5-19-2020

Visual and verbal working memory and its relationship to subcortical regions in statistically-determined mild cognitive impairment

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VISUAL AND VERBAL WORKING MEMORY AND ITS RELATIONSHIP TO SUBCORTICAL REGIONS IN STATISTICALLY-DETERMINED MILD COGNITIVE IMPAIRMENT

by
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A Dissertation

Submitted to the
Department of Psychology
College of Science and Mathematics
In partial fulfillment of the requirement
For the degree of
Doctor of Philosophy
at
Rowan University
May 11, 2020

Dissertation Chair: David J. Libon, Ph.D.

Dedication

I would like to dedicate this dissertation to my parents, Mitra and Joseph, and brothers, Jason, Matthew, and Josh.

Acknowledgment

I would like to show my appreciation to my advisor, Dr. David Libon for his guidance, patience, and mentorship. His ability to teach so eloquently and clearly and his abundance of knowledge is admirable. I look forward to learning more in the future. I would also like to acknowledge and thank Dr. Ganesh Baliga. This work would not have been possible without his expertise and work on this project. Not only is Dr. Baliga a computer science genius, he is also a dedicated mentor, willing to do what is necessary to ensure the success of his students and collaborators. His innovative and creative mind has led to noteworthy products, like Cogniscreen, a digitized way of detecting dementia symptoms via mental status assessments. His work is not only interesting, but generalizable and translatable, two key ingredients of a successful researcher. Dr. Robert Nagele has also been a wonderful mentor. He has challenged my thought process in a positive way and has been an unwavering advocate throughout my graduate career. Finally, I would like to thank and acknowledge Dr. Jim A. Haugh and Dr. Roberta Dihoff for their dedication and willingness to partake in my dissertation defense. Their support during the process of proposing and defending is greatly appreciated.

Abstract

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Background: Fuster (2008) observed that *temporal organization* modulate executive control mechanisms by generating (1) attention towards test parameters (*working memory*), (2) the capacity to execute a task (*preparatory set*), and (3) the ability to inhibit external/internal stimuli (*inhibitory control*). We investigated Fuster's model (2008) using response latency on visual and verbal working memory tasks in patients with suspected mild cognitive impairment (MCI). **Methods**: An iPad-version of the Backward Digit Span Test (BDT) and Symbolic Working Memory Test (SWM) were used. Outcome variables were latency for each correct serial position and volumetric subcortical regions using NeuroQuant® software. **Results**: Mixed-model analyses found within-group differences on both BDT and SWM. Moreover, group by latency interaction for each position as a function of total time was observed on the BDT. Correlations between total time for correct trials and neuropsychological measures of processing speed and visuospatial operations were significant for the BDT. Finally, MRI was not associated with any serial order position. **Conclusions**: Consistent with Fuster's model, BDT latencies illustrate a tripartite neurocognitive construct. The allocation of latency for correct trials differed between the MCI and non-MCI groups to suggest distinct underlying neurocognitive constructs. Together, latency on verbal WM tasks like the BDT may be a cognitive marker for emergent illness.

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Chapter 1

Introduction

Background

Alzheimer's disease (AD) is an insidious onset neurodegenerative dementia characterized by impairment in cognitive and functional abilities, thought to arise as many as 20 years before the clinical manifestation of symptoms (Bateman et al., 2012; Braak et al., 2011 Villemagne et al., 2013). Between the years 2000 and 2017, there has been a 145% increase in deaths from AD (Gaugler et al., 2019), and without the development of medical breakthroughs to modify, prevent, or cure AD, the number of older adults (ages 65 and older) with AD is projected to reach 13.8 million by 2050 (Hebert et al., 2013; Gaugler et al., 2019). As the incidence of dementia increases, so does health care costs and caregiver burden (e.g. unpaid care, mental and physical difficulties; Gaugler et al., 2019). All 413 clinical trials between 2002 and 2012 have failed for many reasons, including the longer-than-anticipated period of recruitment for clinical trials (Cummings, Morstorf, & Zhong, 2014; Getz & Lamberti, 2013). As such, a suggestion put forth is to intervene with immunotherapies earlier on in the disease process (Cummings, Morstorft & Zhong, 2014), a task that has and continues to be researched through neuropsychological means of assessing and identifying prodrome stages of AD (Edmonds et al., 2015; 2019).

Mild cognitive impairment (MCI) is now considered to be a prodrome of dementia such as AD, or an intermediate stage of increased risk to developing dementia, and thus an important construct for early intervention (Petersen et al., 2001; Wilson et al., 2011). Presently, the diagnostic criteria for MCI include 1) subjective complaints of

memory or other neurocognitive problems; 2) objective evidence documenting a decline in one or more cognitive domains; 3) preservation of instrumental activities of daily living; and 4) no signs of dementia (Albert et al., 2011; Petersen et al., 2005; Winblad et al., 2004). Historically, MCI was defined as cognitive deficits associated with only memory (Petersen et al., 2001), however, research now shows that MCI can present with single and/or multiple domain subtypes (Clark et al., 2013; Delano-Wood et al., 2009; Edmonds et al., 2015; Libon et al., 2010).

Significance of Study

Investigating MCI subtypes is important from both theoretical and clinical perspectives. This type of research can enhance our theoretical understanding of what drives brain-behavior relations related to dementia, and aid in the development of neuropsychological tools that can be used for earlier intervention and, therefore, better clinical outcomes. Neuropsychological and neuroimaging research have been instrumental in deriving explanations for the differences in phenotypes and propagation of neuropathology, helping clinicians better distinguish patterns of performance between MCI subtypes (Chao et al., 2009; Delano-Wood et al., 2008, 2009; Eppig et al., 2012; Fuster, 2008). As such, the significance of this study is to elucidate underlying brain-behavior relations by combining neuropsychological assessment using novel technology and link these behaviors to specific brain regions using MRI.

Executive Control and Working Memory as Neuropsychological Constructs

Executive control is a top-down mental process of attention and concentration, inhibition or self-control, working memory, interference control, mental manipulation and flexibility, and concept formation. From these higher-order executive control

processes, we are able to utilize reasoning, problem-solving, and mental planning for effective responding (Collins & Koechlin, 2012; Schoenberg & Scott, 2011). The use of executive control is essential in everyday life – resisting sweet foods, taking notes during a meeting, playing Sudoku, building furniture, or even more automatic behaviors like putting on and taking off clothing.

Under the umbrella of executive control is working memory (WM), or the ability to retain and mentally manipulate items of information for prospective execution of an action or multiple actions, done purposefully to accomplish a goal. WM operates when one is asked to remember a phone number for a short period, follow a recipe, or a series of directions. Similar to executive control, WM relies on a top-down approach, and involves sustained temporary activation and integration of neurocognitive networks (Fuster, 2008). The *neural scaffold* on which WM functions is through the prefrontal cortex (PFC), comprised of dorsolateral, orbitofrontal, medial, and frontal/anterior cingulate areas. These brain regions are known to intimately connect and process cognitive and emotional information by incorporating multiple sensory and motor information from other brain areas (Miller & Cohen, 2001; Sakai & Passingham, 2003).

Fuster's Model of Executive Control

Fuster's model of executive control is centered on the construct of temporal ordering, or the temporal gradient of neural networks that integrate information to complete the task at hand. The frontal lobe, which coordinates the *neural scaffold*, works with other brain regions and shares smaller neurocognitive networks (Hebb, 1947; Fuster, 2009). These neurocognitive networks, referred to as nodes, comprise of relative functional specializations, or "mini-networks" for visuospatial, visual, auditory, tactile, or

other memoranda (Fuster, 2009). The function of these "mini-networks" is to recruit and retrieve long-term memory for specific behaviors; executive control is dependent on previously established associations and temporary activation of long-term memoranda (Fuster, 2009). Thus, upon the first trial of an executive task, the activated network is updated by the requirements of that task (Fuster, 2009). Then, the updated network of long-term memoranda becomes operational and the networks create temporary retention of memoranda within the context of the new task (Fuster, 2009). It is important to note that while prefrontal activation *increases* as a function of the complexity of tasks, practice (i.e. operating within the context of the task) *decreases* prefrontal load-related activation (Fuster, 2009). Fuster posited that there are three subordinate mechanisms that underlie these executive abilities – working memory, preparatory set, and inhibitory control (Fuster, 2008).

Working memory. According to Fuster (1973, 2002, 2003, 2008), *working memory* is the ability to temporally and retrospectively reclaim and retain items from recent and past experiences. *Working memory* is *'memory'* for the short term, rather than short-term memory, and is best understood as attention focused on the internal representation of the task at hand (Fuster, 2002). It is here that preexisting networks of long-term memoranda begin to activate (Fuster, 2009). Studies have shown that *working memory*, specifically related to selectiveness and divided attention, can be derailed by dysfunction in the lateral PFC (Fuster, 2008).

Preparatory set. *Preparatory set*, or *set*, is the preparation of neural resources for expected actions contingent on previous events and information from *working memory* (Fuster, 2002, 2003, 2008). *Working memory* can be seen as attention directed to the past,

while *preparatory set* is attention directed to the future. Simply put, *preparatory set* is the prospective intentions and behaviors to act according to the task at hand. *Preparatory set* requires executive representations of higher-order neurocognitive schemas, gestalts, and rules of actions that cascade to subordinate non-prefrontal cortical areas, including premotor and motor regions that execute partial goals and more concrete actions (Fuster, 2008). These partial *sets* are suggested to be nested within larger ones, monitored and corrected at every step (Badre and D'Esposito, 2007; Koechlin et al., 2003, 2007). The lateral PFC is involved in *working memory* and *preparatory set*, and the medial and anterior cingulate regions of the PFC are involved in drive and motivation (Fuster, 2002).

Inhibitory control. The medial and orbital PFC appear to mediate *inhibitory control*, or the ability to discriminate and/or suppress internal and external inputs that can derail or interfere with the structure of behavior in use to produce a goal-directed action (Fuster, 2002, 2003, 2008). *Inhibitory control* is an exclusionary aspect that protects what is in focus from interference by other stimuli not germane to the present task. The orbitomedial area appears to perform opposite, but complementary functions to the lateral prefrontal region by retaining memory relevant to the behavioral structure while suppressing interfering memories (Fuster, 2008). Individuals with orbitomedial prefrontal lesions often exhibit impulsivity, irritability, hyperactivity, disinhibition, perseverations, and other commissions of discrimination (Fuster, 2002; 2008).

Temporal organization. Superordinate to Fuster's concepts of *working memory*, *preparatory set*, and *inhibitory control* is the construct of *temporal organization*. An essential function of the lateral PFC is to mediate ambiguous information in an efficient and timely fashion toward new and goal-directed behaviors, a term coined *temporal*

organization (Luria, 1966; Fuster, 1997). Fuster's construct of *temporal organization* can be viewed as a means by which information is temporally integrated. Successful completion of an executive task requires cross-temporal integration of information for both *working memory* and *preparatory set*.

Studies from monkeys suggest that *temporal organization* requires neural processing that often begins in the PFC and ends in the motor cortex, narrowing from global to concrete actions. Therefore, as one brings executive tasks to fruition, behavior becomes increasingly selective. The rate-limiting step towards temporal ordering is neural processes that integrate information along the time axis, i.e., the temporal gradients (Fuster, 2002). Finally, in order to maintain selective focus, *inhibitory control* processes are initiated to filter and suppress concurring and past stimuli (Fuster, 2003; 2008). Over continuous performance of a temporally related task, neurons in the PFC begin to associate relevant sensory stimuli, thus becoming a learned response (Fuster, 2002).

Frontal Lobe Pathways, Thalamus, Hippocampus, and Basal Ganglia

Thalamus. Fuster maintained that the logical anatomical posterior boundary of the PFC can be found within the thalamus. It is hypothesized that the process by which networks are activated is through a "top-down" approach of the cortico-thalamic loops (Fuster, 2008; Kastner and Ungerleider, 2000). This activity occurs downward and in a feed-forward fashion through an executive hierarchy, simultaneously monitoring and receiving feedback from each level to its precursor level; feedback allows the monitoring by higher levels of actions at lower levels. Two seminal studies (Alexander & Fuster, 1973; Fuster & Alexander, 1973) examined the role of the reciprocal connections

between the PFC and mediodorsal nucleus of the thalamus. For the hypothesis of reciprocity of connections to be true, the inactivation of one of the two brain regions should disrupt neuronal activity in the other and impair WM. These researchers found that, in fact, cooling of the lateral PFC during a delayed-response task in monkeys resulted in a diminished firing frequency in the parvocellular portion of the thalamic nucleus. Other studies (Nishino et al., 1984) found similar results with different brain regions, like the caudate nucleus, that negatively impacted motor response. In sum, these studies confirm: (1) the widely distributed nature of the cortical and subcortical regions involved in WM operations and (2) the controlling role of the PFC over the selection and maintenance of its content.

Other human and non-human primate studies have found the thalamus to play a key role in cortico-cortical information flow and the modulation of cortical networks implicated in executive functions (Saalmann & Kastner, 2015; Theyel et al., 2010; Yuan et al., 2016). In addition to the PFC, the thalamus is widely connected with other brain regions including the medial orbitofrontal cortex, temporal and frontal gyri, hippocampus, cingulate, caudate, insula, premotor and supplementary motor cortex, putamen, cerebellum, parietal and occipital regions including the visual cortex, visual association areas, and ventral temporal cortices, amongst other areas (O'Muircheartaigh et al., 2015).

Hippocampus. Since the early 1970s, sustained activity during delayed-response tasks in the PFC and posterior cortical brain regions have been thought to be essential for working memory (Collette et al., 2005; Fuster & Alexandre, 1971; Goldman-Rakic, 1995; Koenigs et al., 2009). Recent research suggests that in addition to the thalamus, the

hippocampus, a brain region well-known to the contribution of episodic memory, is also involved in working memory (Fuster, 2009). The anatomical connections between the hippocampus and PFC are well established (Amaral, 2011; Van Hoesen, 1982). Findings from humans and non-human primates suggest that the PFC is reciprocally connected with the hippocampus and posterior association cortices, contributing to the networks involved in both working memory (Fuster, 2002; Jones & Powell, 1970; Pandya & Yeterian, 1985) and episodic memory (Amaral, 2011; Cavada et al., 2000). In fact, one of the first conclusions of the synaptic concept that suggested hierarchical organization of memory also applied to executive memory (Cajal, 1923).

Basal ganglia. Almost all PFC connections are reciprocal (Fuster, 2008). A notable exception includes the basal ganglia and pontine nuclei, to which the PFC sends unreciprocated direct projections (Fuster, 2008; Schoenberg & Scott, 2011). The basal ganglia is comprised of the caudate and putamen (together called the corpus striatum), globus pallidus, substantia nigra, and subthalamic nucleus. Basal ganglia nuclei are involved in a wide range of cognitive, limbic, and motor functions (Albin et al., 1989; Alexander and Crutcher, 1990; Alexander et al., 1990; Haber and Calzavara, 2009; Temel et al., 2005). McNab and Klingberg (2008) found basal ganglia activity to be positively correlated with working memory capacity and preparatory activity via the fronto-striatal loops, consistent with other studies (Alexander, DeLong, & Strick, 1986). Despite the acknowledgment of the basal ganglia's involvement in working memory (Lewis et al., 2004; Postle & D'Esposito, 1999), little is known about the intricacies of its involvement.

Verbal and Visual Working Memory

Brain regions that underlie visual and verbal WM are somewhat divergent. Overall, studies have found that the left hemisphere is activated during verbal WM, perhaps due to the involvement of Broca's area in verbal rehearsal (Buchsbaum, Olsen, Koch, & Berman, 2005; Crottaz-Herbette, Anagnoson, & Menon, 2004; Goldstein et al., 2005; Narayanan et al., 2005). Moreover, performance on mental arithmetic tasks is predominantly associated with the left hemisphere (De Pisapia, Slomski, & Braver, 2006; Kondo et al., 2004). In contrast, spatial WM has been found to activate bilateral parietal cortex with greater right-sided participation (Nee et al., 2013; Owen et al., 2005; Reuter-Lorenz et al., 2000; Smith & Jonides, 1999; Smith et al., 1995). Prior research has shown that lesions involving the temporal cortex affect visual WM test performance but not spatial WM (Owen et al., 1996), while parietal lesions show the opposite pattern (Pisella et al., 2004).

Neuropsychological Tests for Working Memory

Tests frequently used to assess WM include subtests from the Wechsler Adult Intelligence Scale (WAIS-IV) like mental arithmetic, letter-number sequencing, and most commonly administered digits backward and sequencing (Lezak et al., 2004, Wechsler, 2008). An analogous test to the WAIS-IV digits backward is the Backward Digit Span Test (BDT), described by Lamar and colleagues (2007, 2008), a test used to operationally define WM deficits in MCI and dementia by using serial order recall. Lamar and colleagues (2007) found that performance on the BDT was able to differentiate vascular dementia (VaD) from AD patients. Specifically, VaD patients were less able to accurately repeat numbers backward in the correct serial order, suggestive of greater frontally-

mediated WM impairment. A follow-up study found BDT performance to be associated with greater MRI-defined white matter disease (Lamar et al., 2008). Moreover, a recent study by Emrani et al. (2018) found the BDT to distinguish mixed/dysexecutive MCI patients from other patient groups by an absence of a recency effect. Finally, using fMRI technology, Bezdicek et al. (2020) found that better SERIAL order recall performance was associated with increased functional connectivity between the bilateral dorsolateral PFC and left insula, inferior frontal gyrus, and putamen in patients with Parkinson's disease-MCI and controls.

Purpose of Study

Prior research has shown worse performance as a function of time for patients diagnosed with both mixed and dysexecutive MCI (Eppig et al., 2012), and an attenuated recency effect using serial order parameters in patients with a mixed/dysexecutive MCI (Emrani et al., 2018). This prior research was interpreted to reflect a greater impairment in marshalling the necessary neurocognitive resources to establish mental set (i.e., *working memory*); and coordinating these neurocognitive resources prospectively to sustain mental set or bring the task to a fruition (i.e. *preparatory set*). In the current research, data was obtained from memory clinic patients diagnosed with either non-MCI or MCI. Less is known about serial order recall using visual WM paradigms in MCI. Therefore, in the current research both verbal and visual tasks were administered. Time measuring response for each serial order position for correct test trials was obtained. Collectively, these *intra-component latencies* were employed to provide an operational definition of Fuster's construct of *temporal organization*.

As such, the first goal of the current research was to assess behaviors related to

verbal and visual WM by examining correct *intra-component latency* (i.e. reaction time; described below) in neuropsychologically well-defined MCI and non-MCI patients. Fuster's model (2008) relies on precise temporal ordering and brain-behavior relations to accurately complete the task at hand. This is to say, that in order to correctly complete any WM task, the constructs (i.e. *working memory, preparatory set,* and *inhibitory control*) within Fuster's model (2008) must be successfully implemented. As such, in order to analyze the constructs in Fuster's model (2008) we analyzed correct trials only. Together, we examined correct *intra-component latency* both between and within-group to understand how behaviors (i.e. the time to accurately respond to serial order position) relate to Fuster's model (i.e. *working memory*, *preparatory set*, and *inhibitory control).*

The second goal of the current research was to assess which brain regions are related to which correct *intra-component latency* positions in patients with and without MCI. Interfering sensory stimuli and memory representations, through *inhibitory control*, have been associated with the orbitofrontal inhibitory impulses from the posterior cortical regions, and possibly the thalamus (Fuster, 2008). Hippocampal inputs mediate the formation of executive cognitive networks in the PFC through *working memory* and *preparatory set*, processing co-occurring proprioceptive inputs and preparing for future actions (Fuster, 2008). Activity in the PFC and basal ganglia have been shown to affect WM capacity by filtering irrelevant sensory information. For example, activity in the globus pallidus predicts the extent to which only relevant information is stored (McNab & Klingberg, 2008). Finally, previous research has suggested a left versus right separation of verbal and visual tasks, respectively. Thus, in the current research, detailed analyses of correct *intra-component latencies* described below were assessed in relation

to left, right, and total subcortical brain regions known to produce behaviors on verbal (BDT) and visual (Symbolic WM) WM tasks according to Fuster's model (2008).

Chapter 2

Methods

Participants

Patients in this current research study (n= 58) were recruited from the New Jersey Institute for Successful Aging Memory Assessment Program (MAP). All MAP patients underwent a comprehensive neuropsychological evaluation and were also examined by a social worker and a board-certified geriatric psychiatrist. An MRI study of the brain and appropriate blood serum tests were obtained to evaluate reversible causes of dementia. A clinical diagnosis was determined for each patient at an interdisciplinary team conference. Patients diagnosed with MCI presented with evidence of cognitive impairment relative to age and education, preservation of general functional abilities, and the absence of dementia. Exclusion criteria of patients included: history of head injury, substance abuse, and major psychiatric disorders including major depression, epilepsy, B12, folate, or thyroid deficiency. For all patients, a knowledgeable family member was available to provide information regarding functional status. This study has been approved by the Rowan University institutional review board with consent obtained consistent with the Declaration of Helsinki.

Neuropsychological Assessment

The neuropsychological protocol used to classify MCI subtype is the same as described by Emrani et al. (2018). Three domains of cognition were assessed: executive control, naming/ lexical access, and declarative memory. Nine parameters, three from each neurocognitive domain, were used to classify MCI subtype as described below (Table 1). All tests were expressed as z-scores derived from normative data. We

acknowledge that other neuropsychological tests/domains of cognitive functioning could have been used. The rationale for using the protocol described above was based on prior research showing that these tests are able to illustrate key neurocognitive constructs and differentiate between MCI subtypes (see Bondi et al., 2014; Thomas et al., 2017; Libon et al., 2011).

Table 1

Neuropsychological Domains

Executive Function Domain	**Language/Lexical Access Domain**	**Declarative Memory Domain**
WMS – Mental Control Subtest	Boston Naming test	Immediate Free Recall
Letter Fluency – 'FAS'	'Animal' Fluency	Delayed Free Recall
Trail Making Test – Part B	WAIS-III Similarities Subtest	Delayed Recognition

Determination of Mild Cognitive Impairment Subtypes

Single and multi-domain MCI. Jak-Bondi et al. (2009) criteria was used to determine MCI subtype. According to this neuropsychologically-derived approach, single domain MCI is diagnosed when participants score >1.0 standard deviation below normative expectations on two of three measures within any single cognitive domain. Mixed MCI is diagnosed when participants score >1.0 standard deviation below normative expectations on two of three measures within two or more cognitive domains.

Non-MCI group. Patients who either scored above 1sd above all nine neuropsychological parameters, or scored 1sd below the mean on up to two of the nine neuropsychological parameters across different domains of cognitive functioning do not meet Jak-Bondi et al. (2009) criteria for MCI. These patients are labeled as non-MCI.

Intra-Component Latency and Average Total Time for Correct Responses

The current research collected data in real-time via iPad-administered BDT and SWM tasks through voice and touch recognition, respectively. The iPad technology collected *intra-component latency* for each response, defined as the time to begin a response for each position (i.e. time zero to first response, time from the end of the first response to the beginning of the second response etc.), and is averaged across each serial order position for each span. Average total time is the aggregated time for all trials of a specific span divided by the number of trials.

The Backward Digit Span Test (BDT)

The BDT is comprised of seven trials of 3-, 4- and 5-digit span lengths for a total of 21 trials. As described by Lamar et al. (2007, 2008) 4- and 5-span trials were constructed so that contiguous numbers were placed in strategic positions. Thus, in 4-span trials contiguous numbers were placed in either the first and third or second and fourth digit positions, e.g., 5269 or 1493. For 5- span trials contiguous numbers were placed in the middle three digits positions, e.g., 16579.

The iPad administrated BDT used Wechsler Adult Intelligence Scale procedures except that all 21 test trials were administered with no discontinue rule. The iPad verbally plays numbers and the patient is then tasked to repeat numbers backwards. The utility of

recording responses on the iPad includes the ability to measure total time to completion for each trial, as well as time to complete each *intra-component latency*.

WRAML-2 Symbolic Working Memory (SWM)

A less frequently used WM task is the Symbolic Working Memory (SWM) subtest from the Wide Range Assessment of Memory and Learning (WRAML-2; Adams & Sheslow, 2003; Sheslow & Adams, 2003). The Symbolic WM task consists of two subtests. The first subtest (numbers) instructs patients to point to digits in ascending order on an iPad. The string of digits expands from two- to seven-span with three test trial for each span length. The second subtest (numbers/letters) instructs patients to point to digits in ascending order followed by letters in alphabetical order. Similar to BDT, the iPad plays all test stimuli after which the patient is asked to reorder. Programmed iPad touch screen software records all patients' responses. Outcome variables included correct 5-span and 4-span *intra-component latency* and average total time for both BDT and SWM, respectively.

Neuroquant™

A portion of our sample had MRI volumetric data available. Patients were scanned using either 3.0T or 1.5T magnets compatible with the analysis software. Acquisition protocol details are as follows: TR/TE= 2300/1.87/900, 192×192 matrix, 160 slices, voxel size=1×1×1.2 mm. The scanners are detailed as follows: Siemens 3T Verio scanners with 16 and 32-channel head coils (Siemens Medical Systems, Erlangen, Germany), Siemens 3T Skyra scanners with a 32 channel head coil (Siemens Medical Systems, Erlangen, Germany), and Siemens 1.5T Aera scanners with a 16 channel head coil (Siemens Medical Systems, Erlangen, Germany). Following acquisition, images

from the sagittal 3D T1 SPGR sequence underwent volumetric analysis using NeuroQuant® software, a computer-automated method for measuring brain MRI volume (CorTechs Labs, Inc., San Diego, CA, USA; http://www.cortechs.net/products/neuroquant.php), an FDA-approved software program used to obtain volumetric MRI data. Left and right side ratios were summed and then normalized for age and gender using a database consisting of over two thousand healthy participants.

MRI outcome variables. NeuroQuant® compares MRI of a patient's brain to a database of people of the same age, sex, and skull size of healthy individuals (Luo, Airriess, & Albright, 2015). NeuroQuant® produces a General Morphometry Report that includes both cortical and subcortical brain regions. The regions of interest (ROI) and outcome variables include the cortical gray matter, hippocampus, caudate, putamen, pallidum, and thalamus. All outcome variables were expressed as left, right, or total volume.

Statistical Analyses

Using IBM SPSS, within- and between-group differences for each *intra-component latency* on the BDT and Symbolic WM were assessed using a mixed-design ANOVA, with *intra-component latencies* as the dependent variable. The independent variable was diagnostic group (non-MCI and MCI). Follow-up analyses included both within- and between-group t-tests to compare differences on *intra-component latencies*. Moreover, between-group t-tests were used to assess differences on average total time for correct trials. Each correct *intra-component latency* was transformed to a fraction (each correct *intra-component latency* over the total time for correct trials) for both BDT and SWM and were analyzed using a mixed-design ANOVA. Correlations between correct

average total time and neuropsychological tests were also conducted.

Hierarchical multiple linear regression analyses using block wise entry of predictors were conducted to assess the relation between MRI ROI (dependent variable) and correct *intra-component latencies* for each serial order position (independent variables). Separate regression analyses were implemented for BDT and SWM. In the regression models, MMSE and intracranial volume were entered into block 1. BDT and SWM correct *intra-component latencies* positions one through five/four, respectively, were entered into block 2. Results produced from block 2 were interpreted to assess the brain regions in relations to the productivity of position effects of both BDT and SWM controlling for MMSE and intracranial volume. The MRI ROIs include: cortical gray matter, hippocampus, caudate, putamen, pallidum, and thalamus for left, right, and total volumes. Significance was set at $p < 0.050$.

All continuous variables were screened for outliers and evaluated for departures of normality through quantitative examination of skewness and kurtosis, as well as visual inspection of frequency distributions. When analyzing the data, some variables were non-normal. To address this issue, we assigned outliers a lower weight (Dixon, 1960). Due to the smaller sample size, patients were classified as either non-MCI or MCI based on the actuarial neuropsychological algorithm described above.

In addition to latency analyses, accuracy data was undertaken to see how well the current research comports with previously published data (Emrani et al., 2018; see Supplemental). Due to unequal sample sizes, the assumption of homogeneity of variance was violated. To correct this violation, we applied Welch's F, which adjusts F and the residual degrees of freedom to combat problems arising from violating this assumption

(Fields, 2005). The Bonferroni correction was used when possible to correct for inflated alphas.

Chapter 3

Results

Demographic Characteristics for Intra-Component Latency for BDT

Table 2 lists demographic and clinical information. No between-group differences were found on age, education, the Geriatric Depression Scale (Yesavage et al., 1982), projected premorbid general intellectual abilities assessed with the Wide Range Achievement Test Reading subtest-IV (WRAT-IV), gender, or Instrumental Activities of Daily Living (Lawton, & Brody, 1969). There was statistical significance between group ($t(56)=2.18$, $p < .035$) on the Mini-Mental State Examination (MMSE; Folstein et al., 1975).

Table 2

Demographic and Clinical Information BDT Latency: Means and Standard Deviations

	non-MCI (n= 36)	MCI (n= 22)	Significance
Age	73.19 (7.15)	72.45 (5.62)	ns
Education	15.81 (2.45)	15.23 (2.60)	ns
MMSE	28.61 (1.48)	27.68 (1.73)	MCI<non-MCI; p< .035
WRAT-IV Reading subtest	115.61 (14.71)	109.50 (17.06)	ns
IADL abilities	15.83 (2.09)	14.86 (2.61)	ns
Geriatric Depression Scale	2.78 (2.72)	2.64 (2.17)	ns
Gender	22 Females 14 Males	17 Females 5 Males	ns
MCI= Mild cognitive impairment; IADL= instrumental activities of daily living; WRAT-IV= Wide Range Achievement Test-IV; ns= not significant			

5-Span Backward Digit Span Latency

Between group differences for total correct trials was statistically significant (non-MCI; Mean= 4.20, SD= 1.54; MCI; Mean= 2.38, SD=1.92, t(60)= 4.05, p < .001, Cohen's d= 1.05). By contrast, independent sample t-test assessing between-group differences for the average total time of correct responses was not statistically significant (non-MCI; Mean = 7.34, SD = 3.94; MCI; Mean = 6.72, SD = 2.46). Group by serial order *intra-component latency* was analyzed using a mixed-design ANOVA with a within-subjects factor (latency for correct positions 1-5) and a between-subject factor (non-MCI= 36, MCI= 22; Figure 1). Mauchly's test indicated that the assumption of sphericity had been violated ($X^2(9)=176.14$, p< .001), therefore the degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity (ε=.374). A main effect of independent group on latency for each serial position was significant (F[1.50, 83.71]=33.77, p < .001, $\eta_p^2=0.376$; see Figure 1). There was no significant interaction between serial order position latency and diagnosis.

Follow-up independent sample t-tests were used to measure differences between group (MCI; N=36; non-MCI; N=22) on correct *intra-component latencies* positions one through five. Correct latency positions two (t(53.52)=2.66, p < .011, Cohen's d=0.66), three (t(56)=-2.63, p < .012, Cohen's d=0.71) and four (t(56)=2.10, p < .012, Cohen's d=0.59) were statistically significant such that non-MCI patients had longer (i.e. slower) latencies on positions two and four, and MCI patients displayed a longer latency on position three. Paired-sample t-tests were used to assess within-group differences on positions one versus three and positions three versus five. Non-MCI patients statistically differed on both positions one versus three (t(35)=4.31, p < .001, Cohen's d= 0.93) and

positions three versus five ($t(35)=4.48$, $p < .001$, Cohen's $d= 0.85$), while MCI patients statistically differed only on positions three versus five ($t(21)=6.32$, $p < .001$, Cohen's $d= 1.90$).

Table 3

Serial Order Position Latency: Means and Standard Deviations

Serial Order Position Latency	Mean (SD)
Position 1	
Non-MCI	1.96 (1.78)
MCI	1.93 (1.91)
Positon 2	
Non-MCI	0.47 (0.50)
MCI	0.21 (0.24)
Position 3	
Non-MCI	0.71 (0.69)
MCI	1.19 (0.67)
Position 4	
Non-MCI	0.76 (0.51)
MCI	0.48 (0.43)
Position 5	
Non-MCI	0.26 (0.30)
MCI	0.22 (0.27)

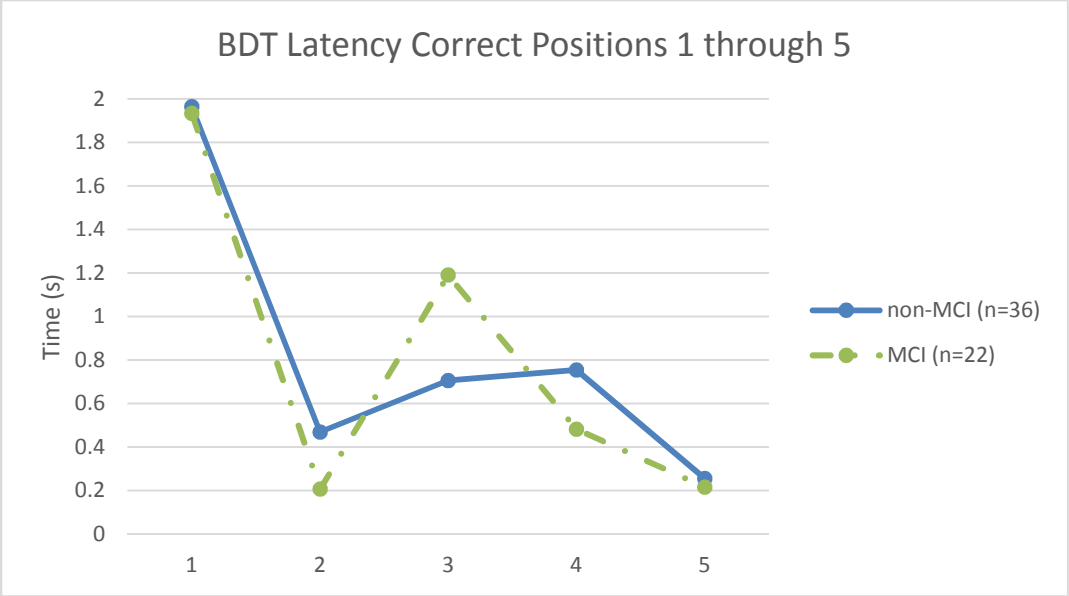

Figure 1. 5-Span BDT

Each Position Latency as a Fraction of Average Total Time

Each correct *intra-component latency* was transformed to a fraction by dividing each correct *intra-component latency* by the average total time and assessed using a mixed-design ANOVA. Mauchly's test indicated that the assumption of sphericity had been violated ($X^2(9)=101.84$, $p< .001$), therefore the degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity ($\varepsilon= .501$). The main effect of independent groups on latency for each serial position was significant ($F[2.00, 112.16]=47.63$, $p< .001$, $\eta_p^2=0.460$; Figure 2). Moreover, there was a significant serial order position latency by group interaction ($F[2.00, 112.16]= 3.88$, $p< .024$, $\eta_p^2=0.07$). Follow-up independent sample t-tests were used to measure differences between group (MCI; N=36; non-MCI; N=22) on the transformed latency positions. Groups statistically differed on positions two (non-MCI; M=.07, SD=.07; MCI; M=.03, SD=.03; $t(55.08)=2.83$, $p< .007$, Cohen's D=0.70), three (non-MCI; M=.09, SD=.08; MCI;

M=.18, SD=.09; t(56)=-3.75, p< .001, Cohen's D=1.07), and four (non-MCI; M=.11, SD=.07; MCI; M=.07, SD=.05; t(56)=2.30, p< .026, Cohen's D=0.63), non-MCI patients spending more time on positions two and four and less time on position three.

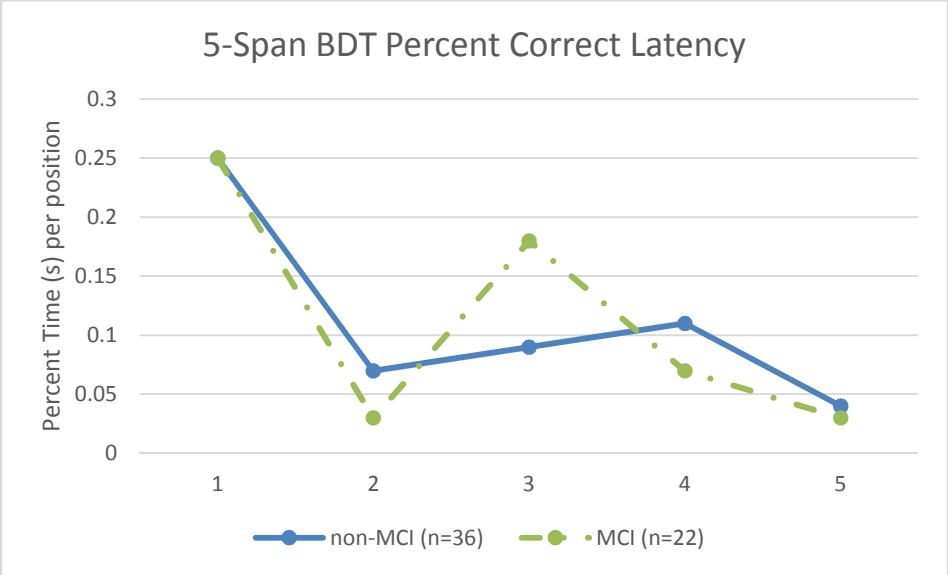

Figure 2. 5-Span BDT as Fractions of Total Time

Demographic Characteristics for Intra-Component Latency for Symbolic WM

Table 4 lists demographic and clinical information. No between-group differences were found for age, education, Geriatric Depression Scale (Yesavage et al., 1982), projected premorbid general intellectual abilities assessed with the Wide Range Achievement Test Reading subtest-IV (WRAT-IV), or gender. There were statistical significance between group on the Mini-Mental State Examination (t(39.45)= 2.90, p< .007) (MMSE; Folstein et al., 1975) and Instrumental Activities of Daily Living (t(49)= 2.28, p< .028) (Lawton, & Brody, 1969).

Table 4

Demographic and Clinical Information Symbolic WM Latency: Means and Standard Deviations

	non-MCI (n= 33)	MCI (n= 24)	Significance
Age	73.91 (7.94)	72.38 (5.35)	ns
Education	15.64 (2.22)	15.04 (2.65)	ns
MMSE	28.73 (1.35)	27.42 (1.89)	MCI<non-MCI; p< .007
WRAT-IV Reading subtest	115.10 (16.29)	110.04 (16.46)	ns
IADL abilities	15.96 (2.32)	14.26 (3.02)	MCI<non-MCI; p< .028
Geriatric Depression Scale	2.36 (2.47)	2.75 (2.11)	ns
Gender	20 Females 13 Males	19 Females 5 Males	ns
MCI= Mild cognitive impairment; IADL= instrumental activities of daily living; WRAT-IV= Wide Range Achievement Test-IV; ns= not significant			

4-Span Numbers/Letters Symbolic WM Latency

A total of 57 patients were administered the Symbolic WM test; 46 patients completed the 4-span numbers/letters trial, while only 26 continued on to the 5-span numbers/letters trials. Due to the differences in the number of patients administered 4- versus 5-span numbers/letters on the Symbolic WM task, we examined if difficulty was related to motor as compared to auditory output modalities. Paired-sample t-tests for serial order percent correct (accuracy) on 4- and 5-span numbers conditions on Symbolic WM versus BDT were employed (non-MCI; N=33, and MCI; N = 23). Non-MCI and MCI patients' performance on 5-span modalities was not statistically significant (non-MCI; Symbolic WM Mean= 88.48, SD= 12.83; BDT Mean= 84.68, SD=9.31; MCI;

Symbolic WM Mean= 74.93, SD= 22.74; BDT Mean= 67.83, SD= 16.53). Comparatively, 4-span modalities were significant (non-MCI; t[32]= 2.93, p< .007; MCI; t[22]=3.66, p< .002) such that both groups did better on the 4-span Symbolic WM numbers condition as compared to the 4-span BDT condition (non-MCI; Symbolic WM Mean= 97.73, SD=5.22; BDT Mean= 92.97, SD=8.26; MCI; Symbolic WM Mean= 92.75, SD=12.13; BDT Mean= 82.45, SD=16.16).

Between group differences on correct trials was statistically significant (non-MCI; Mean = 2.30, SD= 0.95; MCI = 1.33, SD= 1.24; t(41.47)=3.21, p< .004, Cohen's d= 0.88). Independent sample t-tests assessing between-group differences for the average total time of correct responses on 4-span numbers/letters was not statistically significant (non-MCI; Mean = 7.00, SD = 2.69; MCI; Mean = 7.57, SD = 3.84). Group by serial order *intra-component latency* was analyzed using a mixed-design ANOVA with a within-subjects factor (*latency* for correct positions 1-4) and a between-subject factor (non-MCI= 31, MCI = 15). Mauchly's test indicated that the assumption of sphericity had been violated ($X^2(5)= 58.78$, p< .001), therefore the degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity (ε= .662). A main effect of independent groups on latency for each serial position was significant (F[2.0, 87.43]= 49.84, p< .001, $\eta_p^2=0.531$). There was no significant interaction between serial order position latency and diagnosis. Follow-up independent sample t-tests were used to measure differences between group (MCI; N=31; non-MCI; N=15) on correct latencies positions one through four. There were no statistically significant differences between group on any correct position latency. Paired-sample t-tests were used to assess within-group differences on positions one versus three and positions three versus four. Results showed statistical

differences for non-MCI patients on both positions one versus three ($t(31)= 2.20$, $p< .037$, Cohen's $d= 0.45$) and positions three versus four ($t(30)= 6.12$, $p< .001$, Cohen's $d= 1.44$), while MCI patients statistically differed only on position three versus position four ($t(14)= 4.12$, $p< .002$, Cohen's $d= 1.72$).

Table 5

Means and Standard Deviations for 4-Span Symbolic WM Latencies

Serial Order Position Latency	Mean (SD)
Position 1	
Non-MCI	3.22 (1.10)
MCI	3.97 (2.70)
Positon 2	
Non-MCI	1.13 (0.73)
MCI	1.14 (0.62)
Position 3	
Non-MCI	2.46 (1.51)
MCI	3.24 (1.73)
Position 4	
Non-MCI	0.82 (0.58)
MCI	0.97 (0.70)

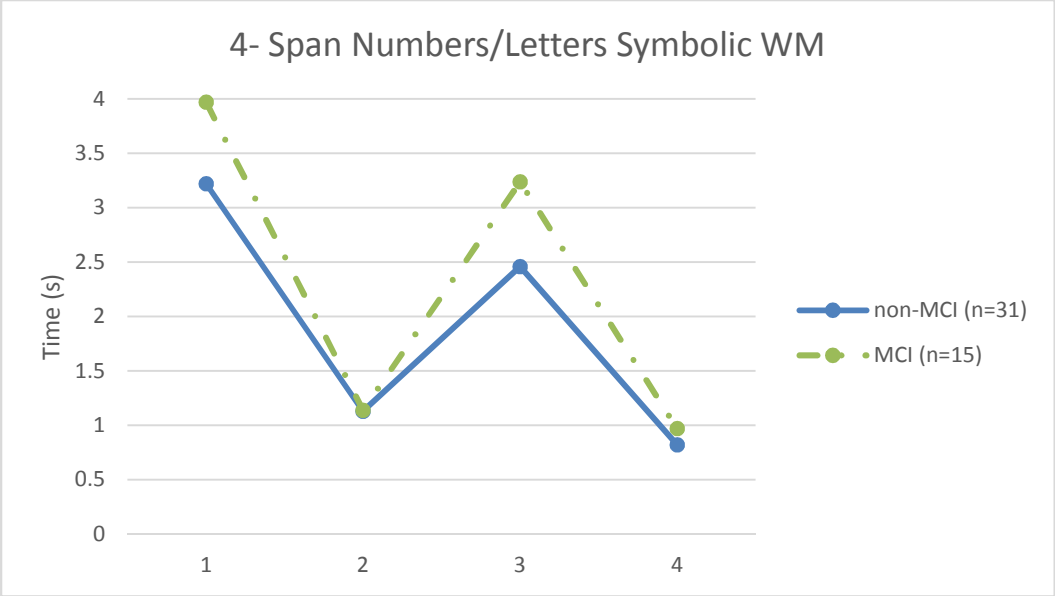

Figure 3. 4-Span Symbolic WM Numbers/Letters

Each Position Latency as a Fraction of Average Total Time

Each correct *intra-component latency* was transformed to a fraction, dividing each correct position *latency* by the average total time, and assessed using a mixed-design ANOVA. Mauchly's test indicated that the assumption of sphericity had been violated ($X^2(5)=35.10$, $p < .001$), therefore the degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity ($\varepsilon=.748$). A main effect of independent groups on latency for each serial position was significant ($F[2.24, 98.68]= 70.09$, $p< .001$, $\eta_p^2=0.614$; Figure 4). There was no significant interaction between serial order position latency and diagnosis.

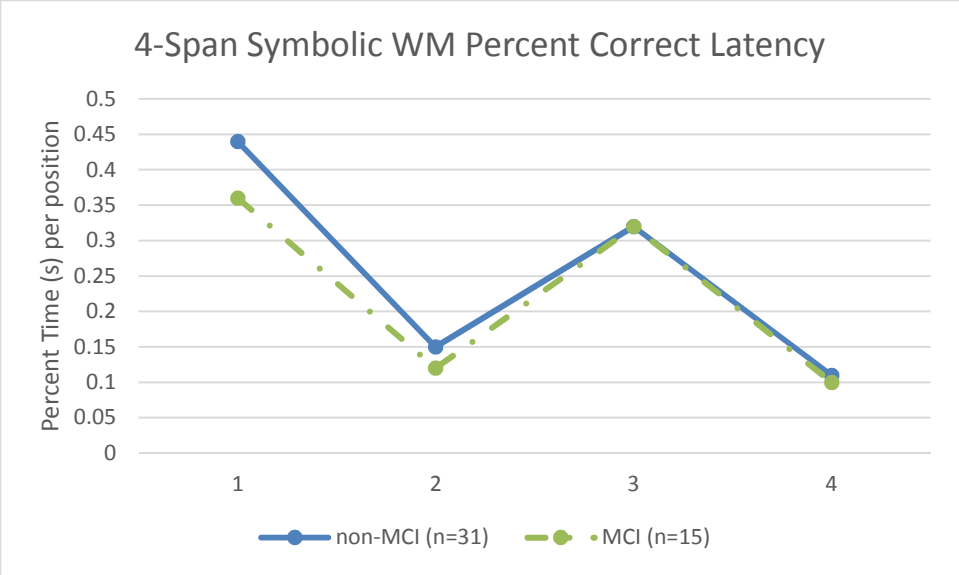

Figure 4. 4-Span SWM as a Fraction of Total Time

Correlations for Correct Average Total Time

Correlations assessing correct average total time and neuropsychological tests were employed. Neuropsychological tests measuring motor output, processing speed, and/or visuospatial abilities (WAIS-III Digit Symbol subtest, Psychological Corporation, 1997; Judgment of Line Orientation [JOLO], Benton et al., 1983; WMS-IV Symbol Span, Wechsler, 2009) were included in the analyses. To account for violating the assumption of heterogeneity of variance on 4-span numbers/letters Symbolic WM latency, spearman's rho was used. Correct average total time for 5-span BDT was significantly correlated with WAIS-III Digit Symbol and JOLO (Table 6 & 8). Comparatively, 4-span numbers/letters Symbolic WM correct average total time was not statistically correlated with any neuropsychological variable (Table 7 & 8).

Table 6

Correlations between 5-Span BDT Average Correct Total Time and Neuropsychological Tests

WAIS-III Digit Symbol	r= -.306, p< .021 (n= 58)
Trails B	r= -.054, ns (n=58)
JOLO	r= .311, p< .049 (n=41)
ns= not significant	

Table 7

Correlations between 4-Span Symbolic WM Average Correct Total Time and Neuropsychological Tests

WAIS-III Digit Symbol	r_s= -.228, ns (n= 55)
Trails B	r_s= -.202, ns (n=55)
JOLO	r_s= .042, ns (n=37)
r_s = spearman's rho; ns= not significant;	

Table 8

Average Total Time and Neuropsychological Measures: Means and Standard Deviations

Variables	Mean	Standard Deviation
5-span BDT Correct Average Total Time	7.00	2.90
4-span Symbolic WM Correct Average Total Time	6.57	3.75
WAIS-III Digit Symbol	-0.31	0.89
Trails B	-0.47	1.07
WMS-IV Symbol Span	0.40	2.53
JOLO	-0.16	1.06

MRI ROIs and Intra-Component Latencies

The NeuroQuant quantitative MR imaging output uses a normative database to compare individual patient's regional brain volumes, correcting for sex and age (Luo, Airriess, & Albright, 2015). Image processing from the NeuroQuant software package (CorTechs Labs Inc, La Jolla, CA) was compared with manual segmentation and on the basis of studies that have received Food and Drug Administration 510K approval for clinical use in measuring volumes of brain structures in MR imaging. The procedural details are described elsewhere (Brewer, Magda, Airriess, and Smith, 2009). Briefly, the protocol includes a quality check, correction or gradient non-linearity/B1 field inhomogeneity, and skull stripping. These procedures are then followed by a discrete cosine transformation and registration onto a probabilistic atlas, where an anatomic label is assigned to each voxel based on estimates from the probabilistic atlas.

MRI regions of interest (ROI) included hippocampus, thalamus, putamen, caudate, pallidum, and gray matter (BDT; n=32; Magnet; 1.5T= 11, 3T = 21; Symbolic WM; n=26; Magnet 1.5T =7, 3T = 19) for right, and left volumetric measure. The caudate, pallidum, and putamen were consolidated to form a basal ganglia index. Hierarchical regressions were employed to determine if the addition of each position *latency* improved prediction of neuroanatomic volumetric measures above and beyond MMSE and intracranial volume measures. Normality, linearity, and homoscedasticity of residuals were within normal limits.

For all hierarchical regressions, MMSE and intracranial volume were entered into the first block (step 1), and each *intra-component latency* for either the BDT or Symbolic WM were entered into the second block (step 2). When using BDT *intra-component*

latencies as the independent variables (IVs), model two for total hippocampal, basal ganglia, thalamic, and cortical gray matter were statistically significant (see Appendix A for results from each regression model). Putamen and pallidum did not have statistically significant models for total volume. Likewise, when using Symbolic WM *intra-component latencies* as the IVs, total thalamic, caudate, and gray matter volumes showed statistical significance on model 2 (see Appendix A). Hippocampal, putamen, and pallidum did not have statistically significant models. While model 2 on these brain regions remained statistically significant, the addition of *latencies* did not result in a significant increment in R^2 and therefore did not reliably improve the models. Moreover, no independent *latencies* had statistically significant betas. Rather, the covariates in model 1 resulted in significant values on model 2.

Chapter 4

Discussion

In prior research, Emrani et al. (2018) found that serial order recall performance on the BDT differentiates MCI subtypes. In appendix B, we replicated and validated findings from Emrani and colleagues (2018). Since its inception, the BDT generates two gross aggregate variables (total ANY recall; i.e. total percent recall regardless of the correct serial order position; and, total SERIAL order recall; total percent recall of digits in the exact serial order) that provide a measure of working memory and the capacity for mental manipulation (Lamar, 2007, 2008).

Underlying impairment in serial order recall is a working memory deficit, where the ability to hold and mentally manipulate information is attenuated. An illustration of derailed performance as a function of serial order position has been outlined in Figure 1 of Emrani et al. (2018). In this exemplar of derailed performance, the mixed/dysexecutive MCI group displayed a lack of a recency effect, where performance of the last digit never improved. In contrast, non-MCI and amnestic MCI groups displayed a spike in performance on the final digit. Similar results showing a relentless negative slope in performance of patients with a dysexecutive feature were reported by Eppig and colleagues (2012). Together, these studies conclude that the observed working memory deficits observed in these patient groups reflect a greater impairment in establishing and sustaining mental set, a behavior consistent with Fuster's (2008) model of *temporal organization*.

An early study by Fuster (1973) suggests that sustained activation of PFC "*memory neurons*" during executive control tasks have four main features: (1) the

magnitude of neuronal activity is related to the accuracy of the performed task; (2) neuronal activity is dependent on the act of prospective motor output; (3) neuronal activity is not necessarily dependent on the expectation of a reward; and (4) neuronal activity can be suppressed or diminished by distraction. Upon the precise completion of such features, *temporal organization* has successfully been implemented. In analyzing only correct trials, the 5-span BDT and 4-span SWM meet the behavioral features proposed by Fuster (1973), and thus the requirements of a successful *temporal organization*. The current research sought to further examine Fuster's model (2008) by assessing *intra-component latency*, or time to complete the task at hand, of correct responses on working memory paradigms. To expand upon the original study by Emrani et al. (2018), the BDT and an analogous test of working memory, Symbolic WM, were digitized to gather latency data.

Overview of Results

BDT latency. There were no between-group differences on the average total time for correct responses. However, *intra-component latency* patterns for serial order position diverged within- and between-group. Specifically, between-group analyses showed that the non-MCI group took longer than the MCI group on positions two and four, but less time to respond to position three (see Figure 1). Follow-up within-group analyses comparing first, middle, and last *intra-component latencies* found that non-MCI patients spent more time to generate responses for position one as compared to position three, and position three as compared to position five. The MCI group did not significantly differ on time to respond to positions one versus three, however, took more time to respond to position three compared to position five. These data suggest that while total time does not

differ between-group, there are meaningful differences in the allocation of time for each *intra-component latency* on correct trials.

To further assess within- and between-group distinctions in the distribution of time per position, the data was transformed and expressed as fractions by dividing the average total time for correct trials by each *intra-component latency*, or the average time for each correct serial position. Results from the 2 x 5 mixed-model analyses found within-group differences on performance, consistent with the results above (see Figure 2). Moreover, an interaction between performance and group was observed, suggesting that while there are no differences in the average total time to correctly provide responses, the ways in which the groups behave on positions as a fraction of total time is significantly different. This pattern of performance continues to show that there are differences in the allocation of time to respond to positions between group.

Consistent with Fuster's model of *temporal organization*, longer latencies may be a means by which to operationally define the constructs of *working memory* and *preparatory set*. *Working memory* is attention focused retrospectively on the internal representation of the task at hand, in this case the instructions and numbers to be recruited. The coordination between temporal and/or visuospatial information on backward digit paradigms (Hoshi et al., 2000; Larrabee & Krane, 1986) synchronized with recent and long term memory are all necessary to prospectively establish an effective *preparatory set* (Fuster, 2008). Together, these tasks prepare and begin the intention and behavior to act, respectively. Of course, position one provides a thorough illustration of these theoretical constructs; both non-MCI and MCI groups took the longest time to respond to this position. Succeeding longer latency positions slightly

diverge between group, particularly on serial order positions three and four. Specifically, the MCI group had its second and only longer latency on position three, while the non-MCI group took longer to respond on positions three and four. These secondary longer latencies may be suggestive of an iterative 'check in,' where patients revisit *working memory* and *preparatory set* to ensure correct implementation of instructions, intentions, and behaviors.

Longer latency on position four may also be a marker of *inhibitory control*. The final mechanism of Fuster's model (2008) is *inhibitory control*, or the ability to discriminate and/or suppress inputs that can derail or interfere with the structure of behavior in use to produce a goal-directed action (Fuster, 2002, 2003, 2008). When comparing the number of correct trials on the 5-span BDT, the non-MCI group had more 5-span correct trials as compared to the MCI group. Previous studies have shown derailed recency effects in patients with a dysexecutive/mixed MCI (Emrani et al., 2018; Eppig et al., 2012), which is likely why the MCI generated fewer correct trials. As such, it can be extrapolated that derailed performance is a dysfunctional *inhibitory control* process, where internal or external stimuli interfere with the behavior to produce a correct action. Therefore, differences in the latency on position four may be a result of behaviors that lead to increased *inhibitory control*, where the non-MCI group allocates more time to ensure successfully completely trials.

Symbolic WM. The 5-span Symbolic WM numbers/letters task appeared more difficult than the 5-span BDT. When applying within-group comparisons on 4- and 5-span correct trials on the BDT span versus Symbolic WM *numbers only* tasks, neither analysis found any group to perform measurably better on one task than the other. This

data suggests that motor versus auditory output is not the cause for difficulty on the Symbolic WM numbers/letters condition. Rather, it is likely that the addition of letters with numbers is simply too difficult, resulting in a floor effect on the 5-span Symbolic WM condition. As such, we used 4-span numbers/letters Symbolic WM for our analyses.

Similar to the BDT analyses, the mixed-model showed within-group differences on *intra-component latency* for correct serial order position, but no group by performance interaction (Figure 3). Follow-up analyses found that the non-MCI group took longer to correctly respond to position one as compared to position three, and longer on position three versus four. Comparatively, the MCI group only took longer on position three than four. Unlike the BDT, both groups had a similar pattern of latency performance, and no significant differences between-group were found on any correct latency. Finally, only within-group differences on the transformed fraction of average total time for correct trials divided by latency for each serial position was statistically significant. Overall, Symbolic WM appears less robust in assessing serial latency between-group. However, the latencies on the 4-span Symbolic WM numbers/letters condition corroborate the 'check-in' notion described above. As seen in the Symbolic WM task graph (see Figure 3), there is an increased latency for position three, the position where one is tasked to switch from numbers to letters. It is reasonable to assume that *working memory* and *preparatory set* would be in full effect for this transition, thus creating an increased latency, similar to that in position three of the 5-span BDT.

Correlations and MRI outcome. The JOLO test has been shown to be associated with working memory, information processing speed, and mental set (Wasserman et al., 2020), while WAIS-III Digit Symbol is associated with sustained attention, psychomotor

control, speed, and (incidental) memory (Joy, Kaplan, & Fein, 2004). Correct average total time on the 5-span BDT was associated with WAIS-III Digit Symbol and JOLO. Comparatively, 4-span Symbolic WM numbers/letters was not related to any of the neuropsychological tests. The negative association between WAIS-III Digit Symbol suggests that better performance on the WAIS-III Digit Symbol is related to less total time to complete correct trials, consistent with the overlapping neurocognitive constructs (i.e. attention, speed, and memory) necessary to successfully complete these tasks. JOLO z-score was positively correlated with correct average latency, likely showing the synergistic relationship between an ability to maintain mental set and provide correct responses. This is to say that the capacity to hold instructions and information for longer time is more likely to result in correct responses.

Finally, the addition of 4-span Symbolic WM numbers/letters or 5-span BDT *intra-component latencies* did not reliably improve R^2 on any of the MRI brain region regression models, nor was there right versus left neuroanatomic involvement on either WM task. Likely, the lack of findings is a result of an underpowered sample size. Nonetheless, prior studies have found a handful of regions known to affect one's ability to successfully complete WM tasks. For example, connections between the frontal lobe and thalamus are necessary for encoding and retrieval of episodic memory tasks and others involving feedback information (Tsujimoto et al., 2011; Fuster, 2008; Klein et al., 2010; Petrides & Pandya, 2002). The basal ganglia has been shown to be activated during planning and set shifting (Dubois & Pillon, 1996; Monchi et al., 2006; Taylor & Saint-Cyr, 1995). Moreover, the hippocampus is recruited during WM processing for novel (Axmacher et al., 2007, 2010; Leszcyzynski, 2011; Ranganath & D'Esposito, 2001) and

past items (Collette et al., 2005; Fuster & Alexandre, 1971; Goldman-Rakic, 1995; Koenigs et al., 2009). In executive control tasks, representational networks are modified, updated by the present context, and activated for prospective action. Together, successful executive control task responding is the result of various combinations and accompaniment of neural networks for the maintenance and integration of information to complete the task (Cowan et al., 2001; D'Esposito & Postle, 2015; Eriksson et al., 2015; Fuster, 2009; Jonides et al., 2008).

Limitations, Conclusions, and Future Work

The current study has several strengths including novel technology to measure latency, or time to generate a response, neuroradiological information, the use of objective criteria to classify MCI and non-MCI. However, several limitations are acknowledged. First, our sample size was modest with unequal sizes in each group. Second, our definition of MCI was limited to three neurocognitive domains. Finally, there are discrepancies in the administration of the WM paradigms, like trials per span, which may have complicated measurements and analyses. Despite these limitations, our findings provide evidence that assessing *latency* of serial order recall in working memory follow a behavioral pattern consistent with Fuster's model (2008). Moreover, the BDT is able to dissociate MCI from non-MCI group by assessing the proportion of each response time as a function of total time to complete correct trials.

To expand upon the current findings, future work should investigate whether MCI subtypes can further differentiate behaviors in *latency* output. Moreover, replicating these findings may be a way in which to detect emergent illness earlier on in the disease process. Specifically, the digitized version of the BDT can be utilized as a cognitive

biomarker to predict cognitive decline in those with MCI. Finally, studying these digitized variables using machine learning may provide additional information regarding variables that are most likely to predict cognitive decline that can ultimately be applied in primary care settings.

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Appendix A

MRI Regression Models

Regression Models for MRI ROI and 5-Span BDT Intra-Component Latencies

Outcome	Step	R^2	AdjR^2	ΔR^2	ΔR^2 *p-value*
Total Hippocampal Volume	1	.30	.26	.30	ns
	2	.42	.25	.11	ns
Right Hippocampal Volume	1	.25	.20	.25	ns
	2	.43	.26	.18	ns
Total Gray Matter Volume	1	.40	.35	.40	ns
	2	.57	.45	.18	ns
Right Gray Matter Volume	1	.37	.33	.37	ns
	2	.59	.47	.22	ns
Left Gray Matter Volume	1	.41	.36	.41	ns
	2	.54	.41	.14	ns
Total Thalamic Volume	1	.74	.72	.74	ns
	2	.79	.73	.05	ns
Right Thalamic Volume	1	.67	.65	.67	ns
	2	.76	.69	.09	ns
Left Thalamic Volume	1	.75	.73	.75	ns
	2	.78	.72	.03	ns
Total Basal Ganglia Volume	1	.32	.28	.32	ns
	2	.43	.25	.10	ns
Left Basal Ganglia Volume	1	.36	.31	.36	ns
	2	.47	.31	.11	ns

Note. AdjR^2= Adjusted R^2

Regression Models for MRI ROI and 4-Span SWM Intra-Component Latencies

Outcome	Step	R^2	AdjR^2	ΔR^2	ΔR^2 *p-value*
Total Gray Matter Volume	1	.55	.51	.55	ns
	2	.57	.44	.02	ns
Right Gray Matter Volume	1	.54	.50	.54	ns
	2	.55	.41	.01	ns
Left Gray Matter Volume	1	.55	.51	.55	ns
	2	.59	.47	.05	ns

Appendix A (Continued)

Total Thalamic Volume	1	.55	.51	.55	ns
	2	.60	.47	.05	ns
Right Thalamic Volume	1	.55	.51	.55	ns
	2	.58	.45	.03	ns
Left Thalamic Volume	1	.66	.63	.66	ns
	2	.75	.67	.10	ns

Note. AdjR^2= Adjusted R^2

Appendix B

Supplemental

Demographic characteristics. No between-group differences were found for age (M=75.20, SD=6.61), education (M=14.78, SD=2.66), the Geriatric Depression Scale (M=3.15, SD=2.59; Yesavage et al., 1982), projected premorbid general intellectual abilities assessed with the Wide Range Achievement Test Reading subtest-IV (WRAT-IV; M=112.76, SD=16.10), gender (Male=49, Female=93) or Instrumental Activities of Daily Living (M=14.72, SD=2.79; Lawton, & Brody, 1969). There was statistical significance between group ($F[2, 140]=11.53$, $p < .001$) on the Mini-Mental State Examination (MMSE; Folstein et al., 1975) such that non-MCI patients (M=28.25, SD=1.66) performed better than both aMCI (M=26.50, SD=2.27, $p < .001$) and mixed/dys MCI (M=27.05, SD=1.86, $p < .006$).

Correct response, ANY order, and SERIAL order. We replicated our original study (Emrani et al., 2018) and found similar results. The number of correct responses for the seven 5-span trials was tallied (range 0-35, correct). Comparing each group (non-MCI = 76; aMCI = 29; mixed/dysMCI = 37) using a one-way analysis of variance (ANOVA) for the number of correct responses showed statistical significance (Welch's $F[2,58.25]=18.42$, $p < .001$). *Post-hoc* analyses found that mixed/dysMCI patients recalled fewer correct responses compared to both non-MCI ($p < .001$) and aMCI ($p < .002$) patients. ANY order recall (total percent recall of digits regardless of their correct serial order) and SERIAL order recall (total percent recall of digits in the exact serial order) were assessed with a multivariate analysis of variance (MANOVA), with an adjusted alpha level of .01 to minimize type 1 error due to heterogeneity of variance.

Moreover, we used Pillai's trace, a robust index for heterogeneity of variance. The MANOVA found a significant effect for group (Pillai's Trace = $F[4,278]=9.42$, $p < .001$, $\eta_p^2=0.12$). Differences were found for both ANY order recall ($F[2,139]=10.61$, $p < .001$, $\eta_p^2=0.132$; not previously seen) and SERIAL order recall ($F[2,139]=20.42$, $p < .001$, $\eta_p^2=0.227$) where Bonferroni *post-hoc* analyses found that mixed/dysMCI patients (ANY order mean = 89.88, SD=0.95; SERIAL order mean = 62.24, SD=2.47) scored lower than non-MCI patients (ANY order mean = 95.22, SD=0.66; SERIAL order mean = 81.28, SD=1.73) on ANY order ($p < .001$), and lower than both non-MCI ($p < .001$) and aMCI (ANY order mean = 93.30, SD=1.08; SERIAL order mean = 78.13, SD=2.80; $p < .001$) on SERIAL order.

Serial order position, and primacy/ recency effects. The total percent correct for each of the five serial order positions was also tallied. Recency *recall* was defined as the first number heard and participants' subsequent last response. *Primacy recall* was determined as the last number heard and participants' subsequent first response. This terminology regarding primacy and recency effects is standard in serial order position research (Hurlstone, Hitch, & Baddeley, 2014 p. 5; 23-24). Data was analyzed using a mixed-design ANOVA with a 3 within-subjects factor (percent correct for positions 1-5) and a 5 between-subject factor (MCI subtype; non-MCI= 76, aMCI = 29, mixed/dysMCI = 36). Mauchly's test indicated that the assumption of sphericity had been violated ($X^2(9)=119.48$, $p < .001$); therefore, degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity ($\varepsilon=.739$). Moreover, Bonferroni methods were used to reduce Type 1 error in *post-hoc* tests. Main effects of the 3 group x 5 serial order position repeated measured ANOVA yielded significant within-group differences

(F[2.95,552]=166.06, p < .001, η_p^2=0.546) and serial order position by group interaction (F[5.91,552]=10.67, p < .001, η_p^2=0.134). Follow-up ANOVAs found differences for serial positions two (F[2,138]=7.64, p < .002, η_p^2=0.100), three (F[2,139]=13.25, p < .001, η_p^2=0.160), four (F[2,139]=14.22, p < .001, η_p^2=0.170) and five (Welch's F; F[2,57.96]=23.53, p < .001, η_p^2=0.306). *Post-hoc* (Bonferroni) comparisons found that mixed/dysMCI patients recalled less information than non-MCI and aMCI serial order position 2 (non-MCI, p < .006; aMCI, p < .002), serial order position 3 (non-MCI, p < .001; aMCI, p < .006), serial order position 4 (non-MCI, p < .001; aMCI, p < .013) and serial order position 5 (recency; non-MCI, p < .001; aMCI, p < .001). Finally, paired sample t-tests to assess recency effect were employed by analyzing 3rd response percent correct versus 5th response percent correct. Only within-group differences for mixed/dysMCI conditions were statistically significant (3rd response percent correct mean= 53.28; 5th response percent correct mean= 41.31; t(36)=2.51, p<.018; Cohen's d=0.41).

Total transpositions and transposition gradient. Transpositions are defined as the degree of displacement in relation to their correct serial position. *Anticipation transposition* errors are described as out-of-sequence errors where the patient provided a number *before* its actual position. These types of errors were scored using a negative displacement value because they occurred in advance or ahead of their correct serial position. *Postponement transposition* errors are described as out-of-sequence errors where the patient provided a number *after* its actual position and were scored using a positive displacement value because they occurred after their correct serial position. Correctly recalled test items were assigned a value of zero to reflect the absence of any

displacement. Due to the multi-collinearity of the dependent variables (Total 5-span Transposition and Total 5-span Anticipation Pearson's r= 0.951, p < .001; Total 5-span Transposition and Total 5-span Postponement Pearson's r= 0.918, p < .001), independent one-way ANOVAs were used (Tabachnick & Fidell, 2007). Significant effects were found for total transposition errors (Welch's F; F[2,58.38] = 12.81, p < .001; η_p^2=0.209), total anticipation transposition errors (Welch's F; F[2,59.92] = 11.85, p < .001; η_p^2=0.206), and total postponement transposition errors (Welch's F; F[2,55.85] = 9.29, p < .001; η_p^2=0.156). *Post-hoc* (Bonferroni) comparisons found that mixed/dysMCI patients made more total transposition errors than non-MCI (p< .001) and aMCI (p<.001), more anticipation transposition errors than non-MCI (p< .001) and aMCI (p<.001), and more postponement transposition errors than non-MCI (p<.001) and aMCI (p<.007). A MANOVA measuring the effect of group on average anticipation and postponement transposition displacement was significant (Pillai's Trace F[4,278]=8.61, p <.001, η_p^2=0.110). Group effects were obtained for both average anticipation F[2,139]=18.41, p<.001, η_p^2=0.209) and F[2,139]=12.65, p<.001, η_p^2=0.154). *Post-hoc* (Bonferroni) analyses found that mixed/dysMCI patients generated greater anticipation displacements on average as compared to both non-MCI (p < .001) and aMCI (p < .001), as well as greater postponement displacements on average as compared to both non-MCI (p < .001) and aMCI (p < .007).

Item errors. Non-transposition, out-of-sequence errors including omissions and perseverations were calculated. These item errors include: between-trial perseverations, when a number from the preceding two trials was pulled into the current response; within-trial perseverations, when a number within a trial was repeated; between trial

capture errors, when a number from either of the preceding two trials is pulled into the current response creating a contiguous, automatized string of digits; within-trial capture errors, when number(s) within the same trial were incorrectly repeated, also creating a contiguous string; and omissions, when the patient responded with less than the number of digits administered. Because of the low frequency of some of these errors all perseveration and capture errors were summed and labeled dysexecutive errors. Omissions and total dysexecutive errors were summed to create a total item error score. Due to the multi-collinearity (Total dysexecutive errors and total item error Pearson's r=.966, p <.001), we used one-way ANOVAs (Bonferroni). Between group differences were significant for total omissions (Welch's F; F[2,53.76]=3.62, p<.034; η_p^2=0.072), total dysexecutive errors (F[2,139]=12.78, p<.001; η_p^2=0.155), and total errors (F[2,139]=15.83, p<.001; η_p^2=0.185). *Post-hoc* analyses found significant differences between mixed/dysMCI and non-MCI on total omissions (p<.005), total dysexecutive errors (p<.001), and total errors (p<.001). Moreover, significant differences were found between mixed/dysMCI and aMCI on total dysexecutive errors (p<.016), and total errors (p<.007).