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Neural Correlates of Memory Encoding in Subtypes of Mild Cognitive Impairment

A dissertation submitted in partial satisfaction of the
requirements for the degree Doctor of Philosophy

in

Clinical Psychology

by

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2014

The Dissertation of Lindsay R. Clark is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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Dedication

This doctoral dissertation is dedicated to my loving husband, Mark Clark, without whom I would not be the person I am today. I am incredibly grateful for his endless support throughout graduate school and continuously impressed by his unwavering optimism, kindness, and sense of adventure.

This dissertation is also dedicated to my parents, Ray and Nalene Termini, who taught me the importance of hard work and education. I would also like to dedicate this to my grandmother, Arline Larson, and to the memory of my grandfather, Larry Larson.

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Abstract of the Dissertation

Neural Correlates of Memory Encoding in Subtypes of Mild Cognitive Impairment

by

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Alzheimer's disease (AD) affects approximately 5 million adults over age 65 in the U.S. Examining brain function in individuals at risk for AD, such as those with Mild Cognitive Impairment (MCI), may improve identification of potential markers of AD prior to the onset of significant clinical symptoms, which will be important to

prevention efforts and extending quality of life. Subtypes of MCI with primary memory (amnestic) or non-memory (non-amnestic) impairments may reflect different neuropathologic etiologies. However, evidence to support this notion is mixed, possibly due to a lack of comprehensive neuropsychological definitions of MCI or examination of cerebrovascular dysfunction that may contribute to cognitive decline.

In the current study, functional cerebral blood flow (CBF) and blood-oxygenation level dependent (BOLD) responses were simultaneously acquired in an MRI scanner while older adults with amnestic MCI (aMCI; *n* = 14), non-amnestic MCI (naMCI; *n* = 13), and normal cognitive functioning (CN; *n* = 20) completed a face-name associative encoding paradigm. Region of interest analyses were conducted in the hippocampus, parahippocampal gyrus (PHG), precuneus, and anterior cingulate cortex (ACC).

At rest, reduced CBF within medial temporal regions (MTL) was observed in aMCI, but there were no differences between the CN and naMCI group. During face-name encoding, the aMCI group exhibited greater percent change BOLD in the MTL, whereas the naMCI group exhibited significantly greater percent change CBF in the left precuneus. Relationships between MTL BOLD/CBF and memory performance (e.g., list learning, face-name recognition) were observed in the MCI groups only. There were no significant group differences in stroke risk, and the relationships among stroke risk, resting CBF, and CBF/BOLD during encoding were not significant.

Overall, the current findings support distinct patterns in CBF at rest and in BOLD/CBF during encoding between aMCI and naMCI groups, and suggest that these individuals – although all diagnosed with mild cognitive impairment – exhibit distinct alterations in neurovascular function that may underlie their varied cognitive

deficits on neuropsychological tests and may be associated with a unique trajectory of cognitive decline. Further research using CBF/BOLD to predict disease progression in individuals with MCI may be indicated.

Neural Correlates of Memory Encoding in Subtypes of Mild Cognitive Impairment

Introduction

Alzheimer's disease (AD), the leading cause of dementia in older adults, is characterized by the development of neuritic plaques and neurofibrillary tangles. Plaques appear to be more diffusely distributed, whereas tangles initially accumulate in the medial temporal lobe (MTL) and spread to association cortices over time (Braak & Braak, 1991). Consistent with this neuropathologic development, MTL-dependent episodic memory performance is often affected earliest, followed by declines in semantic memory, visuospatial skills, executive functioning, and attention (Bondi et al., 2008). Current estimates report that approximately 5.2 million individuals (13%) in the U.S. over age 65 have AD (Alzheimer's Association, 2014; Hebert, Scherr, Bienias, Bennett, & Evans, 2003), and the risk for AD increases with advancing age (Katzman & Kawas, 1999). As the aging population is rapidly growing, it is important to assess methods of early detection as well as to prevent or delay cognitive decline in older adults (Alzheimer's Association, 2014).

Longitudinal studies demonstrate that underlying neural changes associated with AD often begin several years prior to onset of clinical symptoms. These changes include volume loss and cerebral blood flow (CBF) or metabolic changes, most notably in the temporal lobe, that lead to subtle cognitive deficits detected several years or more prior to AD diagnosis (Albert, Moss, Tanzi, & Jones, 2001; Backman, Jones, Berger, Laukka, & Small, 2005; Twamley, Ropacki, & Bondi, 2006). Identification of these changes in its prodromal stage is crucial as emerging

treatments will be most effective in delaying the onset of symptoms, thus having a greater impact on preserving quality of life (DeKosky & Marek, 2003; Tariot & Federoff, 2003). As even small delays in the onset of AD are predicted to significantly reduce the global burden of this disease, a better understanding of factors interacting to increase risk are imperative in improving the lives of individuals in our increasingly aging society (Brookmeyer, Johnson, Ziegler-Graham, & Arrighi, 2007).

Mild Cognitive Impairment

One approach to identifying potential cognitive and biological markers of preclinical AD is to examine brain function in individuals at higher risk of developing AD, such as those diagnosed with Mild Cognitive Impairment (MCI). MCI describes individuals who demonstrate impairment on tests of cognitive function but generally maintain intact global cognition and daily functioning (Petersen, 2004). Historically, MCI was considered an intermediate stage between normal aging and dementia, but current definitions characterize MCI as a distinct construct representing a risk factor for AD and other dementias. However, the lack of a universal operational definition of MCI among clinical and research practices (e.g., see varying criteria from Winblad et al., 2004 and Dubois, et al., 2007) results in widely varying prevalence and progression rates (Ganguli et al., 2011; Jak et al., 2009b). More recently, the definition of MCI has evolved into specific clinical subtypes describing individuals with primary memory impairments (amnestic) or non-memory impairments (non-amnestic) involving single or multiple cognitive domains (Peterson & Morris, 2005). Further, some evidence suggests that the variable cognitive impairments across MCI subtypes may reflect different underlying neuropathologic processes. For example,

individuals with focal memory deficits often demonstrate MTL volume loss whereas those with broader cognitive deficits exhibit greater involvement of association areas or white matter damage (Jak et al., 2009a; Hughes, Snitz, & Ganguli, 2011). However, some longitudinal studies have noted that individuals diagnosed as amnestic or non-amnestic MCI were both likely to progress to a probable AD diagnosis (Fischer et al., 2007) and to have comparable percentages of underlying AD, ischemic and other neuropathologies at autopsy (Schneider, Arvanitakis, Leurgans, & Bennett, 2009).

One reason for these mixed findings may be lack of the use of comprehensive neuropsychological definitions of MCI that more accurately document spared and impaired cognitive functions and reflect underlying etiology. For instance, individuals are often classified as MCI based on global screening instruments or low scores (i.e., 1.5 standard deviations below normative means) on one measure in a neuropsychological battery (see Petersen et al. 2004). These definitions may contribute to poorer sensitivity and specificity in identifying those individuals at highest risk of AD. Available evidence suggests that conventional methods for MCI diagnosis may be susceptible to 'false positive' diagnostic errors (Clark et al., 2013; Edmonds et al., 2014; Saxton et al., 2009) and that the use of more comprehensively defined MCI diagnoses requiring both low performances (1 standard deviation [SD] below demographically-matched norms) on two tests within a cognitive domain and intact activities of daily living demonstrate increased reliability and stability of diagnosis over time compared with conventional 'one test' methods for MCI diagnosis (Bondi et al., 2014; Chang et al., 2010; Chang et al., 2011; Clark et al., 2013; Jak et al., 2009b; Loewenstein et al., 2009).

Functional MRI Studies in MCI

To capture subtle neural changes occurring during MCI, it is important to use a sensitive measure of brain activity. Functional magnetic resonance imaging (fMRI) is an *in vivo* measure of functional brain activation during complex cognitive processes and may be particularly useful because alterations in brain function tend to precede structural decline in preclinical samples, including adults with MCI (Dickerson & Sperling, 2008; Wierenga & Bondi, 2007). Furthermore, it is important to use measures that involve brain regions affected in MCI, such as the hippocampus and other medial temporal regions (e.g., entorhinal and perirhinal cortices) that are typically the earliest regions impacted by neurofibrillary pathology and cell loss in prodromal stages of AD. A key function of the hippocampal formation in episodic memory encoding is to form new associations between unrelated pieces of information (Sperling, 2007), and this ability to remember associations may be impaired in MCI compared to single-item memory (Hanseeuw et al., 2011). One particularly complex associative memory process requiring the integration of visual and verbal information is the recollection of faces and names, and loss of this ability is a common complaint among older adults with cognitive difficulties. Functional MRI studies using face-name associative encoding paradigms have been shown to reliably activate the hippocampus across healthy older adults as well as those with cognitive impairments (Putcha et al., 2011) indicating that face-name encoding tasks can be used to measure subtle brain changes that occur in regions affected in the early stages of AD.

There is also evidence that successful memory formation requires coordinated neural activity between hippocampal and posteromedial regions including the precuneus and posterior cingulate cortex (Sperling et al., 2003). Specifically, task-induced deactivation of posteromedial regions during encoding has demonstrated benefits to learning and subsequent successful remembering of material (Miller et al., 2008). However, activity in these regions may be altered during aging and early AD and thus examining both MTL and parietal regions can provide a more comprehensive understanding of neural correlates underlying cognitive impairment in preclinical AD. In AD, decreased activation during face-name encoding has been observed in MTL structures such as the hippocampus and parahippocampal gyrus (Dickerson et al., 2005; Machulda et al., 2003; Sperling et al., 2001), but increased activation has been found in the precuneus and posterior cingulate gyrus (Petrella et al., 2007a; Sperling et al., 2001). Similarly, increased posteromedial activation during cognitive performance has also been implicated in MCI (Petrella et al., 2007a) and loss of expected parietal deactivation has been shown to predict conversion to AD (Petrella, Prince, Wang, Hellegers, & Doraiswamy, 2007b).

Functional MRI studies of episodic memory encoding in MCI have primarily focused on the amnestic subtype. In general results have been inconsistent, as some studies have observed increased neural activity during memory performance in the MTL (Dickerson et al., 2004; Hamalainen et al., 2007; Sperling, 2007), whereas others report decreased MTL activity (Hampstead, Stringer, Stilla, Amaraneni, & Sathian, 2011; Johnson et al., 2006; Mandzia, McAndrews, Grady, Graham, & Black, 2009). Two studies that specifically focused on encoding of items that were subsequently recognized (i.e., successful encoding) found that an MCI group had

increased activation in hippocampal regions and decreased frontal activity during successful encoding (Kircher et al., 2007; Trivedi et al., 2008). These findings support the interpretation that increased activation may be a compensatory change enabling these individuals to maintain normal functions despite early pathophysiologic alterations.

Face-Name Encoding in MCI

Although few studies have specifically examined face-name associative encoding in MCI, existing evidence supports increased hippocampal activation in individuals with MCI compared to controls (Dickerson et al., 2005), but decreased activity in other regions including the bilateral frontal cortex (Petrella et al., 2006). Additionally, cognitively intact older adults typically exhibit a reduction in activity over the course of an experiment, indicating a normal habituation response to repeated face-name stimuli. In contrast, Johnson and colleagues (2004) observed that individuals with MCI did not demonstrate reduced hippocampal activity with increasing repetitions of face-name pairs, suggesting a lack of adaptation to the stimuli, and this fMRI response was associated with poorer learning. Similar impairments in MTL reduction during repeated face-name pairs in AD has been observed and shown to correlate with impaired task-induced parietal deactivation and poorer recognition performance (Pihlajamaki, DePeau, Blacker, & Sperling, 2008). These latter findings suggest episodic memory impairment in AD may partially relate to failure of normal suppression and loss of beneficial deactivation in the MTL-parietal memory networks.

The mixed findings from fMRI encoding tasks in MCI noted above may be partially due to differences in study design, as well as differences in MCI classification scheme or level of MCI severity. One hypothesis suggests that hyperactivation of MTL circuits, possibly representing compensatory strategies, may occur in early MCI when only mild memory deficits and hippocampal atrophy are present. However, in more severe MCI, MTL regions may no longer be able to activate during encoding (Dickerson & Sperling, 2008). For example, one study found that less impaired MCI participants had increased hippocampal activation and hyper-deactivation of parietal regions, whereas those with greater impairments exhibited hippocampal hypoactivation and reduced parietal deactivation compared to controls (Celone et al., 2006). Additionally, discrepancies may also be related to various definitions of MCI used across studies (i.e., differences in cut-off scores, inclusion of a mix of subtypes) leading to wide ranging levels and domains of cognitive impairment.

Few studies have compared MCI subtypes using fMRI. Using a visual scene encoding and recognition paradigm, one study found both amnestic and non-amnestic MCI subtypes to exhibit reduced bilateral temporoparietal and frontal activation during encoding compared to controls. During recognition, the amnestic group demonstrated reduced activation in bilateral temporoparietal regions and the non-amnestic group exhibited additional reduction in frontal regions (Machulda et al., 2009). A separate study that focused on the single-domain amnestic MCI subtype observed increased activation compared to controls across several brain regions during a variety of fMRI paradigms examining language, visuospatial attention, recognition memory, and empathy (Lenzi et al., 2011). No studies to date have

compared amnestic and non-amnestic MCI subtypes on a face-name associative encoding paradigm.

Cerebrovascular Function in MCI

Additionally, conflicting findings may relate to complications involved in interpreting the blood-oxygenation level dependent (BOLD) signal in older adults at risk for AD. The BOLD signal is generally interpreted as an indirect measure of neural activity. However, this signal reflects local changes in deoxyhemoglobin content, which in turn exhibits a complex dependence on changes in CBF, cerebral blood volume, and the cerebral metabolic rate of oxygen consumption ($CMRO_2$) (Buxton, Uludag, Dubowitz, & Liu, 2004; see Figure 1).

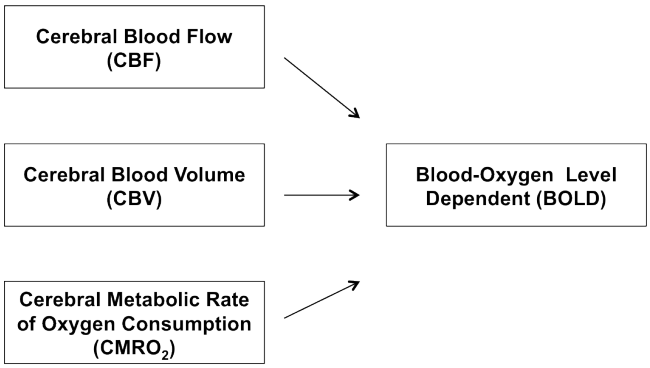


Figure 1. Components that contribute to the BOLD signal

Further, there is growing evidence that changes in the cerebrovascular system due to age or disease can significantly alter the BOLD signal and complicate its interpretation (D'Esposito, Deouell, & Gazzaley, 2003). Age or disease-related factors include altered cerebrovascular ultrastructure, reduced elasticity of vessels, increased atherosclerosis, reduced resting-state CBF, decreased resting $CMRO_2$, and reduced vascular reactivity to chemical modulators (Bentourkia et al., 2000; D'Esposito et al.,

2003; Claus et al., 1998; Kawamura et al., 1993; Takada et al., 1992; Yamaguchi et al., 1986). Increased AD risk is associated with several vascular (e.g., cardiovascular disease, hypertension, diabetes) and cerebrovascular disease risk markers such as white matter hyperintensities (WMH) on MRI—thought to represent axonal injury and possible loss of blood flow (Luchsinger et al., 2005; Rocchi, Orsucci, Tognoni, Ceravolo, & Siciliano, 2009; Qiu, Xu, & Fratiglioni, 2010; Troncoso et al., 2008). WMH may be associated with an increased risk of converting from normal cognitive status to MCI (Smith et al., 2008), and periventricular WMH and decreased hippocampal volumes are associated with an increased risk of AD, suggesting that cerebrovascular disease risk may contribute to AD onset in individuals vulnerable to the disease (Godin et al., 2010; Van Straaten et al., 2008). Additionally, in individuals with MCI, deep WMH and periventricular hyperintensities predicted progression to a non-AD dementia, whereas MTL atrophy predicted progression to AD (Staekenborg et al., 2009). Some evidence suggests that the non-amnestic MCI subtype may be more strongly associated with vascular risk factors, such as metabolic syndrome, coronary heart disease, or history of transient ischemic attacks and strokes compared to amnestic MCI (Roberts et al., 2010a; Roberts et al., 2010b). Furthermore, several studies have found increased markers of cerebrovascular disease risk on MRI in non-amnestic MCI (Di Carlo et al., 2007; Delano-Wood et al., 2010; He et al., 2009; Kantarci et al., 2008; Zanetti et al., 2006) with one study reporting that MTL atrophy was more evident in individuals with amnestic MCI (suggesting AD as the underlying cause), whereas an interaction between MTL atrophy and WMH was present in the non-amnestic MCI group (Van de Pol et al., 2009). These findings suggest that, although both subtypes have increased vascular risk factors, the relationship between

cerebrovascular functioning and neural change may vary between subtypes and play a role in increased risk for AD and other non-AD dementias.

Cerebral Blood Flow in AD and MCI

Due to the vascular changes often present in individuals at risk for AD, it is possible that increases and/or decreases in BOLD response in this population may be explained by changes both in neural activity and cerebrovascular functioning. One method that may reduce this ambiguity is to use an MRI method that combines arterial spin labeling with the blood-oxygenation level dependent (ASL/BOLD) signal. Arterial spin labeling (ASL) is a magnetic resonance imaging method that magnetically labels arterial water and uses it as an endogenous tracer to measure CBF. Due to its ability to quantify CBF, it has the potential to more accurately estimate the location and magnitude of neural function (Liu & Brown, 2007). As the proposed study plans to examine early disease states, as well as the influence of cerebrovascular function, using a sensitive measure that accounts for vascular differences is essential in accurately evaluating neural changes in older adults with MCI. ASL studies of individuals with AD have reported consistent widespread reductions in resting CBF compared to healthy older adults (Alexopoulos et al., 2012; Alsop, Detre, & Grossman, 2000; Asllani et al., 2008; Dai et al., 2009; Johnson et al., 2005; Sandson, O'Connor, Sperling, Edelman, & Warach, 1996; for review of ASL in AD see Alsop, Dai, Grossman, & Detre, 2010), although some regions have demonstrated increased levels particularly after correcting for regional gray matter atrophy (e.g., anterior cingulate, hippocampus) (Alsop, Casement, de Bazelaire, Fong, & Press, 2008; Dai et al., 2009). The most consistent observation across

studies is decreased precuneus and/or posterior cingulate blood flow in AD (Alsop et al., 2010).

Several studies have examined resting-state CBF using ASL in individuals with MCI, although few have specified subtype of MCI. Decreased CBF in the posterior cingulate, precuneus and cuneus, inferior parietal lobe, and medial temporal lobe has been reported in MCI compared to cognitively intact older adults (Alexopoulos et al., 2012; Bangen et al., 2012; Chao et al., 2009; Dai et al., 2009; Johnson et al., 2005; Xu et al., 2007), although two studies have observed regionally-specific increased CBF in the hippocampus, superior temporal gyrus, inferior frontal gyrus, amygdala, and basal ganglia in individuals with MCI (Dai et al., 2009; Wierenga et al., 2012). A longitudinal study found decreased CBF in the right inferior parietal lobe, right middle frontal cortex, right precuneus, and right middle cingulum in individuals with MCI who subsequently developed dementia (Chao et al., 2010). One study to specifically examine non-amnestic MCI observed reduced resting CBF in the left middle frontal gyrus, left posterior cingulate, and left precuneus relative to amnestic MCI (Chao et al., 2009). Few studies have examined CBF change during cognitive tasks. Xu and colleagues (2007) reported that individuals with MCI exhibited hypoperfusion during encoding in the precuneus/cuneus and posterior cingulate relative to controls. The authors also noted that the MCI group did not exhibit increased percent signal change in the parahippocampal gyrus during encoding whereas the controls had a 23% increase in CBF in this region (Xu et al., 2007). A separate study used a face-name paradigm to measure CBF during encoding and found elevated MTL CBF at rest in middle-aged individuals at genetic risk for AD via possession of the APOE ε4 allele and family history of AD, but no differences

between risk and control groups in activation levels during encoding (Fleisher et al., 2009).

Hypotheses and Specific Aims

The overarching aims of the current study were to better characterize the neurovascular underpinnings of MCI subtypes and provide information to anchor various cognitive changes in MCI to specific neural substrates. As described above, growing evidence suggests different neuropathologic etiologies, distinct regional distributions of neuropathologic substrates (Duara et al., 2013; Murray et al., 2011), or both, may underlie amnestic and non-amnestic MCI and such findings support a neurophysiologically-driven examination of distinctions between neuropsychologically-defined MCI subtypes. Three experiments were conducted to assess neurovascular function across MCI subtypes. Hypothesized results are described below and displayed in Figure 2.

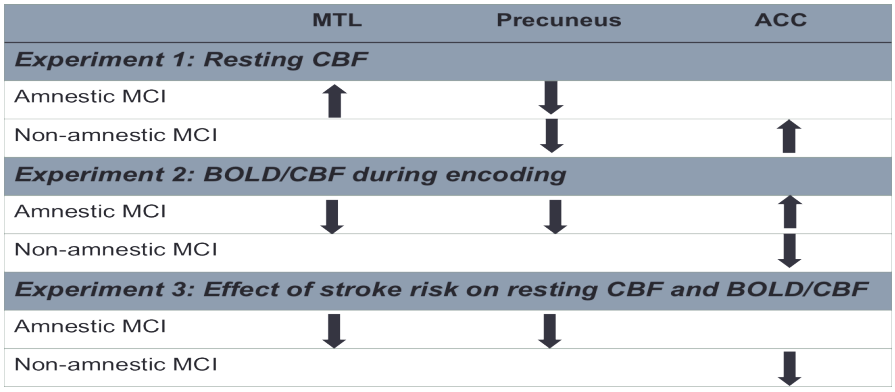
The first experiment examined CBF patterns during the resting-state in all groups. Based on previous literature, it was expected that older adults with MCI would demonstrate altered CBF patterns at rest compared to cognitively intact older adults. We hypothesized that individuals with MCI would exhibit globally reduced mean CBF but regionally-specific increases in perfusion reflecting compensatory mechanisms. Specifically, we expected the amnestic MCI group to demonstrate increased perfusion in the hippocampal region and the non-amnestic MCI group to demonstrate increased perfusion in the ACC.

The second experiment examined CBF and BOLD activation patterns during encoding to inform how altered patterns change during effortful cognitive tasks. It was

hypothesized that the amnestic MCI group would exhibit reduced hippocampal/PC activity and increased AC activity reflecting recruitment of frontal regions to compensate for reduced activity in medial temporal and posterior regions that support memory function. Conversely, it was hypothesized that the non-amnestic group would exhibit reduced AC activation reflecting diminished frontal task-related activity.

The third experiment investigated an interaction between group and stroke risk, as measured by the Framingham Stroke Risk Profile, on resting CBF and on CBF/BOLD responses during encoding. It was predicted that stroke risk would interact with both MCI subtypes in different ways. Specifically, we hypothesized that stroke risk would interact with non-amnestic MCI to reduce perfusion in anterior regions, whereas stroke risk would interact with amnestic MCI to reduce perfusion in medial temporal/posterior regions.

The Introduction section is currently being prepared for submission for publication of the material. Clark, Lindsay R.; Wierenga, Christina E.; Bangen, Katherine J.; Shin, David D.; Salmon, David P.; Jurick, S.M.; Ewald, I.; Liu, Thomas, T.; Bondi, Mark. W. The dissertation author was the primary investigator and author of this paper.



Note. Arrows refer to expected direction of CBF or BOLD activity compared to the cognitively normal group.

Figure 2. Hypotheses for the three experiments

Methods

Participants and Recruitment

A total of 55 older adult participants were enrolled into the study. Participants were recruited from Dr. Mark Bondi's ongoing longitudinal study (Cognitive Abilities of At-Risk Elderly for Dementia), the UCSD Alzheimer's Disease Research Center (ADRC), and community senior centers. Participants were screened prior to being enrolled in the study to ensure they met eligibility criteria. Exclusion criteria for the study included a current diagnosis of dementia, current or history of other major neurological disorders such as Parkinson's disease or stroke, history of a head injury involving a loss of consciousness, current or history of a serious mental illness or alcohol/substance abuse, major hearing or vision difficulties that could interfere with the functional MRI scan, and a pacemaker or other MRI contraindications. Participants were selected without regard to ethnicity or race. This study was reviewed and approved by the Institutional Review Board at the UCSD Human Research Protections Program. Written informed consent was obtained from all participants.

Diagnostic criteria. Individuals were classified as MCI or cognitively normal (CN) using comprehensive diagnostic criteria developed by Jak, Bondi, and colleagues (2009b) that required low performances (defined as greater than 1 standard deviation below normative means) on at least two measures within a cognitive domain, or at least one measure across three cognitive domains, for an individual to be classified as MCI. Additionally, it was required that performance-based measurement of instrumental activities of daily living and global cognition remained intact

(Independent Living Scales (ILS) T-scores ≥ 40; Loeb, 1996; Dementia Rating Scale (DRS) total raw scores ≥ 127; Mattis, 1988). MCI diagnoses were based on performance in five cognitive domains (attention, language, visuospatial function, episodic memory, and executive function), with each domain made up of at least three measures (see Table 3 for list of specific measures used in diagnoses). Two neuropsychologists made diagnoses of CN, aMCI, or naMCI independently. The neuropsychological assessments were administered as part of the 'parent' studies from which the participants were recruited. Additional data collected as part of the 'parent' studies included APOE genotype, depressive symptoms (Geriatric Depression Scale [GDS]; Yesavage et al., 1983), and family history of Alzheimer's disease.

Study sample. Five participants were excluded due to ineligibility or early withdrawal. Specifically, two MCI participants exhibited global cognitive impairment based on DRS total raw score less than 127 (specific scores were 123 and 115, respectively), one CN participant exhibited functional impairment on the performance-based IADL assessment (ILS T-score < 40), two MCI participants discontinued the MRI procedure early due to back pain or claustrophobia, and one MCI participant's functional MRI data was unable to be analyzed due to an error in data acquisition. Datasets from three additional female CN participants were removed from analyses to ensure that the three study groups were matched on gender. Final sample sizes consisted of a total of 46 participants included in functional MRI analyses and 47 participants included in resting CBF analyses. Of the total sample size, 20 were classified as cognitively normal, 14 were classified as aMCI, and 13 were classified as naMCI. Although the two MCI groups had some differences in single- vs. multiple-domain

subtype percentages, this comparison did not approach a statistically significant difference (aMCI = 5 single-domain, 9 multi-domain; naMCI = 8 single-domain, 5 multi-domain; χ^2 = 1.80, p = .18). A majority of the naMCI group exhibited impairments on measures of executive functioning (n = 5) or visuospatial functioning (n = 6); however, two participants exhibited primarily attention or language deficits.

Power analysis. Using an alpha of .05, the final sample size of 47 provided 80% power to detect a large effect size (f = .47) and 41% power to detect a medium effect size (f = .30) by comparing means using an ANOVA. Past studies of resting CBF or BOLD response to face-name encoding reported medium to large effect sizes (i.e., calculated Cohen's d from reported means/standard deviations = 0.3 to 2.0) for detecting differences. Thus, our sample size of approximately 50 participants was considered comparable to prior studies in its power to detect group differences. Moreover, improvements in CBF collection sequences (e.g., optimized pseudo-continuous arterial spin labeling over its pulsed ASL predecessor) as well as use of a blocked fMRI design were expected to improve upon signal-to-noise capabilities and thereby provide for improvements in detecting group differences beyond those observed in prior studies.

Materials and Procedure

Prior to the MRI scan, participants completed a stroke risk questionnaire and a brief computer practice task. Participants then completed an MRI scan that lasted approximately 1.5 hours and consisted of an anatomical scan of the brain (T1), a whole-brain resting ASL scan, calibration scans, and a combined ASL/BOLD functional scan during a face-name memory encoding task (Sperling et al., 2003).

Following the MRI procedures, participants completed a recognition task for the faces and names on a computer.

Face-Name Associative Encoding Paradigm. A practice session of the encoding task was conducted outside the magnet before the scan that involved 6 face-name pairs. Inside the MRI scanner, the encoding paradigm consisted of 60 different pairs of faces and names displayed over the course of four imaging runs in a blocked design (see Figure 3 for illustration of stimuli presentation). Faces were standardized in terms of age, gender, image size and minimization of uniquely identifying features unrelated to the face. The image was centered on a black background with the corresponding name positioned directly below the image and written in white type. Each run lasted approximately six minutes and consisted of three blocks of novel face-name stimuli and three blocks of repeated face-name stimuli. Within each run, repeated blocks were repeated one or two times during the run. No stimuli were repeated across runs. Each block consisted of five stimuli presented for 5600 ms each. Blocks were separated by a fixation cross that was presented on the screen for 28 seconds.

Stimuli were presented via a projector onto a screen that was viewed through a mirror mounted on the receiver head coil. Stimuli presentation was performed using ePrime software. Participants requiring vision corrections were fitted with plastic framed glasses with interchangeable lenses closely matching their prescription. Head movement in the receiver head coil was minimized by foam fittings. Participants were instructed to remember the face-name pairs and to make a subjective judgment about each pair to ensure adequate attention and promote associative encoding of the faces and names during stimuli presentation. Specifically, the question “Does this

name suit this face?" was presented at the top of the screen above each stimulus and participants were instructed to respond either "yes" or "no" using a button box.

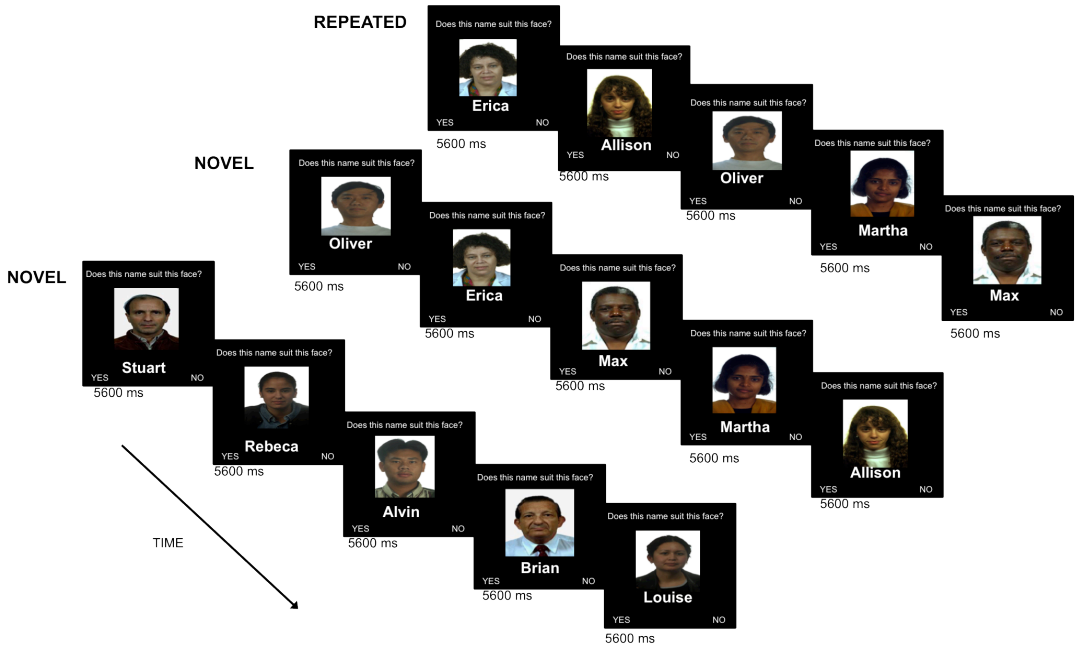


Figure 3. Face-name associative encoding task

Face-Name Recognition Task. Immediately following the MRI scan (approximately 30 minutes after completion of the encoding task), participants completed a computerized recognition task consisting of the previously viewed face-name pairs and never before seen face-name pairs to quantify encoding accuracy of face-name pairs. The recognition task consisted of a face and three choices for a response: correct name, incorrect name, and "neither of these." Half of the incorrect names were previously seen for other faces and half were completely new names. After responding, subjects were asked to report the confidence of their choice as "very confident", "not very confident", or "not at all confident."

Stroke Risk. Stroke risk was measured with the Framingham Stroke Risk Profile (FSRP; D'Agostino, Wolf, Belanger, & Kannel, 1994), which assesses age, systolic

blood pressure, diabetes, cigarette smoking, cardiovascular disease, atrial fibrillation, left ventricular hypertrophy, and the use of antihypertensive medication to determine the percentile risk for stroke within 10 years.

MRI Data Acquisition

Participants were scanned in a 3-Tesla GE MR750 Discovery scanner equipped with quantum gradients providing echo planar capability housed at the UCSD Center for Functional MRI. Both mid-sagittal and axial localizer slices were obtained to confirm the adequacy of head placement.

Structural MRI**.** A high resolution T1-weighted Fast Spoiled Gradient Recall (3D FSPGR) scan was acquired to provide anatomic reference (172 1 mm contiguous sagittal slices, FOV = 25 cm, TR = 8 ms, TE = 3.1 ms, flip angle = 12, T1 = 600, 256 x 192 matrix, Bandwidth = 31.25 kHZ, frequency direction = S-I, NEX =1, scan time = 8 min 27 sec).

Resting CBF. Whole-brain ASL data was acquired during a resting state using a multi-phase pseudo-continuous ASL (MPPCASL) sequence. Parameters included 20 5 mm axial slices, FOV = 24, post-saturation and inversion times of TI1 = 0 msec and TI2 = 3600 msec, TR= 4200 ms, TE = 3.3 ms, volumes = 64, scan time = 5 min 28 sec. Additionally, a scan with the inversion pulses turned off was acquired to obtain an estimate of the magnetization of cerebrospinal fluid (CSF). A minimum contrast scan was also acquired to adjust for coil inhomogeneities during the CBF quantification step. A field map was also acquired to correct for field inhomogeneities.

Simultaneous ASL/BOLD. Functional BOLD and ASL data were simultaneously acquired using an optimized pseudo-continuous ASL (OptPCASL) sequence (Shin,

Liu, Wong, Shankaranarayanan, & Jung, 2012). OptPCASL parameters included: TR/TE1/TE2 = 3500/2.8/30 ms, tag duration = 1500 ms, post labeling delay = 1500 ms, 104 volumes, scan time = 6 minutes, 4 seconds. Nine contiguous axial slices, each 6 mm thick, parallel to the hippocampus were prescribed. This functional scan volume provided coverage of the MTL as well as the anterior cingulate and precuneus (see Figure 4).

(4a) (4b)

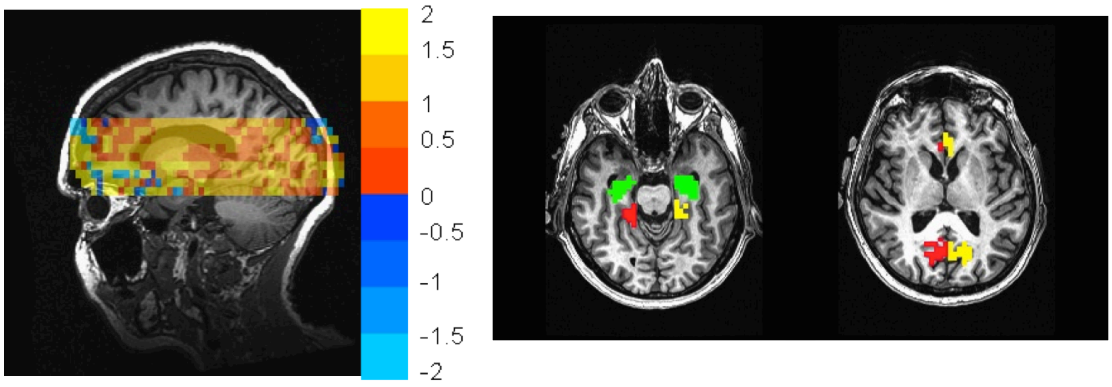


Figure 4. OptPCASL nine-slice brick placement (a). Regions of interest included bilateral hippocampus, parahippocampal gyrus, precuneus, and anterior cingulate cortex (b).

A series of calibration scans were conducted to calculate and correct for phase tracking errors that can significantly deteriorate the quality of perfusion signal in the pseudo-continuous ASL tagging scheme. First, a time-of-flight scan was acquired to define the tagging plane and to determine the spatial coordinates of the three feeding arteries needed for the vascular territory imaging (VTI) scan. Second, a vascular territory imaging (VTI) scan (Wong, 2007) was acquired to select vascular territories. Third, a multiphase PCASL technique was completed to estimate and compensate for the phase errors in each of the arteries (right/left carotid, right/left vertebral). Lastly, CSF, minimum contrast, and field map sequences were acquired for use in CBF quantification and to correct for field inhomogeneities.

Physiological Monitoring. During the four simultaneous ASL/BOLD runs, cardiac and respiratory activity was monitored using a pulse oximeter and respiratory belt, and the waveforms were recorded using the physiological monitoring program provided through the GE MR750 3T scanner. Physiological noise reduction is critical for obtaining reliable CBF measures in the medial temporal lobe.

MRI Pre-Processing and Individual Subject Analysis

Data processing was completed using Analysis of Functional NeuroImages (AFNI; afni.nimh.nih.gov; Cox, 1996), Freesurfer (surfer.nmr.mgh.harvard.edu), and in-house Matlab scripts.

Structural MRI. Using AFNI software, a three-dimensional brick was created from the structural scan slices. Regions of interest (ROIs) were created using Freesurfer, a freely available cortical and subcortical segmentation and parcellation software. The specific ROIs created for this study included the hippocampus, parahippocampal gyrus (PHG), precuneus, and anterior cingulate cortex (ACC) (see Figure 4b). For use in the resting CBF and functional CBF/BOLD analyses, the Freesurfer parcellations were aligned with the resting CBF data and with the simultaneous ASL/BOLD data. Additionally, ROIs were resampled to the resolution of the functional data.

Resting CBF. Processing of the resting CBF (MPPCASL) data was completed through a processing pipeline available via the Cerebral Blood Flow Biomedical Informatics Research Network (CBFBIRN; cbfbirn.ucsd.edu). Field map correction and motion correction (using the middle volume as reference) were completed. A mean ASL image was formed for each participant from the average difference of

control and tag images using surround subtraction (e.g., the difference between each control image and the average of the two surrounding tag images and vice versa). The mean ASL image was converted to absolute units of CBF (mL/(100g-min)) using information on the relationship between the intensities of CSF and Water (Chalela et al., 2000). The CBF data were corrected for partial volume effects using the following formula: $CBF_{corr} = CBF_{uncorr}/(GM + 0.4 * WM)$, which assumed that CSF has zero CBF and that CBF in GM is 2.5 times greater than in WM (Johnson et al., 2005). Information from the high-resolution structural image and the FSL Automated Segmentation Tool (FAST) was used to determine the tissue content of each perfusion voxel. The CBF data were skull-stripped using an automated program, spatially smoothed using a 4.0 mm full-width, half-maximum Gaussian filter, and thresholded to only include voxels with at least 90% probability of containing gray matter. Following the CBFBIRN pipeline procedure, the CBF data for each participant were further thresholded by removing outlier voxels that contained CBF values greater than at least three standard deviations from the mean of the total sample (removed voxels with CBF values > 165). Mean CBF values were then extracted from each ROI (hippocampus, PHG, precuneus, ACC) and from across the whole brain, and these values were used in between-group analyses.

Simultaneous ASL/BOLD. Data for each participant was entered into an automated pre-processing pipeline created using in-house Matlab scripts that completed the following steps: field map correction, exclusion of the first 4 images to ensure the MRI had reached a steady state, alignment of the anatomical scan to the functional scans, segmentation of gray, white, and csf data from the anatomical scan using FSL's FAST, skull-stripping, creation of motion regressors using AFNI's 3dVolReg

(registration within each functional run to the middle time point), physiological data correction to remove cardiac and respiratory confounds (Restom, Behzadi, & Liu, 2006), and CBF quantification using the CSF and miniature contrast calibration scans. Functional CBF time series were generated from the running subtraction of the control images (magnetization of arterial blood fully relaxed) and tag images (longitudinal magnetization of arterial blood is inverted or saturated) (Liu & Wong, 2005) and functional BOLD time series were computed from the running average (average of each image with the mean of its two nearest neighbors) of the second echo (see Figure 2).

Following the pre-processing procedure, individual subject analyses were completed within AFNI. The number of outlier volumes within each time series file for each run (BOLD, CBF) was calculated using AFNI's 3dToutcount program, and data spikes were removed from each time series using AFNI's 3dDespike program. Additionally, the CBF and BOLD times series were spatially smoothed using a 4.0 mm full-width, half-maximum Gaussian filter and normalized for extraction of percent signal change values. The four runs were then concatenated to form one times series per voxel for BOLD and one time series per voxel for CBF, and analyzed with a general linear model (GLM) framework using AFNI's 3dDeconvolve program. A multiple regression containing the four stimuli parameters (Novel, R1, R2, Fixation) and three motion correction parameters (Roll, Pitch, Yaw) was conducted on each individual subject. The following contrasts were calculated: Novel faces versus Repeated faces, Novel versus Fixation, and Repeated versus Fixation. This resulted in a bucket file for each participant that contained statistics of interest for each contrast. Mean percent change BOLD and percent change CBF values were then

extracted from each ROI using AFNI's 3dROIstats program. These values were included in between-group analyses.

Statistical Analyses

Between-group statistical analyses were conducted in SPSS Statistics version 21.

Demographic and clinical characteristics. One-way ANOVA (continuous variables) or chi-square (dichotomous variables) analyses compared age groups on demographic and clinical variables.

Cognitive performance. One-way ANOVAs were conducted to compare the three groups on neuropsychological test performance and face-name recognition performance. All analyses were conducted on standardized scores adjusted for demographic characteristics. Post-hoc Tukey HSD tests were conducted for each significant ANOVA to examine pairwise differences between the three groups.

Structural volumetrics. Prior to group analyses, the tissue compartments (whole-brain volume, whole-brain gray matter) and ROIs (hippocampus, PHG, precuneus, ACC) were normalized using total intracranial volume (TIV) to correct for inter-subject differences in brain size. One-way between group ANOVAs compared the three groups on the normalized volumes.

Resting CBF and simultaneous ASL/BOLD. One-way between-group ANOVAs were conducted to compare the three groups (CN, aMCI, naMCI) on mean resting CBF, mean percent change BOLD, and mean percent change CBF within each ROI.

Additionally, to estimate absolute change in CBF during encoding from the resting state, the percent change in CBF was multiplied by the mean resting perfusion rate in each ROI. This provided an estimate of *absolute change in CBF* or flow change from baseline in response to encoding in physiologic units of CBF (ml/(100 mg min); Fleischer et al., 2009). Post-hoc Tukey HSD tests were conducted for each significant ANOVA to examine pairwise differences between the three groups. Pearson bivariate correlations were conducted to examine the relationships between percent change BOLD and percent change CBF within each ROI, as well as between resting CBF, percent change BOLD/CBF, and performance on the face-name recognition task and memory measures.

Stroke risk. Hierarchical multiple regression was used to examine the hypothesis that stroke risk would interact with group to influence resting CBF, and percent change CBF/BOLD during encoding. Specifically, the following predictors were included in the model: group (intact, aMCI, naMCI), stroke risk percentile, and an interaction term of group x stroke risk.

The Methods section is currently being prepared for submission for publication of the material. Clark, Lindsay R.; Wierenga, Christina E.; Bangen, Katherine J.; Shin, David D.; Salmon, David P.; Jurick, S.M.; Ewald, I.; Liu, Thomas, T.; Bondi, Mark. W. The dissertation author was the primary investigator and author of this paper.

Results

Demographic and Clinical Characteristics

Demographic and clinical characteristics of the sample are displayed in Table 1. The CN, aMCI, and naMCI groups were similar in terms of age (p = .90; range = 64-94 years), years of education (p = .24; range = 12-20 years), gender (p = .13), and handedness (p = .56). The majority of the study participants were of Caucasian ethnicity (44 Caucasian, 3 Hispanic). The amnestic MCI group had a greater distribution of APOE ε4 positive carriers than the other two groups (p < .01). There were no significant group differences in premorbid functioning estimates (p = .13), depressive symptoms (p = .28), overall stroke risk percentile (p = .14), family history of dementia (p = .14), or everyday functioning performance as measured by the Independent Living Scales (p > .27). Four participants were currently prescribed a cognitive-enhancing medication (donepezil; 3aMCI, 1naMCI).

Table 1. Demographic and clinical characteristics

	CN	aMCI	naMCI	*F or* χ^2	*p*
N	20	14	13		
Age (years)	76.0 (7.6)	77.3 (8.6)	76.4 (8.9)	.11	.90
Gender (Male / Female)	6/14	9/5	5/8	4.08	.13
Education (years)	16.4 (2.3)	17.1 (2.0)	15.8 (1.7)	1.49	.24
Handedness (R / L)	19/1	12/2	11/2	1.17	.56
APOE (non-ε4 / ε4)	15/5	4/10	11/2	11.05	< .01
GDS	3.1 (3.4)	5.1 (6.5)	6.3 (7.5)	1.30	.28
Single vs. Multi-Domain	N/A	5/9	8/5	1.80	.18
FSRP Stroke Risk (%)	10.9 (6.5)	17.6 (11.2)	15.7 (12.9)	2.02	.14
Family History of Dementia (Y / N)	4/16	7/7	3/10	3.93	.14
Premorbid Estimate (ANART VIQ)	121.5 (5.0)	118.1 (6.0)	118.1 (5.9)	2.12	.13
ILS Money T-Score	54.8 (4.8)	52.8 (8.5)	51.9 (8.9)	0.66	.52
ILS Health/Safety T-Score	54.4 (3.5)	56.3 (4.0)	53.9 (4.8)	1.35	.27

Note. GDS = Geriatric Depression Scale, FSRP = Framingham Stroke Risk Profile, ANART = American National Reading Test; ILS = Independent Living Scales

Neuropsychological and Behavioral Performance

Table 2 displays neuropsychological performances across the three groups. A Bonferonni correction was applied to correct for multiple comparisons in assessing group differences across the various measures (alpha = .05/25 variables = .002). Significant group differences were exhibited on measures of verbal memory and semantic knowledge, including California Verbal Learning Test – 2nd Edition (CVLT-II) trials 1-5 total ($p < .001$), CVLT-II long-delay free recall ($p < .001$), Wechsler Memory Scale-Revised (WMS-R) logical memory delayed recall ($p < .001$), and Boston Naming Test total correct ($p < .001$).

The three groups also differed on total percent correct on the face-name recognition task ($F = 3.88$; $p < .05$). Post-hoc analyses revealed that the aMCI group performed significantly worse than the CN group ($p < .05$), whereas performances did not differ between the CN and naMCI group ($p = .29$) or between the two MCI groups ($p = .54$). The three groups did not differ in reaction time ($p = .71$). Additionally, no between-group differences were observed in frequency of confidence ratings (mean number of “very confident” responses: $p = .62$; mean number of “somewhat confident” responses: $p = .40$; mean number of “not at all confident” responses: $p = .81$).

Table 2. Neuropsychological performance

	CN	aMCI	naMCI	*F*	*p*
Global Cognition					
DRS Total raw score	141 (2.1)	137.1 (5.0)	138.6 (4.4)	4.65[a]	<.05
Memory					
CVLT-II Immediate T	62.9 (10.6)	43.2 (7.1)	58.7 (9.7)	18.76[a,c]	< .001
CVLT-II Long-Delay Free z	1.1 (0.8)	-1.6 (0.8)	0.7 (0.8)	32.25[a,c]	< .001
LM Immediate MOANS	14.5 (2.4)	11.0 (4.2)	14.1 (2.6)	6.98[a,c]	<.01
LM Delayed MOANS	16.0 (2.0)	9.6 (3.8)	13.9 (2.1)	23.27[a,c]	< .001
VR Immediate MOANS	11.9 (3.1)	9.8 (2.4)	11.1 (2.4)	2.48	.10
VR Delayed MOANS	11.6 (2.8)	8.5 (3.9)	11.3 (2.8)	4.48[a]	< .05
Attention					
DRS Attention T	52.0 (9.0)	52.6 (6.0)	48.7 (8.5)	0.92	.41
WAIS-R Digit Span MOANS	12.8 (2.8)	11.1 (2.1)	10.5 (3.1)	3.13[b]	.05
TMT Part A MOANS	11.7 (2.3)	11.6 (3.3)	10.9 (3.8)	0.29	.75
Language					
BNT T	60.1 (6.1)	45.5 (13.7)	54.4 (6.8)	10.42[a,c]	<.001
Letter Fluency T	55.0 (9.2)	50.4 (7.2)	47.0 (11.4)	2.90[b]	.07
Animal Fluency T	52.6 (8.9)	43.2 (11.1)	49.1 (11.3)	3.33[a]	<.05
Visuospatial Functioning					
WISC-R Block Design T	51.7 (9.4)	48.0 (9.8)	44.2 (11.4)	2.19	.12
D-KEFS Visual Scanning SS	10.4 (2.7)	10.9 (2.1)	9.7 (3.0)	0.68	.51
D-KEFS Design Fluency SS	11.8 (2.9)	11.9 (3.1)	11.9 (2.3)	.01	.99
DRS Construction T	53.0 (0.0)	46.0 (12.4)	47.8 (14.7)	2.17	.13
Clock Drawing raw score	2.8 (0.4)	2.6 (0.6)	2.2 (0.8)	2.68	.08
Executive Functioning					
WCST Categories T	53.4 (9.0)	49.1 (12.4)	44.3 (14.1)	2.36	.11
WCST Perseverative T	48.5 (4.7)	45.6 (9.1)	43.5 (10.2)	1.60	.22
TMT Part B MOANS	11.9 (2.6)	10.1 (3.9)	10.5 (3.0)	1.45	.25
D-KEFS CWIT Inhibition SS	12.7 (2.5)	11.4 (2.3)	11.2 (2.2)	2.02	.15
D-KEFS CWIT Inhibition/Switch SS	12.4 (2.5)	10.8 (4.0)	10.5 (3.6)	1.62	.21
D-KEFS Verbal Fluency Switch SS	12.5 (2.3)	10.0 (2.0)	10.1 (3.9)	4.37[a,b]	< .05
D-KEFS Design Fluency Switch SS	11.7 (3.0	11.8 (2.6)	10.5 (3.0)	0.79	.46

[a] Difference between aMCI and CN groups, [b] Difference between naMCI and CN groups, [c] Difference between aMCI and naMCI groups; DRS = Dementia Rating Scale, CVLT-II = California Verbal Learning Test – 2nd Edition, LM = Wechsler Memory Scale – Revised Logical Memory subtest, VR = Wechsler Memory Scale – Revised Visual Reproduction subtest, WAIS-R = Wechsler Adult Intelligence Scale – Revised, TMT = Trailmaking Test, BNT = Boston Naming Test, WISC-R = Wechsler Intelligence Scale for Children – Revised, D-KEFS = Delis-Kaplan Executive Function System, WCST = Wisconsin Card Sorting Test – 48 Card Modified version, CWIT = Color-Word Interference Test, MOANS = Mayo's Older Americans Normative Study, T = T Score, SS = Scaled Score

Structural volumes

The three groups did not differ on mean whole-brain volume or whole-brain gray matter (*ps* > .25). Significant group differences were observed in the hippocampus ($p < .01$), PHG ($p < .05$), and precuneus ($p < .05$). Post-hoc Tukey HSD tests revealed that the aMCI group had significantly lower hippocampal volumes compared to both the CN ($p < .01$) and naMCI ($p < .05$) groups. The aMCI group also exhibited significantly smaller PHG and precuneus compared with the CN group ($p < .05$), but did not significantly differ from the naMCI group.

Resting CBF

Resting CBF data across the whole-brain and within each of the ROIs are displayed in Table 3. The three groups exhibited similar levels of resting CBF when averaged across the whole brain ($F(2,43) = 1.58$, $p = .22$). However, there was a nearly significant difference between groups in bilateral hippocampal CBF ($F(2,43) = 3.03$, $p = .06$). Examination of the left and right hippocampal ROIs separately revealed a significant difference between groups in right hippocampal CBF ($p < .05$), but no differences in left hippocampal CBF ($p = .22$). Post-hoc analyses revealed that the aMCI group had significantly lower right hippocampal CBF compared to the CN group ($p < .05$), but did not significantly differ from the naMCI group. Additionally, there were no significant differences between the naMCI and CN groups in mean CBF in this region.

No significant group differences in resting CBF were observed in bilateral PHG ($p = .09$), precuneus ($p = .18$), or ACC ($p = .56$) regions. However, examination of the left and right regions separately revealed significant differences between

groups in left PHG CBF ($p < .01$) and nearly significant differences in left precuneus CBF ($p = .07$). Post-hoc analyses revealed significantly lower left PHG CBF in the aMCI group compared with both the CN ($p < .05$) and naMCI ($p < .05$) groups. Additionally, the aMCI group had nearly significantly lower resting CBF in the left precuneus compared with the naMCI group ($p = .06$), but there were no significant differences between the aMCI and CN groups in this region ($p = .28$). Figure 5 displays mean resting CBF across the three groups within the hippocampal, PHG, and precuneus regions.

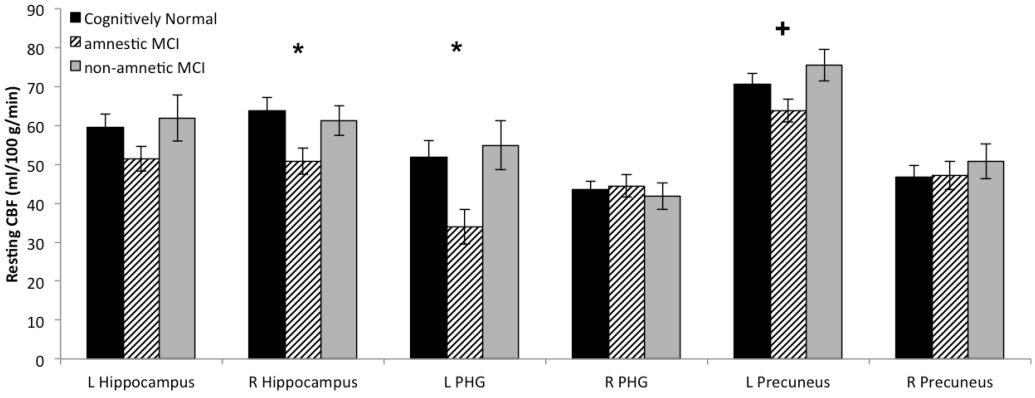
Table 3. Resting cerebral blood flow and structural volumes

	CN (n = 20)	**aMCI** (n = 14)	**naMCI** (n = 12)	***F***	***p***
Whole-Brain Resting CBF	60.7 (8.0)	57.1 (5.5)	61.8 (8.0)	1.58	.22
Mean Resting CBF in ROIs					
Bilateral Hippocampus	61.7 (14.2)	51.2 (9.4)	61.6 (15.3)	3.03	.06
Left Hippocampus	59.5 (15.3)	51.5 (12.0)	61.9 (20.4)	1.59	.22
Right Hippocampus	63.8 (15.1)	50.8 (12.5)	61.3 (13.3)	3.77	< .05
Bilateral PHG	47.7 (11.2)	39.2 (10.5)	48.4 (15.2)	2.53	.09
Left PHG	51.8 (19.2)	34.0 (16.7)	54.9 (21.7)	4.89	.01
Right PHG	43.6 (9.2)	44.5 (10.9)	41.8 (11.6)	0.22	.81
Bilateral Precuneus	58.7 (9.8)	55.5 (9.1)	63.2 (12.8)	1.76	.18
Left Precuneus	70.6 (12.6)	63.8 (10.8)	75.5 (14.0)	2.90	.07
Right Precuneus	46.7 (13.7)	47.1 (13.7)	50.8 (15.5)	0.35	.71
Bilateral Anterior Cingulate	47.0 (9.5)	49.9 (15.8)	51.5 (14.3)	0.49	.62
Left Anterior Cingulate	52.4 (12.3)	49.8 (11.6)	54.3 (11.8)	0.59	.56
Right Anterior Cingulate	41.7 (12.4)	50.1 (22.7)	48.1 (24.3)	0.88	.42
Structural Volumes					
Whole brain (% of TIV)	0.29 (.02)	0.28 (.02)	0.29 (.02)	1.45	.25
Whole brain GM (% of TIV)	0.40 (.03)	0.39 (.03)	0.40 (.03)	1.03	.37
Hippocampus (% of TIV)*	.46 (.06)	.38 (.08)	.45 (.06)	6.07	< .01
PHG (% of TIV)*	.09 (.01)	.08 (.01)	.08 (.01)	3.95	< .05
Precuneus (% of TIV)*	.49 (.05)	.45 (.05)	.48 (.04)	3.33	< .05
ACC (% of TIV)*	.10 (.01)	.10 (.02)	.10 (.02)	0.25	.78

Note. TIV = Total Intracranial Volume; *Values multiplied by 100; CBF = cerebral blood flow; PHG = parahippocampal gyrus, ACC = anterior cingulate cortex

To examine the impact of group differences in structural volume on significant resting CBF findings, an analysis of covariance (ANCOVA) was conducted that

included the structural volume as a covariate in the analysis of group differences in regional CBF. An ANCOVA that incorporated the right hippocampal volume as a covariate revealed that group differences in resting CBF in this region no longer reached significance (*F(2,42)* = 2.75, *p* = .08). A second ANCOVA demonstrated that group differences in left PHG CBF remained significant after inclusion of left PHG volume into the model as a covariate (*F(2,24)* = 4.72, *p* = .01). Lastly, group differences in left precuneus CBF remained as a non-significant trend after inclusion of the left precuneus volume as a covariate (*F(2,42)* = 2.84, *p* = .07).

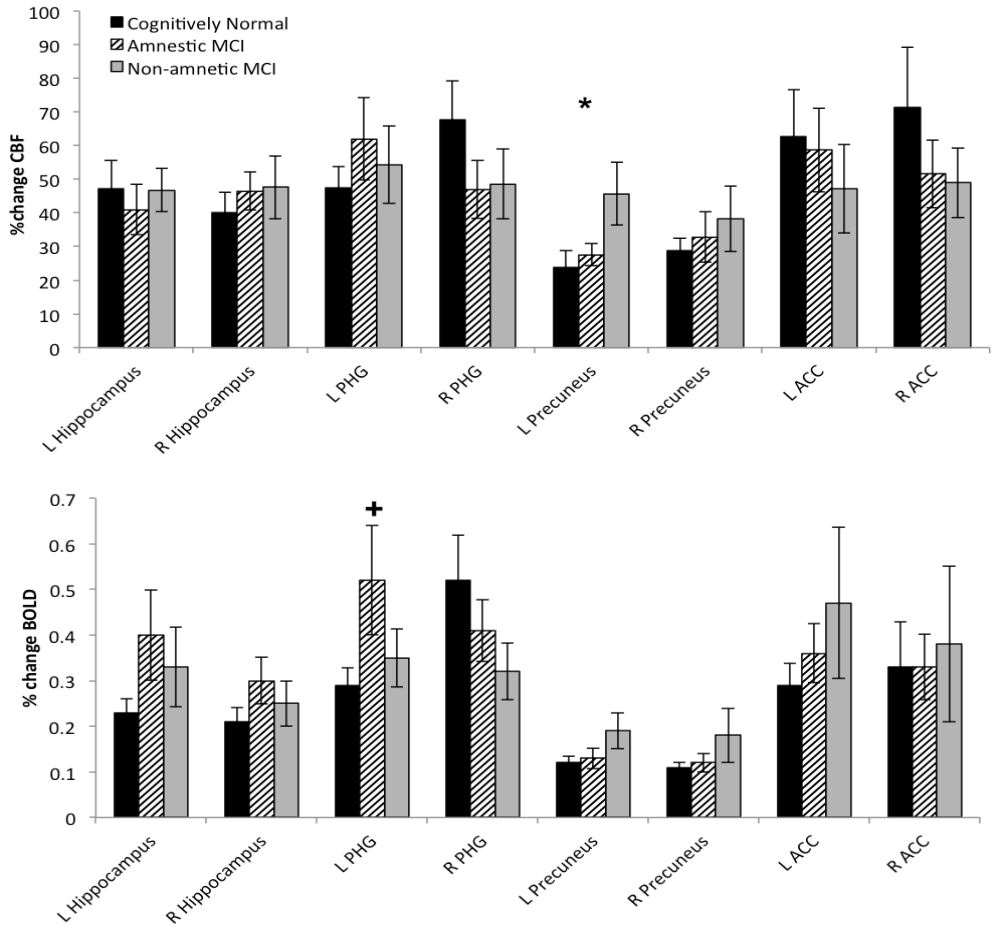


Note. * denotes significance at *p* < .05, + denotes trend (*p* = .07)
Figure 5. Resting cerebral blood flow in each group

BOLD and CBF During Face-Name Encoding

Percent change in BOLD and CBF signal was compared across groups for the contrasts of interest (Novel versus Repeated, Novel versus Fixation, Repeated versus Fixation) averaged across each ROI. One CN subject was removed from BOLD analyses due to significantly outlying percent change values (e.g., > 4). There were no significant differences between groups for the Novel versus Fixation or Repeated versus Fixation conditions in percent change BOLD or CBF. However, for the primary contrast of interest (Novel versus Repeated), there was a significant

difference between groups in percent change CBF in the precuneus (left side; $F(2,43) = 3.54$, $p < .05$), and a nearly significant difference in percent change BOLD in the parahippocampal gyrus (left side; $F(2,41) = 2.72$, $p = .08$). Post-hoc analyses revealed that the naMCI group exhibited significantly greater percent change CBF in the precuneus for Novel versus Repeated stimuli than the CN group ($p < .05$), but did not differ from the aMCI group. Additionally, post-hoc analyses revealed that the aMCI group exhibited nearly significantly greater percent change BOLD in the left PHG compared to the CN group ($p = .07$), but did not differ from the naMCI group. Additionally, there was a significant difference between groups in absolute CBF change in the left precuneus ($F(2,42) = 3.60$, $p < .05$), in which the naMCI group exhibited significantly greater absolute CBF change relative to the CN group. Figure 6 displays mean percent change CBF and percent change BOLD for each group within each ROI.



Note. * denotes significance at the $p < .05$ level, + denotes trend ($p = .08$)
Figure 6. Percent change CBF and BOLD during face-name associative encoding in each group

Follow-up ANCOVAs incorporating structural metrics for the corresponding region of interest indicated that group differences in percent change remained significant in the left precuneus ($F(2,42) = 3.50$, $p < .05$) and increased significance in the left PHG ($F(2,41) = 3.33$, $p < .05$). Additionally, a significant positive correlation was observed for the aMCI group only between percent signal change BOLD in bilateral PHG and total percent correct on the face-name recognition task ($r = .66$, $p = .01$).

Pearson bivariate correlations were conducted to examine the relationship between percent change BOLD and percent change CBF within each ROI for the Novel versus Repeated contrast. Collapsed across all participants, significant positive correlations were observed between BOLD/CBF in the hippocampus (r = .48, p < .001) and the precuneus (r = .69, p < .001). Examination of the relationships within each group revealed a significant positive correlation between BOLD/CBF in the PHG (r = .49, p < .05) within the CN group, significant positive correlations between BOLD/CBF in the hippocampus (r = .58, p < .05) and precuneus (r = .59, p < .05) within the aMCI group, and positive correlations in the hippocampus (r = .80, p = .001), precuneus (r = .74, p < .01), and ACC (r = .55, p = .06) in the naMCI group.

Stroke Risk and Association with CBF and BOLD

The three groups exhibited similar estimates of stroke risk (FSRP; p = .14). Examination of the individual variables that make up the stroke risk percentile indicated that the three groups exhibited no significant differences in systolic blood pressure ($F(2,44)$ = 0.50, p = .61), diastolic blood pressure ($F(2,44)$ = 1.06, p = .35), presence or absence of diabetes (X^2 = 0.25, p = .88), presence or absence of cigarette smoking (X^2 = 0.57, p = .97), presence or absence of cardiovascular disease (X^2 = 1.07, p = .59), and history of left ventricular hypertrophy (X^2 = 1.38, p = .50). The aMCI group was comprised of a greater number of individuals with a history of atrial fibrillation than the other two groups (X^2 = 7.24, p < .05). There was no difference between groups on history of TIA or stroke (X^2 = 2.11, p = .35) or use of antihypertensive medications (X^2 = 1.90, p = .39).

There were no significant interaction effects between group and stroke risk on resting CBF (all *ps* > .19) within the ROIs. Similarly, there were no significant interaction effects between group and stroke risk on percent change for the Novel versus Repeated contrast for either CBF (all *ps* > .23) or BOLD (all *ps* > .54) within any of the ROIs. There were also no main effects of stroke risk on resting CBF or percent change CBF or BOLD.

Relationship between CBF, BOLD, and neuropsychological performance

Across the total sample, there was a trend towards a significant relationship between bilateral hippocampal and PHG resting CBF and immediate recall (r = .27, p = .06) and delayed recall (r = .27, p = .06) of a word list (CVLT-II Trials 1-5 T-Score, CVLT-II Long-Delay Free Recall z-score) (see Figure 7). There were no relationships between these regions and the other two memory measures (WMS-R Logical Memory and Visual Reproduction Delayed Recall), or between the CVLT-II and the other ROIs.

There were no relationships between percent change CBF (Novel vs Repeated) in the four ROIs and the four neuropsychological memory measures. However, if examined separately across diagnostic groups, there was a significant positive correlation between hippocampal percent change CBF during encoding and CVLT-II Long Delay Free Recall in the aMCI group (r = .56, p < .05) and in the naMCI group (r = .58, p < .05), but not in the CN group (r = -.02, p = .95) (see Figure 7). There were no relationships between percent change BOLD during encoding collapsed across the sample. However, when examined separately there was a positive correlation between BOLD percent change in the ACC and delayed recall for

visual material (WMS-R Visual Reproduction; $r = .56$, $p < .01$) in the CN group only, but not in the MCI groups.

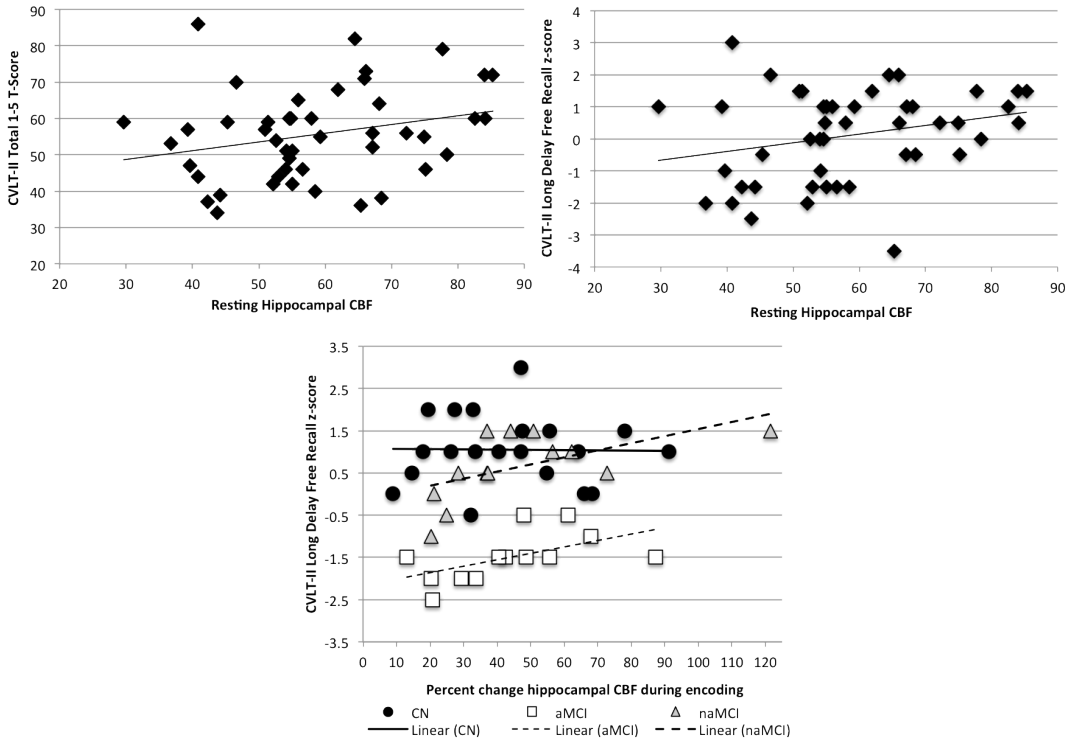


Figure 7. Relationship between resting CBF and verbal memory across entire sample (Top) and relationship between CBF during encoding and memory within each group (Bottom)

The Results section is currently being prepared for submission for publication of the material. Clark, Lindsay R.; Wierenga, Christina E.; Bangen, Katherine J.; Shin, David D.; Salmon, David P.; Jurick, S.M.; Ewald, I.; Liu, Thomas, T.; Bondi, Mark. W. The dissertation author was the primary investigator and author of this paper.

Discussion

The overarching aim of this study was to improve characterization of neurovascular activity associated with particular cognitive phenotypes within a sample of older adults. Specifically, we examined differences in cerebrovascular function at rest and during memory encoding in individuals who were classified as cognitively normal, amnestic MCI, or non-amnestic MCI.

Consideration of potential variations in baseline CBF in the interpretation of neural activation is particularly important in clinical populations of older adults who often exhibit cerebrovascular alterations that can influence neurovascular functioning. Results demonstrated that between-group differences were present in CBF at rest. Specifically, the aMCI group exhibited decreased resting CBF in the right hippocampus compared to the CN group, and decreased resting CBF in the left PHG and left precuneus relative to the naMCI group. Importantly, the aMCI group also demonstrated reduced hippocampal volume compared to both the CN and naMCI groups, and reduced PHG, and precuneus volumes compared to the CN group. When structural volume was included in the analyses, only the reduction in resting PHG CBF remained significant whereas differences in hippocampal and precuneus CBF neared significance ($p \leq .08$).

Previous studies have similarly reported lower resting CBF in MCI compared to cognitively intact older adults in precuneus and cuneus, posterior cingulate, inferior parietal lobe, and medial temporal lobe regions (Alexopoulos et al., 2012; Bangen et al., 2012; Chao et al., 2009; Dai et al., 2009; Johnson et al., 2005; Xu et al., 2007). Reduced resting CBF in the precuneus and posterior cingulate is consistently

reported in individuals with AD (Alsop et al., 2010), and has been shown to be predictive of progression to dementia in individuals with MCI at follow-up (Chao et al., 2010). Our aMCI group exhibited a pattern similar to previous findings of resting CBF in AD, supporting reports that this subgroup is most likely to progress to a diagnosis of Alzheimer's disease. Our results differ from one previous study that reported reduced resting CBF in naMCI in precuneus and medial frontal regions (Chao et al., 2009), perhaps due to differences in MCI diagnostic scheme, as their diagnosis of naMCI was defined based on at least one performance below the 10th percentile (e.g., 1.28 standard deviations) within the executive function domain, whereas our definition required at least two performances below the 16th percentile within the domains of executive function, visuospatial functioning, attention, or language. Several hypotheses have been proposed to underlie resting hypoperfusion in individuals at risk for AD. These include cerebrovascular alterations such as arteriolosclerosis or capillary dysfunction that contribute to neurovascular dysfunction and development of AD pathology (Ostergaard et al., 2013). Additionally, reduced CBF at rest in the aMCI group may reflect underlying AD pathology, such as increased amyloidosis, that can disrupt perfusion. Given that the groups did not differ on stroke risk profiles, reduced medial temporal CBF in the aMCI group may be more reflective of underlying AD pathology rather than cerebrovascular dysfunction.

On a face-name associative encoding paradigm, individuals in the aMCI group exhibited greater percent change BOLD during encoding of novel face-name pairs compared to repeated face-name pairs in the parahippocampal gyrus compared to the CN group. This finding replicates previous studies demonstrating increased MTL activation for face-name encoding in MCI (Dickerson et al., 2005), particularly for

items that were subsequently recognized (Kircher et al., 2007; Trivedi et al., 2008). Notably, these previous studies only included individuals with aMCI. Increased BOLD activation within MTL regions has been proposed to reflect a compensatory process of recruitment of additional neural resources to compensate for the accumulation of AD neuropathology in memory circuits. Although the aMCI group performed less accurately on a recognition task for the face-name pairs than the other two groups, there was a significant positive relationship between BOLD activation in the PHG and recognition performance within this group only, suggesting that the increased activation during encoding benefited their ability to recall the face-name association—despite their decreased recognition accuracy. However, the aMCI group also exhibited reduced resting-state CBF, and did not exhibit any change in CBF during encoding. Due to the lower baseline CBF state, it is plausible to speculate that decreased $CMRO_2$ (e.g., “decreased neural activity”) in the context of constant CBF during encoding could also result in an increased BOLD response. However, this speculation assumes normal coupling of CBF and $CMRO_2$, which may not be an accurate assumption in older adults (Hutchison et al., 2013; Restom et al., 2007).

In contrast, the naMCI group did not significantly differ from the CN group in percent change BOLD, but did exhibit significantly greater percent change CBF in the precuneus during face-name associative encoding. Interestingly, some previous studies of individuals with MCI and AD found greater BOLD activation compared to cognitively intact older adults during encoding in posteromedial regions, including in the precuneus and posterior cingulate (Petrella et al., 2007a; Sperling et al., 2001). Additionally, loss of expected parietal deactivation has been shown to predict conversion to AD (Petrella, Prince, Wang, Hellegers, & Doraiswamy, 2007b).

Although reduced resting CBF in the precuneus is one of the most consistent findings in AD and MCI, this is the first study to our knowledge to examine CBF using arterial spin labeling during encoding within this region in this population. In addition to demonstrating greater percent change CBF during encoding, the naMCI group also exhibited significantly higher absolute CBF change (e.g., accounting for their resting CBF level) during encoding, suggesting that this finding cannot be completely explained by pre-existing elevations in resting CBF in this group.

The distinct pattern of greater BOLD activation in the MTL region in aMCI and greater CBF activation in the posteromedial region in naMCI during encoding suggests unique disruptions of memory circuits in these two cognitive phenotypes. Growing evidence indicates that a widespread neural network interconnected with MTL structures is critical for successful memory encoding and retrieval. As noted earlier, activation of MTL regions with simultaneous deactivation of posteromedial regions during encoding tends to be associated with improved memory for the material in healthy populations (Celone et al., 2006; Pihlajamaki, DePeau, Blacker, & Sperling, 2008). The MTL and posteromedial regions, together with medial prefrontal regions, comprise the default mode network, important for its typical activation during rest and deactivation during cognitively-demanding tasks (Buckner et al., 2008). Although the default mode network has been almost exclusively examined via the BOLD signal, there is some evidence suggesting that functional connectivity maps measured with CBF exhibit similar spatial distribution patterns to those observed in BOLD (Vivani, Messina, & Walter, 2011). Within this context, our findings suggest that distinct alterations within the default mode network during encoding may occur in older adults with primary memory versus non-memory impairments. Although the

naMCI group exhibited similar levels of CBF to the CN group at rest, this group exhibited reduced deactivation of CBF in the precuneus during encoding, suggesting that modulation of posteromedial CBF during encoding is disrupted in naMCI. Increased percent change CBF in this region during encoding was not associated with recognition performance for the face-name pairs, suggesting that reduced deactivation in this region did not hamper encoding of the material. The lack of an increased BOLD response in this group may suggest that the percent change CBF was accompanied by a comparable increase in $CMRO_2$; however, this speculation assumes normal neurovascular coupling, which was not directly measured in this study.

Moreover, relationships between CBF at rest and during encoding in MTL regions and performance on neuropsychological memory measures were observed. Specifically, greater resting CBF in the hippocampus and PHG was associated with better immediate and delayed recall for a word list across the total sample. Furthermore, within the MCI groups only, greater hippocampal percent change CBF during encoding was associated with better performance on delayed recall of a word-list. The latter finding suggests that exhibiting greater percent change in hippocampal CBF from baseline provides greater resources to encode material for later recall, regardless of specific MCI group.

Several factors have been proposed to interact to modify CBF function in individuals at risk for AD. Vascular changes that become more prevalent during the aging process, such as arterial stiffness, endothelial dysfunction, and blood-brain barrier disruption, may impair intracellular protective mechanisms important to neuronal survival and growth. Additionally, vascular risk factors, such as

hypertension, diabetes, and cardiovascular disease promote degeneration and are associated with increased risk for AD. In conjunction with accumulation of amyloid-beta, these vascular risk factors may contribute to disrupted CBF, cerebral autoregulatory dysfunction, and neurovascular de-coupling (Akinyemi, Mukaetova-Ladinska, Attems, Ihara, Kalaria, 2013). Although previous studies have reported that greater stroke risk is associated with a higher prevalence of AD, the two MCI groups in the current study did not differ from one another or from the CN group on overall stroke risk, or in the prevalence of individual vascular risk factors, such as high blood pressure, diabetes, or cardiovascular disease.

Moreover, stroke risk was not associated with resting CBF or with CBF or BOLD activity during memory encoding in any of the groups. Previous studies have reported reduced perfusion at rest in individuals with hypertension (Dai et al., 2008; Waldstein et al., 2010) and other vascular risk factors (Jennings et al., 2013). The limited range of vascular risk factors in our sample may have restricted our ability to examine the contribution of these factors on neurovascular function. Additionally, this study only examined regions of interest proposed to be involved in memory encoding. It is possible that relationships between stroke risk and CBF occur in regions that were beyond the scope of this study, such as subcortical regions known to exhibit greater levels of small vessel disease. Future voxelwise examinations between stroke risk and resting CBF across the whole-brain, or within additional regions of interest, will be important to further clarify these results.

Additionally, the three groups exhibited varying relationships between percent change CBF and percent change BOLD during encoding. All groups exhibited significant positive correlations between CBF and BOLD within the precuneus.

However, only the MCI groups demonstrated significantly positive associations between percent change CBF and BOLD in the hippocampus, and the naMCI group also demonstrated a nearly significant positive relationship between CBF and BOLD in the ACC. As described earlier, the BOLD signal is dependent on CBF, but also on $CMRO_2$ and CBV. These findings suggest that the hippocampal BOLD response to encoding in MCI may rely more strongly on changes in CBF, whereas other components of the BOLD signal may play a greater role in the CN group. As noted earlier, greater hippocampal CBF activity during encoding was associated with better delayed recall performance within the MCI groups only, suggesting that perhaps these groups require greater synchrony between CBF and BOLD mechanisms to support memory functions. Future studies incorporating measures of $CMRO_2$ as well as CBF will help to further clarify the varying relationships of the contributing factors to the BOLD signal in MCI.

As described earlier, discrepant fMRI findings in MCI (e.g., increased and decreased activation during encoding) may be partly due to the lack of a robust diagnostic scheme for MCI used across research studies. This study provides additional validation of the use of a comprehensive neuropsychological characterization in the diagnosis of MCI. A comprehensive neuropsychological diagnostic scheme of MCI has been shown in recent studies to be a more stable diagnostic method and less prone to false positive errors (Saxton et al. 2009; Clark et al. 2013; Edmonds et al. 2014), more strongly associated with biomarkers of AD, and more reliably predictive of progression to AD (Bondi et al. 2014). Earlier studies that focused on individuals with aMCI who were often diagnosed based on a single low memory performance may have included more false positive MCI participants (e.g.,

individuals who did not progress to AD) and did not provide information about naMCI participants also likely to progress to AD or non-AD dementia syndromes. This suggests that the individuals enrolled in the current study are more likely to progress to a dementia diagnosis than prior studies that have relied on conventional criteria for MCI diagnosis. The current findings indicate that use of a comprehensive neuropsychological definition resulted in aMCI and naMCI subgroups with distinct profiles of structural volumes, resting CBF, and BOLD/CBF activation of memory circuits during encoding, which may reflect different neuropathologic etiologies or distinct regional distribution of AD pathology. For example, previous neuropathological studies have reported that atypical subtypes of AD (e.g., hippocampal-sparing, limbic-predominant) comprise approximately 25% of AD patients (Murray et al., 2011), and similar patterns of distinct cortical atrophy on structural MRI within AD have been reported (Duara et al., 2013). Further longitudinal follow-up will be essential to confirm distinct progression of disease pathology in the individuals that comprise our aMCI and naMCI groups.

Several limitations of the current study should be considered. Although obtaining measures of CBF provides information in addition to BOLD, this study design was not sufficient to directly measure $CMRO_2$, which currently requires the acquisition of a hypercapnia procedure and was not considered feasible for the current study. Future studies incorporating direct measures of $CMRO_2$ will allow further characterization of variations in neurovascular coupling and improved estimates of neural activity in MCI. Additionally, the optimized PCASL procedure was limited to a nine slice brick, which did not provide the ability to conduct voxelwise analyses across the whole brain. Additionally, our sample was restricted in its range

of stroke risk, leading to limitations in studying the relationship between stroke risk and neurovascular function. Importantly, as this was a cross-sectional study, it is difficult to determine the mechanisms underlying distinct CBF and BOLD patterns in this sample. As these participants continue to be followed longitudinally, further characterization of progression over time will be possible in future studies. However, the current study also contains several strengths. For example, previous studies of face-name associative encoding have only examined aMCI participants, and those that examined CBF during encoding in addition to BOLD focused solely on the MTL. This study examined CBF and BOLD signal during encoding in MTL and posteromedial regions involved in the memory circuit in both aMCI and naMCI groups. Additionally, the optimized PCASL method, correcting for physiological noise, has improved signal-to-noise capability than previously reported pulsed ASL methods.

In conclusion, distinct patterns of BOLD and CBF occur between aMCI and naMCI groups at rest and during memory encoding. Although aMCI participants exhibited patterns most consistent with reported findings in AD, naMCI participants exhibited important and distinct alterations in CBF during memory encoding that may underlie their distinct cognitive deficits on neuropsychological testing and may be associated with a unique trajectory of cognitive decline. This study is the first to provide neurovascular characterization of aMCI and naMCI at rest and during memory encoding. Future studies will examine CBF/BOLD patterns in additional brain regions, cognitive decline at follow-up, and provide a comparison of the current study findings to those using the conventional MCI diagnostic criteria. Additional studies of CBF in larger samples of naMCI participants would be helpful in confirming

and further exploring neurovascular alternations within this less frequently studied group.

The Discussion section is currently being prepared for submission for publication of the material. Clark, Lindsay R.; Wierenga, Christina E.; Bangen, Katherine J.; Shin, David D.; Salmon, David P.; Jurick, S.M.; Ewald, I.; Liu, Thomas, T.; Bondi, Mark. W. The dissertation author was the primary investigator and author of this paper.

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