWAT compared to controls (Foster, Drago, et al., 2013). However, our AD group also recorded fewer word responses on the COWAT overall, which made the word frequencies potentially more susceptible to erratic fluctuations when being averaged. The increased verbal spreading activation in our AD group may be explained by the possibility that the AD group experienced a higher degree of spreading activation in their lexical networks to offset the deterioration of semantic networks. Further, increased verbal spreading activation in our AD group may also be explained by the effects of acetylcholine, which has been linked to attentional systems and is known to have decreased levels within AD patients (Foster, Drago, et al., 2013). Since the AD patients in this study were not taking acetylcholinesterase inhibitors, it is expected they had decreased levels of acetylcholine which could result in attentional difficulties and consequently increased verbal spreading activation. Following these findings, it is also known that AD patients commonly experience difficulties with finding words. The possibility exists that this word finding difficulty may be caused by the increased degree of verbal spreading activation, which might make it harder for those suffering with AD to find the more common, and intended, words, thereby delaying their response time.

Additionally, AD begins in the hippocampus and spreads to the temporal lobes, eventually progressing to the parietal lobes and finally reaching the frontal lobes (Braak

& Braak, 1995). However, since this study focused on participants within the early stages of AD, the frontal lobes were not yet affected while the posterior cortex was affected. This could relate to Denny-Brown's concept of transcortical release, meaning that while the parietal lobes produced less activity the frontal lobes consequently increased activity. The findings in this research raise the question of whether or not patients with moderate to severe AD would also exhibit decreased posterior lobe activity and increased frontal lobe activity.

Limitations

There were three main limitations to this study. First, the total sample size was small with a total of 50 participants causing a potential reduction in statistical power. There is a possibility that different results would be found with a larger sample size and hence more power. However, this possibility is tempered by the fact that the probability of the obtained *F* score was considerably high and far from being significant.

Further, the Francis and Kucera word corpus used in this study was dated, with its publication taking place in 1982. Hence, the corpus lacked some modern words used in the English language which are commonly heard or read in today's media. Further, the Francis and Kucera word corpus is made up of words that were found exclusively in books at the time of creation. A more recent corpus, such as the Corpus of Contemporary American English (COCA), may yield different average word frequency results. This is due to the fact that COCA is not only a more recent corpus, but it is also equally constructed from spoken words, fiction, popular magazines, newspapers, and academic texts. However, given the age of our sample, the Francis and Kucera corpus may be the

most appropriate corpus despite its dated publication. A future study comparing results with two separate corpora should be considered.

Finally, the Design Frequency Corpus is a new measure and research is needed to examine it's construct validity. The present findings would be strengthened if future research finds that design frequency is related to right hemisphere functioning. Also, additional research should focus on making within group comparisons to determine if there are differences between verbal and nonverbal spreading activation within healthy individuals as well as those with AD. Unfortunately, this would require a normative database of spreading activation and to date this database does not exist.

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APPENDICES

APPENDIX A

MTSU IRB Approval Letter

IRB
INSTITUTIONAL REVIEW BOARD
Office of Research Compliance,
010A Sam Ingram Building,
2269 Middle Tennessee Blvd
Murfreesboro, TN 37129

MIDDLE TENNESSEE STATE UNIVERSITY

IRBN007 – EXEMPTION DETERMINATION NOTICE

Thursday, September 06, 2018

Principal Investigator	**Christopher Magliacano** (Student)
Faculty Advisor	Paul S. Foster
Co-Investigators	NONE
Investigator Email(s)	*cmm6x@mtmail.mtsu.edu; paul.foster@mtsu.edu*
Department	Psychology
Protocol Title	***Non-verbal spreading activation in Alzheimer's disease***
Protocol ID	**18-1276**

Dear Investigator(s),

The above identified research proposal has been reviewed by the MTSU Institutional Review Board (IRB) through the **EXEMPT** review mechanism under 45 CFR 46.101(b)(2) within the research category *(4) Study involving existing data* A summary of the IRB action and other particulars in regard to this protocol application is tabulated as shown below:

IRB Action	**EXEMPT from furhter IRB review*** **	Date	9/4/18
Date of Expiration	NOT APPLICABLE		
Sample Size	100 (ONE HUNDRED)		
Participant Pool	**Senior Citizens (65 years or older) - 1. Archival medical data collected from patients suffering from Alzheimer's disease during routine clinical visits; 2. Patients who do not have AD to constitute as control group; 3. Age-range is 65-85.**		
Exceptions	NONE		
Mandatory Restrictions	1. Participants must be 18 years or older 2. Informed consent must be obtained from the participants 3. Identifying information must not be collected		
Restrictions	**1. All requirements for exemption apply.** **2. Not applicable for new participant enrollment - existing data only.**		
Comments	NONE		

***This exemption determination only allows above defined protocol from further IRB review such as continuing review. However, the following post-approval requirements still apply:

- Addition/removal of subject population should not be implemented without IRB approval
- Change in investigators must be notified and approved
- Modifications to procedures must be clearly articulated in an addendum request and the proposed changes must not be incorporated without an approval
- Be advised that the proposed change must comply within the requirements for exemption
- Changes to the research location must be approved – appropriate permission letter(s) from external institutions must accompany the addendum request form

- Changes to funding source must be notified via email (irb_submissions@mtsu.edu)
- The exemption does not expire as long as the protocol is in good standing
- Project completion must be reported via email (irb_submissions@mtsu.edu)
- Research-related injuries to the participants and other events must be reported within 48 hours of such events to compliance@mtsu.edu

Post-approval Protocol Amendments:

The current MTSU IRB policies allow the investigators to make the following types of changes to this protocol without the need to report to the Office of Compliance, as long as the proposed changes do not result in the cancellation of the protocols eligibility for exemption:

- Editorial and minor administrative revisions to the consent form or other study documents
- Increasing/decreasing the participant size

Only THREE procedural amendment requests will be entertained per year. This amendment restriction does not apply to minor changes such as language usage and addition/removal of research personnel.

Date	Amendment(s)	IRB Comments
NONE	NONE.	NONE

The investigator(s) indicated in this notification should read and abide by all applicable post-approval conditions imposed with this approval. Refer to the post-approval guidelines posted in the MTSU IRB's website. Any unanticipated harms to participants or adverse events must be reported to the Office of Compliance at (615) 494-8918 within 48 hours of the incident.

All of the research-related records, which include signed consent forms, current & past investigator information, training certificates, survey instruments and other documents related to the study, must be retained by the PI or the faculty advisor (if the PI is a student) at the sacure location mentioned in the protocol application. The data storage must be maintained for at least three (3) years after study completion. Subsequently, the researcher may destroy the data in a manner that maintains confidentiality and anonymity. IRB reserves the right to modify, change or cancel the terms of this letter without prior notice. Be advised that IRB also reserves the right to inspect or audit your records if needed.

Sincerely,

Institutional Review Board
Middle Tennessee State University

Quick Links:

Click here for a detailed list of the post-approval responsibilities.
More information on exmpt procedures can be found here.