2015

EMOTIONAL ENHANCEMENT AND REPETITION EFFECTS DURING WORKING MEMORY IN PERSONS WITH MILD COGNITIVE IMPAIRMENT

Lucas S. Broster
University of Kentucky, lucas.broster@uky.edu

STUDENT AGREEMENT:

I represent that my thesis or dissertation and abstract are my original work. Proper attribution has been given to all outside sources. I understand that I am solely responsible for obtaining any needed copyright permissions. I have obtained needed written permission statement(s) from the owner(s) of each third-party copyrighted matter to be included in my work, allowing electronic distribution (if such use is not permitted by the fair use doctrine) which will be submitted to UKnowledge as Additional File.

I hereby grant to The University of Kentucky and its agents the irrevocable, non-exclusive, and royalty-free license to archive and make accessible my work in whole or in part in all forms of media, now or hereafter known. I agree that the document mentioned above may be made available immediately for worldwide access unless an embargo applies.

I retain all other ownership rights to the copyright of my work. I also retain the right to use in future works (such as articles or books) all or part of my work. I understand that I am free to register the copyright to my work.

REVIEW, APPROVAL AND ACCEPTANCE

The document mentioned above has been reviewed and accepted by the student's advisor, on behalf of the advisory committee, and by the Director of Graduate Studies (DGS), on behalf of the program; we verify that this is the final, approved version of the student's thesis including all changes required by the advisory committee. The undersigned agree to abide by the statements above.

Lucas S. Broster, Student

Dr. Yang Jiang, Major Professor

Dr. Anita Fernander, Director of Graduate Studies

EMOTIONAL ENHANCEMENT AND REPETITION EFFECTS DURING WORKING MEMORY IN PERSONS WITH MILD COGNITIVE IMPAIRMENT

DISSERTATION

A dissertation submitted in partial fulfillment of the

requirements for the degree of Doctor of Philosophy in the

College of Medicine

at the University of Kentucky

By

Lucas S Broster

Lexington, Kentucky

Director: Dr. Yang Jiang, Associate Professor of Behavioral Science

Lexington, Kentucky

2015

ABSTRACT OF DISSERTATION

EMOTIONAL ENHANCEMENT AND REPETITION EFFECTS DURING WORKING MEMORY IN PERSONS WITH MILD COGNITIVE IMPAIRMENT

This dissertation introduces a framework for understanding differences in how emotional enhancement effects might influence memory in aging adults and then summarizes the findings of three studies of how repetition effects and emotional enhancement effects influence working memory in older adults without cognitive impairment (NC), older adults with amnestic mild cognitive impairment (MCI), and older adults with mild Alzheimer's disease (AD). In these experiments, individuals with AD showed cognitive impairment in terms of accuracy and reaction time, but individuals with MCI showed milder behavioral impairment that was confined to manipulations of working memory. Individuals with AD showed relative sparing of repetition effects in behavioral performance, and this sparing was linked to an altered cortical repetition effect using event-related potentials (ERPs). Repetition effects in MCI appear absent in emotional tasks that lack a working memory component, but are present in a neural repetition mechanism that is evoked in the presence of working memory. Finally, persons with MCI showed working memory processing similar to persons without impairment when working with stimuli of low arousal and positive hedonic valence, but when working with stimuli of high arousal and negative hedonic valence, their working memory processing more resembled the AD phenotype.

Keywords: event-related potentials, Alzheimer's disease, emotional memory, working memory, repetition effects

Lucas S Broster

June 22, 2015

EMOTIONAL ENHANCEMENT EFFECTS AND REPETITION EFFECTS DURING WORKING MEMORY IN PERSONS WITH MILD COGNITIVE IMPAIRMENT

By

Lucas S Broster

Yang Jiang, PhD
Director of Dissertation

Anita Fernander, PhD
Director of Graduate Studies

June 22, 2015
Date

Acknowledgements

I would like to thank Chelsea Black, Seth Kiser, Erin Walsh, Chunyan Guo, Adam Lawson, Charles Smith, Gregory Jicha, Nancy Munro, and Lee Hively for their effort in recruitment, data collection, and/or task development with the cohort discussed in Chapters 2 and 3, which partially took place before I joined the Aging, Brain, and Cognition laboratory. In addition to using some of their data in this dissertation, I built significantly on their work in planning the structure of the experiments in Chapters 4 and 5.

I would also like to acknowledge Gregory Jicha, Lindsay Krompak, Shonna Jenkins, Beth Eaves, and Sarah Tarrant, who assisted in recruitment of participants for the cohort described in Chapters 4 and 5.

I would also like to thank Richard Kryscio, Frederick Schmitt, Erin Abner, and the University of Kentucky Alzheimer's Disease Center (UK-ADC) for their help in the neuropsychological characterization of both cohorts used in the current study, as well as guidance in the appropriate interpretation of those data. I suspect that the efforts of the UK-ADC will aid significantly in drawing additional conclusions from these data in future work.

I would also like to thank Andreas Keil, who shared his unpublished data on older adults' evaluations of certain International Affective Picture System images with me upon my consultation and exchanged numerous e-mails to help me to understand his coding system and to interpret his findings appropriately. This effort allowed me to select the stimuli for the experiments discussed in Chapters 4 and 5 in a rational way.

I would like to thank Joseph Dien, who has shown superhuman patience working with me over the course of over a year troubleshooting various bug-fixes and user-errors in use of the ERP PCA Toolkit, which was used in the analyses in Chapter 3, Chapter 4, and Chapter 5. He and I exchanged literally hundreds of e-mails addressing these issues, and I think the analysis approach this enabled has been invaluable. I hope that our correspondence will assist future users of the software package.

I would like to acknowledge the members of my graduate committee: Gregory Jicha, Lee Blonder, Brian Gold, Steven Estus, and Yang Jiang. Their support and guidance has influenced the production of most chapters of this dissertation, whether directly through shared authorship of certain chapters of the source material or indirectly through useful feedback on work-in-progress throughout my graduate work.

Finally, I would like to acknowledge all of the research participants who gave their time and energy over the previous decade to make these experiments possible.

This work was supported by funding from the Department of Energy (DE-AC03-OR22725) and the National Institute of Health's National Institute on Aging (50 AG05144-21; AG000986; 5P30AG028383; 5 T32 AG 242-18) and National Center for Advancing

Translational Sciences (UL1RR033173; UL1TR000117), and a pilot grant from the University of Kentucky Department of Behavioral Science.

Table of Contents

List of Tables

List of Figures

This dissertation summarizes three experiments that have attempted to assess the behavioral viability of discrete memory systems in people with dementia due to Alzheimer's disease (AD); people who are experiencing its preceding clinical state, mild cognitive impairment (MCI); and in otherwise-similar older adults without cognitive impairment (NC). A goal of this enterprise is to identify potential aspects of cognition that might be relatively spared in function or neural implementation as the disease progresses. In these experiments, visual working memory, the capacity to hold visual information in one's mind for intentional manipulation, is assessed as a capacity known to be impaired in persons with clinical Alzheimer's disease. Emotional enhancements effects (i.e., the ability of arousing, pleasant, or unsettling stimuli to be encoded into memory more reliably or vividly than other stimuli) and repetition effects (i.e., the unconscious tendency for repeated stimuli or phenomena to be more reliably encoded into memory, more easily retrieved from memory, and/or differentially processed in the brain) are assessed as capacities believed to be relatively intact in Alzheimer's disease.

In Chapter 1, these ideas have been developed into a review paper, which argues that discrepancies in the literature regarding emotional enhancement effects in mild cognitive impairment merit investigation and may represent an unappreciated clinical opportunity, especially in light of the established clinical benefits of repetition effects. Further, I suggest that emotional enhancement effects likely benefit individuals with milder clinical stages of AD provided that they do not concurrently compete for resources also allocated to spatial attention.

In Chapter 2, I analyze the behavioral results of Experiment 1, where visual working memory and repetition effects were assessed in the absence of emotional enhancement effects. The main findings were that a) nonmatching stimuli (i.e., stimuli distracting research participants from the working memory task at-hand) showed behavioral reaction time slowing at an earlier clinical stage than did matching stimuli, and b) that individuals with AD showed exaggerated benefits from repetition relative to other participants. I suggest that these findings, respectively, correlate to attention dysregulation in dementia and suggest that repetition effects are spared in the current visual working memory paradigm context.

In Chapter 3, I analyze the electrophysiological data from the same experiment and use principal components analysis (PCA) to disentangle the classical electrophysiological waveform into discrete neural phenomena. The major finding was that repetition effects for a neural component measured only at posterior electrode sites showed an effect in AD that was opposite that of individuals with milder impairment or who lacked impairment. Although this effect did not correlate with behavioral differences in reaction time outcomes, I suggest that these findings may nonetheless suggest cognitive plasticity in posterior cortex for maintenance of near-normal repetition effects for this task in AD, perhaps reflecting

plasticity at occipital cortex, which is pathologically spared relative to other cortical regions in AD.

In Chapter 4, I analyze electrophysiological data from two further experiments: one that assesses repetition effects in the presence of emotional enhancement effects, and one that assesses both faculties in the context of a working memory task. In this chapter, I focus on aspects of the results that were related to repetition effects. The major finding is that whereas repetition effects appeared quite impaired in participants with MCI in the context of the task without working memory, incorporating working memory into the experiment stimulated a neural component where individuals with MCI *did* show a typical repetition effect. I suggest that this finding emphasizes that cognitive challenge can reveal capacities of individuals with AD that would otherwise appear extinct. Further, I suggest that the finding may help contextualize disparate findings about the status of repetition effects in AD.

In Chapter 5, I assess findings from those experiments that were unrelated to repetition effects. The main finding was that individuals with MCI showed a reversal of traditional working memory processing that was unique to high arousal negative stimuli. In other words, whereas the processing difference between matching and nonmatching stimuli was approximately equivalent between people with and without impairment for low arousal positive stimuli, high arousal negative stimuli evoked different working memory processing patterns for persons with and without MCI. Further, this altered pattern has been linked to the clinical course of AD in earlier behavioral (e.g., in Chapter 2) and electrophysiological data. I suggest that this finding that high arousal negative stimuli exacerbate effects of AD on memory processing may be generalizable to arousing, unsettling environments of persons with AD.

I would like to thank you, reader, and the rest of my dissertation and evaluation committee for your guidance and evaluating of these materials. I hope that they reflect my progress and effort over the preceding four years and that they feel worthwhile to review.

Chapter 1: A Review of Emotional Memory Enhancement in Aging and Dementia

Adapted from Broster et al. (2012). Does emotional memory enhancement assist the memory-impaired? *Frontiers in Aging Neuroscience* 4.

EXECUTIVE SUMMARY

I review recent work on emotional memory enhancement in aging and demented cohorts and evaluate the viability of incorporating emotional components into cognitive rehabilitation for mild cognitive impairment and mild Alzheimer dementia. First, I identify converging evidence regarding the effects of emotional valence on working memory in healthy aging. Second, I introduce work that suggests a more complex role for emotional memory enhancement in aging and identify a model capable of unifying disparate research findings. Third, I survey the neuroimaging literature for evidence of a special role for the amygdala in mild cognitive impairment and mild Alzheimer dementia in emotional memory enhancement. Finally, I assess the theoretical feasibility of incorporating emotional content into cognitive rehabilitation given all available evidence.

Introduction

Contemporary cognitive rehabilitation, especially when delivered alongside pharmacotherapy, has been shown to improve memory outcomes and delay dementia progression in individuals with amnestic mild cognitive impairment (MCI) and mild Alzheimer dementia (AD) (Mimura & Komatsu, 2007). Historically, however, clinical results of cognitive dementia interventions have been somewhat mixed. In fact, the findings of trials investigating the efficacy of such practices in the 1980s led clinicians to question the validity of the entire behavioral intervention paradigm for the treatment of AD (Hopper, 2003; Mowszowski, Batchelor, & Naismith, 2010).

These early cognitive rehabilitation interventions focused on improving explicit memory as a means of treating the explicit memory loss typical of AD. Other forms of memory, including implicit memory, are relatively spared by AD. Implicit memory includes those aspects of memory of which the individual lacks conscious awareness. For example, procedural memory, the memory of how to perform physical tasks, is one aspect of implicit memory. Repetition learning, the passive, automatic learning of associations upon repeated exposure, is another (Kessels, Remmerswaal, & Wilson, 2011).

The advent of implicit memory-based methods represented a major theoretical shift in the development of more efficacious cognitive rehabilitation protocols. Rather than focusing only on improving explicit memory directly through rehearsal, these protocols also utilize intact implicit memory to compensate for eroding explicit capacity (Mimura & Komatsu, 2007). Pilot studies have suggested improved efficacy for implicit memory-based intervention methods (Jean et al., 2010; Kessels & de Haan, 2003a, 2003b; van Halteren-van Tilborg, Scherder, & Hulstijn, 2007; Zanetti et al., 1997).

The success of this approach leads us to question whether other neurocognitive systems broadly implicated in memory are relatively intact in patients with progressive dementia such that those systems may be analogously harnessed to help compensate for eroded explicit capacity. In other words, much as implicit memory treatment appears promising for ameliorating early explicit memory decline, perhaps recruiting other relatively-intact memory processes in individuals with early impairment can additively help delay significant functional impairment. One candidate system that involves structures relatively spared in AD is the emotional processing system, and its integration with memory systems has garnered significant attention over the past decades (Pessoa, 2008, 2009, 2010; Pessoa & Adolphs, 2010). To evaluate whether this system might show promise in further enhancing cognitive rehabilitation protocols, I first describe how *emotional memory enhancement*, the tendency of emotional content to be better-remembered than non-emotional content, might change with aging and dementia.

Emotional memory enhancement is intact in older adults

A major behavioral basis for the belief that emotional content might improve memory outcomes is the persistent finding that, even in older adults, emotional content is remembered more accurately and/or more quickly than non-emotional content for both short-term and longer-term recall of visual images (F. Boller et al., 2002; Borg, Leroy, Favre, Laurent, & Thomas-Anterion, 2011; Evans-Roberts & Turnbull, 2011; Mikels, Fredrickson, et al., 2005; Mikels, Larkin, Reuter-Lorenz, & Cartensen, 2005; Moayeri, Cahill, Jin, & Potkin, 2000; Nashiro & Mather, 2011a, 2011b). This is independently-demonstrated for emotional stimuli of both positive valence and negative valence relative to non-emotional control, and it is demonstrated in mild AD participants (F. Boller et al., 2002; Borg et al., 2011).

In tests simultaneously evaluating positively and negatively-valenced stimuli relative to non-emotional control, both types consistently increase memory performance better than non-emotional stimuli, and, for older adults, positive valences tend to produce better results than negative valences (Murphy & Isaacowitz, 2008; Nashiro, Mather, Gorlick, & Nga, 2011). The tendency for older adults to perform better on positively-valenced stimuli with regard to measures of attention, recognition, and emotional memory enhancement has been termed the age-related *positivity effect* (Charles, Mather, & Carstensen, 2003; Gruhn, Scheibe, & Baltes, 2007; Isaacowitz, Allard, Murphy, & Schlangel, 2009; Isaacowitz, Toner, & Neupert, 2009; Lockenhoff & Carstensen, 2007; Mather & Knight, 2006), and the positivity effect phenomenon itself is sufficiently well-established that separate attempts to model the phenomenon compete for legitimacy in the emotional aging literature (Carstensen, Pasupathi, Mayr, & Nesselroade, 2000; Knight et al., 2007; Labouvie-Vief, Diehl, Jain, & Zhang, 2007; Labouvie-Vief, Lumley, Jain, & Heinze, 2003; Mather & Knight, 2005; Scheibe & Carstensen, 2010).

One account of the positivity effect holds that changes in valence biases reflect top-down changes in emotional regulation with aging (Carstensen et al., 2000). In other words, it appears that older adults may have unique mental processes that enable them to encode positively-valenced stimuli in a manner categorically different from younger adults (Charles & Piazza, 2007). This perspective suggests that older adults may have special valence-specific cognitive biases that may be used in the context of emotional memory enhancement to improve memory outcomes.

This positivity effect may not be observed in some subpopulations of older adults. For example, individuals with major depressive disorder or who have recovered from major

depressive disorder show preferential attention to negatively-valence stimuli (Kerestes et al., 2012), which may predispose them to encode valence differently from individuals without a history of depression. Whether these effects persist in the face of the positivity effect is unknown, but, given the association between depression and cognitive impairment, the competing trends should be noted in the short term and formally evaluated in future work (Burt, Zembar, & Niederehe, 1995; Korczyn & Halperin, 2009).

For the purposes of this review, the observations that older adults show emotional memory enhancement, particularly with positively-valence stimuli, and that Alzheimer participants may also show a degree of emotional memory enhancement are sufficient for motivating further inquiry. I next look at how emotional memory enhancement differs in old age and dementia.

Dementia changes the emotional realm

While emotional memory enhancement, as prior discussed, is intact to a certain extent in older adults, individuals with MCI, and individuals with AD, all of these groups do significantly differ from younger adults on certain attention and memory measures (E A Kensinger, 2008). The prior-discussed positivity effect between younger and older adults is just one example of such a difference, and the themes implicit in that effect are broadly consistent even for non-visual modalities, attention paradigms, and neurofunctional work (Leclerc & Kensinger, 2011; Orgeta, 2011a, 2011b; L. Yang & Hasher, 2011). However, differences in emotional memory enhancement between non-demented older adults and older adults with AD have been reported for a range of experimental paradigms, and some even report lack of significant emotional memory enhancement. For example, older adults with AD do not appear to benefit from emotional memory enhancement in the processing

of complex information such as verbally-related stories and even some short-term memory delay recognition memory paradigms (Abrisqueta-Gomez, Bueno, Oliveira, & Bertolucci, 2002; E. A. Kensinger & Corkin, 2003a, 2003b; E. A. Kensinger, Krendl, & Corkin, 2006). These differences in patients with AD are attested when investigating both only positively- and only negatively-valenced stimuli (Hamann, Monarch, & Goldstein, 2002; Padovan, Versace, Thomas-Anterion, & Laurent, 2002).

Contrarily, other work indicates that even individuals with AD benefit modestly from emotional memory enhancement (E. A. Kensinger, Brierley, Medford, Growdon, & Corkin, 2002) For example, while emotional memory enhancement was attenuated relative to healthy, age-matched controls, patients with mild AD showed improved memory for emotional items in a free recall paradigm (Nieuwenhuis-Mark, Schalk, & de Graaf, 2009). Indeed, some studies imply that people with AD may show enhanced flashbulb memory (i.e. vivid, visuospatially-detailed memories) for events with particularly intense arousal and emotional content (Kazui, Mori, Hashimoto, & Hirono, 2003). Other controlled work on flashbulb memories suggests that these faculties are intact in AD (Budson et al., 2004; Ikeda et al., 1998; Kazui et al., 2000; Moayeri et al., 2000). The strength of this phenomenon within individuals may be linked to amygdala mass (McGaugh, Cahill, & Roozendaal, 1996; Mori et al., 1999; Phelps, 2004; Phelps, Delgado, Nearing, & LeDoux, 2004). The work reviewed earlier in the context of valence effect differences similarly finds intact emotional memory enhancement of some form in people with AD (F. Boller et al., 2002).

These data demonstrate that different paradigms come to different conclusions about whether people with AD benefit from emotional memory enhancement or the

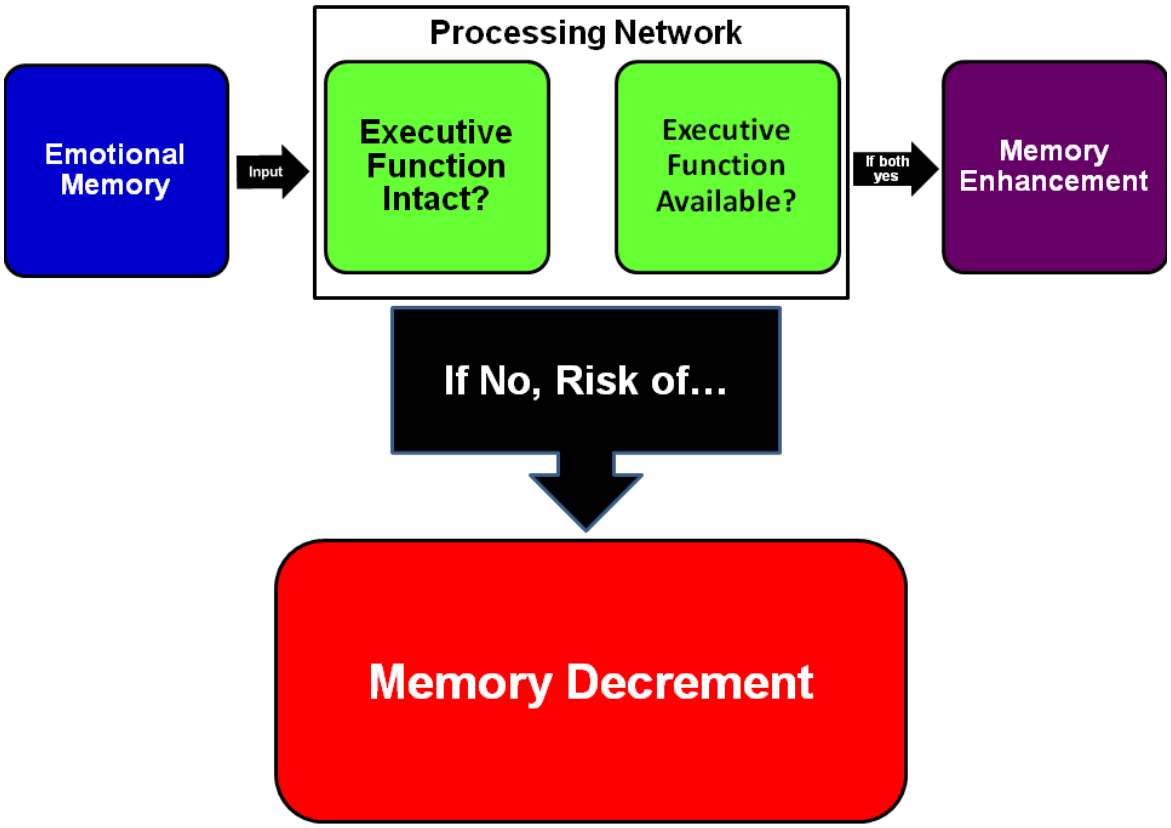

Figure 1.1: Contextual Model of Emotional Enhancement Effects. **A model derived from Borg (2011) and colleagues' view of how occupied or impaired cognitive resources can change how emotion affects memory encoding. If individuals' executive function resources are otherwise engaged or individuals' executive function is impaired, as in Alzheimer dementia, the model predicts greater likelihood of emotional memory decrement. Patients with intermediate executive function impairment, as in MCI or mild AD, would be hypothesized to have relatively normal emotional memory enhancement.**

positivity effect, though studies suggest these phenomena may be partially intact. To attempt to contextualize these disparate findings, I investigate a few studies in more detail.

Can emotional memory decrement occur?

While most studies indicate emotional memory enhancement in older adults and some further observe a form of this in people with AD, I have also cited work that fails to observe this phenomenon in the demented population. Borg (2011) and colleagues have elucidated a model suggesting that emotional content inexorably monopolizes a certain share

of executive function resources (Figure 1.1) based on the finding that memory deficits were greater for emotional than non-emotional stimuli when a task required more executive demand or when individuals had impaired executive resources (e.g., secondary to dementia).

For a simple visual recognition task younger adults, older adults, and mild AD patients all showed emotional memory enhancement. However, older adults and mild AD patients no longer showed emotional memory enhancement in a more executive function-demanding visual binding task, and AD patients also showed a between-task performance difference for non-emotional stimuli. Borg (2011) and colleagues argued that emotional memory enhancement requires executive function resources and that that resource usage could either help or hinder ultimate performance depending upon total available resources, a function of each individual, and resources necessary for a given task.

This contextualization helps explain the disparate findings prior reviewed. Individual differences in the degree of executive dysfunction between cohorts and differences in executive function required for a given task would affect whether emotional memory enhancement, emotional memory decrement, or neither would occur in people with AD. These findings also contextualize research reports outside the dementia literature that appear at-odds with consensus elsewhere. For example, the finding that older adults more than younger adults fail to remember details of complex emotional scenes such as robberies (Aizpurua, Garcia-Bajos, & Migueles, 2011) may be explained in part by such stimuli having more complex, less controlled elements than the simpler stimuli normatively employed in the psychological literature.

This model greatly resembles the "dual competition" framework articulated by Pessoa (2009). That framework, based on work with younger cohorts, suggested, namely,

that interactions between cognition, motivation, and emotion could affect whether emotional memory enhancement or emotional memory decrement would occur.

It is worth noting that this model does not account for the finding that patients with AD appear to have intact flashbulb memory. Whereas the model might predict that memory of complex events requiring concurrent executive function may suffer given emotional context, flashbulb memory, tending as it does to be associated with emotionally-arousing events, shows the opposite trend. One possibility is that recollection per se is what these paradigms test, and that recollection itself does not require extensive executive resources, even though processing the event itself may well have required them. Another possibility is that details of the various events have been confabulated in ways that are not accounted for by the various protocols, and this confabulation masks impairment not otherwise recorded.

Concerns about the specific applicability of flashbulb memory findings aside, this model suggests that while integrating emotional content into cognitive rehabilitation for people with MCI or very mild AD may be efficacious, it may be less useful for more-impaired populations, and emotional memory decrement may even occur if the rehabilitation protocol in question requires intensive executive control.

I next look to neuroimaging for evidence of the neurological mechanism underlying Borg (2011) and colleagues' executive resource hypothesis.

Toward a neural mechanism for Borg (2011) and colleagues' executive resource hypothesis

Neuroimaging of emotional memory enhancement in aging and AD populations remains in its infancy. Most imaging work with patients with AD focuses on memory effects

per se in the absence of emotional context. Nevertheless, these memory findings have revealed intriguing emotional brain region effects. Patients with AD show abnormal connectivity and activation of emotion-related brain regions even when engaging in putatively non-emotional memory tasks (Rosenbaum, Furey, Horwitz, & Grady, 2010). Specifically, increased connectivity between amygdala and pre-frontal cortex for a working memory task was seen in participants with AD relative to controls in spite of no differential indication of arousal correlates during the task. Rosenbaum (2010) and colleagues suggest that this difference represents recruitment of compensatory pre-frontal brain structures, and that the amygdala acts as an intermediary through which pre-frontal resources are accessed. During an emotionally-neutral delayed match-to-sample task, I found significantly more task-related amygdala activation in participants with MCI than in age-matched older adults (Figure 1.2). Our findings are analogous to those reported by Rosenbaum et al. (2010).

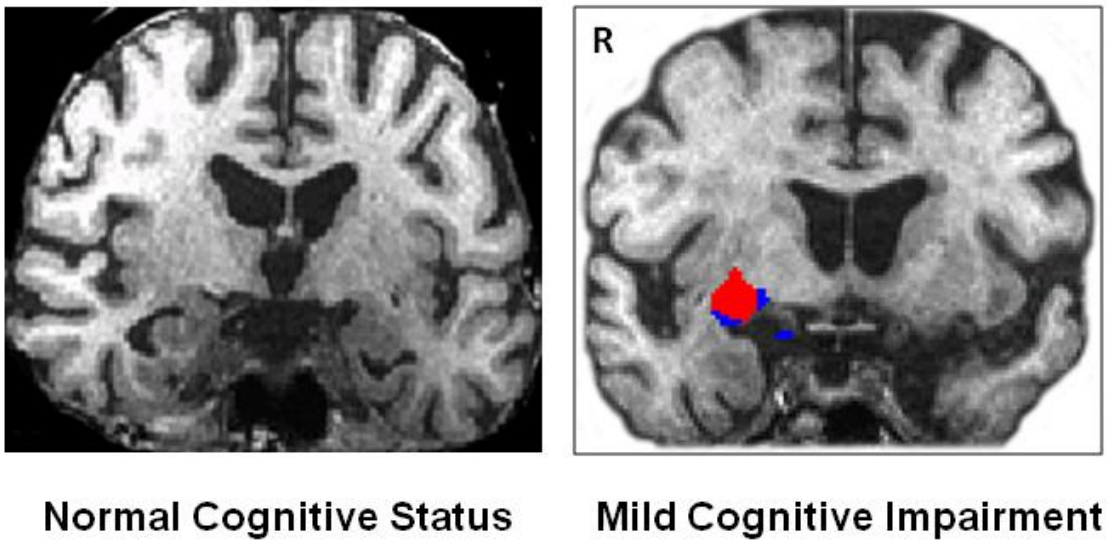

Figure 1.2: Pilot data corroborating Rosenbaum's findings. **I observe significant right amygdala activation during a working memory task in an older patient with mild cognitive impairment (right, white background), but not in an older control participant (left, black background). The red blob shows activation from a Z map of all objects ($p < 0.000001$).**

One possible criticism of both these neuroimaging findings is that memory-impaired cohorts may experience anxiety when asked to perform a task at which they are impaired. In other words, the amygdala and frontal responses in these groups could reflect functionally-irrelevant anxiety about performance. To address this concern, Rosenbaum (2010) and colleagues point to a lack of arousal difference between groups and argue that that similar arousal indicates that anxiety was not responsible for the observed effects.

These findings, if valid, provide a possible neurological mechanism for emotional memory enhancement. They also provide a mechanism for Borg (2011) and colleagues' claim that executive function resources, implicated as they are in pre-frontal cortical structures, determine whether emotional memory enhancement or emotional memory decrement will occur. Specifically, the preoccupation of pre-frontal executive function resources with an executive function-intensive task could disrupt pre-frontal recruitment and explain why emotional memory enhancement fails to occur.

The finding that interaction between the amygdala and prefrontal cortices plays a significant role in implementing cognitive-emotional interactions is consistent with the amygdala's theoretical role as a coordinator of cortical functions regarding affectively-significant events (de Gelder, van Honk, & Tamietto, 2011; Pessoa & Adolphs, 2010). It is further consistent with anatomical connectivity research in the non-human primate, which purports that the relationship of the amygdala to the prefrontal cortex, and to the orbitofrontal cortex in particular, is likely implicated in emotional processing (Ghashghaei & Barbas, 2002). Non-primate animal research also supports this conclusion (Quirk & Beer, 2006).

Future work should investigate this phenomenon while more aggressively measuring correlates of arousal and anxiety. However, even if the effect turns out not to be differentiable from presumed-functionally-irrelevant task anxiety, the mechanism may nonetheless prove interesting. For example, arousal may be an epiphenomenon of the emotional memory enhancement phenomenon.

Summary and relevance for cognitive rehabilitation

I have reviewed evidence that patients with AD better remember emotional content, but only if that content is not accompanied by complex, mentally-taxing phenomena. The neurological mechanism underlying this benefit may lie in the amygdala's role as an intermediary to the executive resources of the frontal cortex. I assert that the available scientific evidence suggests that patients with MCI or mild AD may benefit from integrating emotional memory enhancement into the rehabilitation process. In particular, the evidence implies that coupling positively-valenced stimuli to non-complex elements of the cognitive training process may be of particular use in non-depressed patients identified as having amnestic MCI or mild AD. Some cohorts, such as depressed patients, may have attenuated positivity effects and likewise show reduced benefit from therapy. Also drawing from Borg (2011) and colleagues' model, cognitive rehabilitation could target executive function directly. Increased executive resources could increase patients' ability to benefit from emotional cues in their daily lives (Jean et al., 2010; H. Li et al., 2011; Martin, Clare, Altgassen, Cameron, & Zehnder, 2011).

I have also identified two models, one behavioral (Borg et al., 2011) and one neuroaffective (Rosenbaum et al., 2010), capable of consolidating many of the research findings reported while characterizing interactions between emotional memory enhancement,

aging, the task difficulty at the algorithmic and implementational levels, respectively. Stronger tests of these findings, particularly regarding the role of the amygdala in recruiting prefrontal structures in MCI and dementia, would help confirm a promising model that describes how brain systems compensate for early cognitive impairment.

Chapter 2: Dementia is Associated with Non-Match Deficits and Maintained Repetition Effects

---

Adapted from Broster et al., (2013). Repeated Retrieval During Working Memory Is Sensitive to Amnestic Mild Cognitive Impairment. *Journal of clinical and experimental neuropsychology* 35 (9), 946-959

EXECUTIVE SUMMARY

Study of repeated learning mechanisms has been limited in amnestic mild cognitive impairment, a preclinical stage of Alzheimer disease modifiable by cognitive rehabilitation. I assessed repeated contextual working memory decline as an indicator of amnestic mild cognitive impairment in a sample of 45 older adults recruited from the tertiary care setting. Results indicated that contextual working memory impairment distinguished adults with preclinical disease from those without impairment despite similar overall cognitive performance, and comparison of the indicator with standard-of-care neuropsychological measures indicated discriminant validity. Contextual working memory impairment may represent a novel predictor of Alzheimer disease conversion risk.

Introduction

Decades of experimental and clinical work have identified memory systems disrupted or spared in the course of amnestic mild cognitive impairment (MCI) and its typical successor state, Alzheimer disease (AD) (Baars et al., 2009; Hodges, Erzinclioglu, & Patterson, 2006; Kessels & de Haan, 2003a; Wiggs, Weisberg, & Martin, 2006). Identifying vulnerable cognitive capacities enables early identification of persons at risk for AD so that appropriate early interventions may be delivered, and identifying spared memory capacities informs the development of cognitive training interventions that may serve to delay functional AD impairment (Belleville et al., 2011; Belleville et al., 2006; Carlesimo et al., 1998). Since treatment options at the AD stage of impairment remain limited, identifying persons with preclinical AD has become an important clinical goal.

Despite the traditional focus on the dysfunction of episodic delayed recall in AD, the association of AD with declining working memory (WM), a short-term memory system that holds information on-line for cognitive manipulation, has been appreciated since the 1990s (Baddeley, Bressi, Della Sala, Logie, & Spinnler, 1991; Belleville, Peretz, & Malenfant, 1996; Bisiacchi, Tarantino, & Ciccola, 2008; Borella, Carretti, & De Beni, 2008; Collette, Van der Linden, & Salmon, 1999; Moulin, James, Freeman, & Jones, 2004; Ribeiro, Guerreiro, & De Mendonca, 2007; Rochon, Waters, & Caplan, 2000; Schrijnemaekers, de Jager, Hogervorst, & Budge, 2006; Seelye, Schmitter-Edgecombe, & Flores, 2010). Indeed, cognitive researchers have converged upon an understanding that WM experiences parallel decline in the earliest stages of clinical AD, and neurophysiology has linked disrupted WM processing to progressive MCI (Belleville, Sylvain-Roy, de Boysson, & Menard, 2008; Kramer et al., 2006; Matsuda & Saito, 2009; Missonnier et al., 2007; Missonnier et al., 2006; Saunders &

Summers, 2010, 2011). The similar clinical prognoses of episodic memory and WM in AD have been correlated to their shared neural mechanisms. Functional neuroimaging has implicated a left-lateralized network including the left inferior frontal gyrus, inferior and medial temporal cortices, and posterior parietal cortices in WM, and these regions, particularly medial temporal structures such as the hippocampus, are classically associated with episodic memory (Oztekin, McElree, Staresina, & Davachi, 2009; Parasuraman, Greenwood, Haxby, & Grady, 1992; Ranganath, Cohen, Dam, & D'Esposito, 2004).

In contrast to WM and episodic memory, nondeclarative forms of memory such as repetition priming (RP), characterized by unconscious changes in cognitive processing due to mere exposure to associations between phenomena, appear broadly spared in aging and AD (Fleischman & Gabrieli, 1998; Gabrieli, Corkin, Mickel, & Growdon, 1993; Kessels et al., 2011; Wilkinson & Yang, 2012; L. Yang & Krampe, 2009). Individuals with particularly severe AD pathology may even exhibit enhanced nondeclarative memory (Klimkowicz-Mrowiec, Slowik, Krzywoszanski, Herzog-Krzywoszanska, & Szczudlik, 2008). Indeed, cognitive interventions to improve functioning in MCI and AD utilizing this spared nondeclarative capacity have been devised, and they appear efficacious (Jean et al., 2010; Kessels & de Haan, 2003a; Mimura & Komatsu, 2007; van Halteren-van Tilborg et al., 2007; Zanetti et al., 1997). However, the degree of impairment in specific aspects of nondeclarative memory in MCI and AD remains controversial. For example, some studies have reported that persons with clinical AD show impairment in certain nondeclarative memory tasks, especially for tasks where the ability to distinguish related phenomena on-line is implicated or where long-term encoding would be necessary for the observation of nondeclarative effects (Ferraro, Balota, & Connor, 1993; Fleischman & Gabrieli, 1998; Fleischman, Gabrieli,

Wilson, Moro, & Bennett, 2005; Henke, 2010; Mitchell & Schmitt, 2006; Pihlajamaki, O'Keefe, O'Brien, Blacker, & Sperling, 2011).

I suggest that this apparent discrepancy may be partially resolved by an appreciation that despite their dissimilar clinical fates in AD, episodic memory, RP, and WM systems collaborate and interact "on-line" during cognitive processing due to medial temporal and frontal cortical co-involvement (Guo, Lawson, & Jiang, 2007; Koenig et al., 2008). This possibility is highlighted by the tendency of reports of nondeclarative memory impairment in AD to be linked to either a long-term delay or relevance to an on-line task. This interaction presents a potential clinical opportunity. Altered neural mechanisms associated with cognitive decline are potential cognitive or neuroimaging biomarkers of cognitive dysfunction. Indeed, neural structures overlapping with those that subserve WM functions have been used to identify participants at risk for AD conversion with success. For example, the default mode network, a system of brain regions characterized by activity covariation in the absence of an ongoing cognitive task, incorporates medial temporal and prefrontal structures, and resting state analyses have identified systematic changes to these structures both in persons with AD and in at-risk individuals who have not yet received a clinical diagnosis (Buckner et al., 2009; Celone et al., 2006; Sperling, 2007). However, the underlying neural mechanisms subserving the default network and WM are distinct (Greicius, Krasnow, Reiss, & Menon, 2003; Hampson, Driesen, Skudlarski, Gore, & Constable, 2006; Kim et al., 2009; Sambataro et al., 2010). In our opinion, given the special status of WM in clinical AD, WM indicators of MCI are understudied and of potential clinical interest.

In this study, I used a paradigm designed to simultaneously probe WM and RP to test for behavioral and electrophysiological indicators of MCI and mild AD relative to an

age- and education-matched healthy elderly control group. I previously reported that healthy older adults showed disproportionate WM impairment for WM nonmatch stimuli relative to younger adults, but also that older adults benefitted more from RP than did younger adults (Caggiano, Jiang, & Parasuraman, 2006; Lawson, Guo, & Jiang, 2007). I hypothesized that given the underlying neurodegenerative processes, persons with MCI and AD would show an exaggerated form of typical cognitive aging: individuals with MCI and AD would show disproportionate impairment at WM nonmatch stimuli relative to an appropriately-matched control group, but RP would be enhanced in these groups.

Methods

Power Analysis

A priori power analysis was performed using G*Power to identify the sample size necessary to detect mixed interaction terms of moderate effect size or greater for the current study (Faul, Erdfelder, Buchner, & Lang, 2009; Faul, Erdfelder, Lang, & Buchner, 2007). The analysis revealed that 30 participants would be necessary for 80% power to detect such effects.

Participants

45 age- and education-matched participants – 18 normal older control (NC), 17 participants with MCI, 10 individuals with AD – were recruited directly from the *University of Kentucky Alzheimer Disease Center* (UK-ADC) cohort or from tertiary care memory clinics associated with the *Sanders-Brown Center on Aging* (Abner et al., 2012; Schmitt et al., 2012). Recruiting directly from memory clinics reduces the risk that cognitive effects observed result from non-AD memory impairment conditions such as thyroid or vitamin B_{12}

deficiency (Jicha et al., 2008; Luck et al., 2007). NC participants were healthy UK-ADC cohort volunteers (n = 4) or referrals to the memory clinic for evaluation who did not receive a clinical diagnosis and were considered NC based on criteria listed below (n = 14). In keeping with contemporary clinical criteria (Albert et al., 2011; Arsenault-Lapierre et al., 2011; Lekeu et al., 2010; Reid & Maclullich, 2006), MCI was indicated by A) absence of dementia, B) absence of cognitive, clinical, or behavioral symptoms consistent with sources of non-amnestic cognitive impairment, and C) objective memory impairment evidenced by performance more than 1.5 standard deviations below age-standardized normal values on at least one of several memory measures including Wechsler Memory Scale Logical Memory (WMS-R), the California Verbal Learning Test (CVLT-II), and the Benton Visual Retention Test (BVRT-5, Forms C & D). AD was diagnosed using Alzheimer's Disease Dementia Workgroup criteria, which hold, briefly, that insidious-onset dementia is present in the absence of another psychiatric or neurological condition (McKhann et al., 2011). All participants were recruited directly from the tertiary care setting and had received comprehensive work-up to rule-out other psychiatric or neurological causes of cognitive impairment. Individuals with AD and MCI had been diagnosed within 12 months of data collection, all research participants had been evaluated clinically within 12 months of data collection, and all research participants were evaluated clinically on an annual basis to check for conversion to MCI or AD. In other words, all participants were clinically evaluated both prior to and subsequent to research participation to confirm their clinical status. All participants were between age 65 and 90 with visual acuity better than 20/50 with corrective lenses in at least one eye. Exclusion criteria included history of stroke; epilepsy; head trauma; CNS infection, chronic infectious disease; psychiatric illness including substance abuse, major depression, or other mood disorder; or other neurological disease (Robert et al., 2006).

Participants taking medications known to affect cognitive function, such as sedatives or opiates, were similarly excluded.

Neuropsychological data collected from participants nearest in time to their research participation have been summarized in Table 2.1. Because participants who were recruited from the UK-ADC and the Sanders-Brown memory clinic were evaluated through slightly different neuropsychological protocols, some data were missing. Multiple imputation (MI) was used to account for missing data using participant age, education, and non-missing neuropsychological scores as predictors to limit the influence of systematic missingness on the covariance matrix. Mean and standard error values listed are based on non-imputed scores, but omnibus hypothesis-testing was conducted using pooled MI results. Because few AD participants completed the DIGIF, DIGIB, and DSYM tests, I have omitted such mean and standard error estimates as well as pairwise comparisons for the AD group. Note that GDS30 scores lower than 9 indicate non-pathological affect. For all neuropsychological tests except for TRAILA, TRAILB, and the GDS15, a larger score indicates better performance, whereas the opposite is true for TRIALA/B and the GDS15. Hence, the signs of correlations of TRAILA/B and GDS15 have been reversed in this chart for ease of interpretation. Positive ϱ values indicate that large differences in the neuropsychological status of individuals in a dyad were related to large differences in the size of the relevant repetition effect.

All participants provided written informed consent before participation. This study was approved by the Institutional Research Board (IRB) of the University of Kentucky.

Table 2.1: Neuropsychological summary for cohort of experiments discussed in Chapters 2 and 3. NC = normal control, MCI = mild cognitive impairment, AD = Alzheimer's disease; N = number of participants, Females = number of female participants, Age = age of participant in years, Education = formal education of participants in years; MMSE = mini-mental status examination, LOGIMEMI = Logical Memory Story A, Immediate Recall, LOGIMEMII = Logical Memory Story A, Delayed Recall, DIGIF = Digit Span Forward, DIGIB = Digit Span Backward, ANIMALS = Category Fluency (Animals), VEG = Category Fluency (Vegetables), TRAILA = Trailmaking A, TRAILB = Trailmaking B, DSYM = Digit Symbol, BOSTON = Boston Naming Task, GDS30 = Geriatric Depression Scale, long-form; df, F/χ2, and p indicate statistical summaries for the omnibus tests of group differences for each column; Pairwise comparisons p NC-MCI and MCI-AD = pairwise group comparisons, as indicated, for each significant neuropsychological omnibus F test. Welch's robust test of means was used for measures showing heterogeneity of variance. Variance displayed is the standard error of the mean (SEM) for each group.

	N	*Females*	*Age*	*Education*	*MMSE*	*LOGIMEMI*	*LOGIMEMII*	*DIGIF*	*DIGIB*	*ANIMALS*	*VEG*	*TRAILA*	*TRAILB*	*DSYM*	*BOSTON*	*GDS30*
N	18	11	75.1 ± 1.2	16.2 ± 0.7	29.3 ± 0.2	13.9 ± 0.8	13 ± 0.9	9.8 ± 0.4	7.4 ± 0.5	20.3 ± 1.8	14.7 ± 1.2	34.1 ± 1.9	73.0 ± 3.8	49.3 ± 2.0	28.9 ± 0.3	2.4 ± 0.5
MCI	15	5	75.0 ± 2.4	17.0 ± 0.5	27.8 ± 0.5	9.9 ± 0.9	7.0 ± 1.2	8.5 ± 0.5	6.1 ± 0.6	16.9 ± 1.3	12.6 ± 1.2	41.5 ± 3.4	118.2 ± 18.8	39.6 ± 3.9	28.5 ± 1.8	4.5 ± 1.4
AD	13	8	75.8 ± 1.6	17.7 ± 1.3	25.4 ± 0.9	7.2 ± 1.2	2.7 ± 1.0	7.7 ± 0.5	5.7 ± 0.5	11.1 ± 1.6	10.4 ± 1.3	62.8 ± 8.0	158.4 ± 31.4	50.7 ± 8.2	27.8 ± 0.7	6.4 ± 1.4
df		2	2, 25.3	2, 20.4	2, 17.1	2, 38	2, 38	2, 36	2, 36	2, 36	2, 33	2, 14.7	2, 12.7	2, 31	2, 16.1	2, 16.8
F/χ^2		4.85	0.06	0.64	11.83	12.09	21.27	4.47	2.57	5.64	1.95	6.90	5.94	3.12	1.05	4.25
p		0.09	0.94	0.54	0.001	< 0.001	< 0.001	0.02	0.09	0.007	0.16	0.008	0.015	0.06	0.37	0.032
Pairwise comparisons (p)		*NC-MCI*			0.03	0.003	< 0.001	0.05	0.08	0.12	0.23	0.14	0.04	0.02	0.78	0.14
		MCI-AD			0.004**	0.08	0.02*	0.30	0.69	0.05*	0.37	< 0.001**	0.13	0.13	0.68	0.24
Correlation with WM		*ρ*			0.104	0.116	-0.014	0.121	0.029	-0.060	0.008	-0.228	-0.154	-0.014	-0.009	0.046
(NC-MCI)		*p*			0.259	0.248	0.467	0.254	0.438	0.367	0.481	0.176	0.181	0.470	0.480	0.391
Correlation with WM		P			-0.091	0.039	-0.233	-0.081	0.118	-0.214	0.264	-0.017	-0.075	-0.069	-0.131	-0.025
(MCI-AD)		*P*			0.286	0.410	0.083	0.331	0.260	0.108	0.060	0.913	0.330	0.354	0.220	0.439

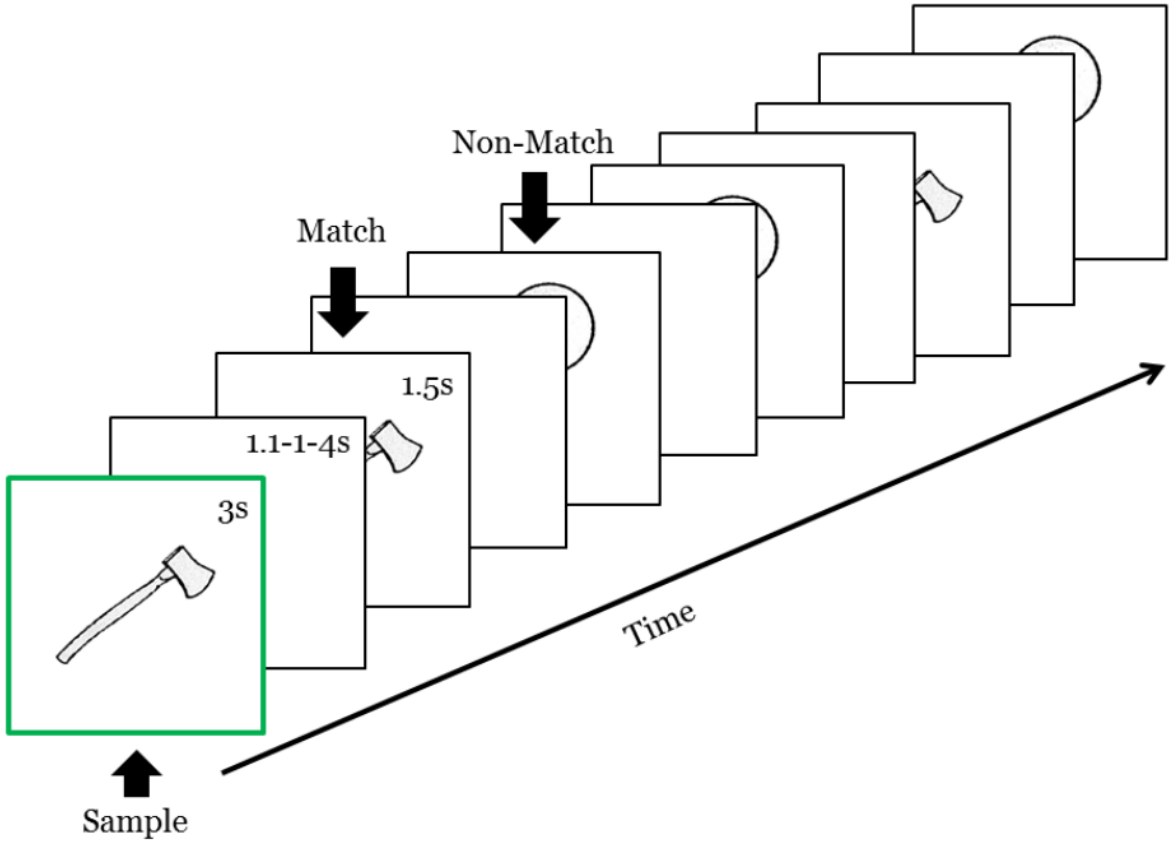

Figure 2.1: Experiment 1 Schematic**. The schematic represents a typical empirical trial. The z-axis represents time. First, a sample image with a green border was shown to the participant. After a jittered delay, the participant indicated whether each of a series of images matched or did not match the sample. Individual images were tested 2-3 times per trial. A new sample image was used in the each trial.**

Participants performed a hybrid delayed-match-to-sample/repetition (DMS-R) task (Figure 2.1) that has been validated in human and nonhuman primate physiological studies (Guo, Lawson, Zhang, & Jiang, 2008; Jiang, Haxby, Martin, Ungerleider, & Parasuraman, 2000; E. K. Miller, Erickson, & Desimone, 1996). Incorporating both WM and RP into a single paradigm, as in the hybrid paradigm used in the current study, facilitates the interpretation of any interaction effects observed (Kennedy, Rodrigue, Head, Gunning-Dixon, & Raz, 2009; Voss & Paller, 2008, 2009). Participants memorized a sample cartoon

image at the beginning of each trial and then indicated whether or not each of 5 serially presented objects matched the sample image via response box with the left or right hand, counterbalanced between participants. One image matching the sample and one nonmatching image were each tested 2-3 times per trial with 5 total repetitions per trial (Howard, Howard, Dennis, & Kelly, 2008). The differential working memory retrieval status of a given stimulus (i.e., whether each stimulus was a match or a nonmatch) was used as a probe of WM while repetition of a given stimulus (i.e., novel or repeated) was a probe of RP. Each image was used in exactly one trial. 60 trials were performed altogether in two blocks of 30 trials each. Each block lasted 5 minutes and 30 seconds. Participants took a short, self-paced break between blocks that typically lasted about 60 seconds. During this time research personnel confirmed the comfort of participants and provided encouragement to participants.

Pilot data suggested that persons with AD responded poorly to negative accuracy feedback during experimental protocols. Consequently, the protocol was modified so that participants would not receive accuracy feedback. As a result of this protocol modification, I expected RP effects to manifest as differences in *reaction times* (RTs) rather than as altered accuracy outcomes.

A 5-minute practice period preceded the entire experiment to ensure that participants were comfortable with the cognitive and motor components of the task. This practice period was also designed to reduce or eliminate the influence of motor learning confounds on any cognitive RP effects. During the practice period a research personnel remained in the experimental room with the participant and provided oral feedback related

to performance. As in the 2 blocks of formal experimentation, computerized feedback was not provided.

Visual Stimuli

Stimuli were 230 two-dimensional, black-and-white 8.3 cm x 5.8 cm pictures of common objects presented with a black background (Snodgrass & Vanderwart, 1980). All stimuli were presented on a high-resolution color monitor using E-prime software. Sample images were presented with a thick green outline for 3s, and each test stimulus was presented for 1.5s. Both individual images and individual trials were separated by a 1.1-1.4s jitter interval, which was employed to prevent bias in RT measures due to participants anticipating stimulus onset. Stimuli were presented at a 65 cm visual distance at a visual angle of approximately 7°. Test images were normalized for image familiarity and complexity across retrieval status (Snodgrass & Vanderwart, 1980).

Data Analysis

Data were aggregated into 4 nested categories for RT and accuracy with respect to WM and RP (i.e., such that the 4 categories were matching novel stimuli, matching repeated stimuli, nonmatching novel stimuli, and nonmatching repeated stimuli). Inaccurate responses were omitted from the RT aggregation. All aggregations showed Cronbach's α values greater than 0.9, suggesting excellent reliability for all stimulus categories. This aggregation was performed to improve measurement reliability and to control for simple motor learning effects. By aggregating RP across all trials in the experiment, within-trial motor practice effects become negligible. A motor training period also preceded data collection to further

mitigate the potential influence of motor learning effects. These steps ensured that image repetition effects result from cognitive RP rather than motor learning.

To account for the possibility that differences in baseline performance could produce spurious interaction terms, the aggregated RT and accuracy values were z-transformed (Faust, Balota, Spieler, & Ferraro, 1999). References to "RT" and "accuracy" after this point refer to the z-transformed variables, but please note that untransformed data has been plotted in Figure 2.2 for ease of visual interpretation.

After z-transformation, both RT and accuracy aggregates showed near-normal skew and kurtosis. Hence, these data were analyzed by a parametric approach. For the RT analysis, 2 x 2 x 3 mixed-model repeated measures analyses of variance (ANOVA) on WM (i.e., whether a stimulus was a match or a nonmatch), repetition (i.e., whether a stimulus was novel or repeated), and clinical group (NC, MCI, or AD) were used. Simple-effects models were used to interpret interaction effects, and Type I error inflation was controlled by the Holm-Bonferroni method. I have provided η_p^2 as an estimate of effect size; please note the rule of thumb that η_p^2 values greater than 0.01, 0.06, and 0.14 indicate small, moderate, and large effects, respectively (Cohen, 1988).

To ensure the novelty of potential WM or RP cognitive indicators identified during analysis, differences between WM and RP conditions were compared to neuropsychological measures collected from research participants using Spearman's ρ to confirm whether existing standard neuropsychological tools duplicated the effects implicated in any WM or RP effects identified. The Trailmaking test difference (i.e., Trailmaking B – Trailmaking A) was used to compare the executive function components of the Trailmaking test to the effects of WM and RP (Corrigan & Hinkeldey, 1987; Giovagnoli et al., 1996).

All significance values listed are based on the one-tailed *p* values. For the sake of brevity, results failing to reach one-tailed significance have been omitted from the report. Statistical tests were performed with JMP 10.

Results

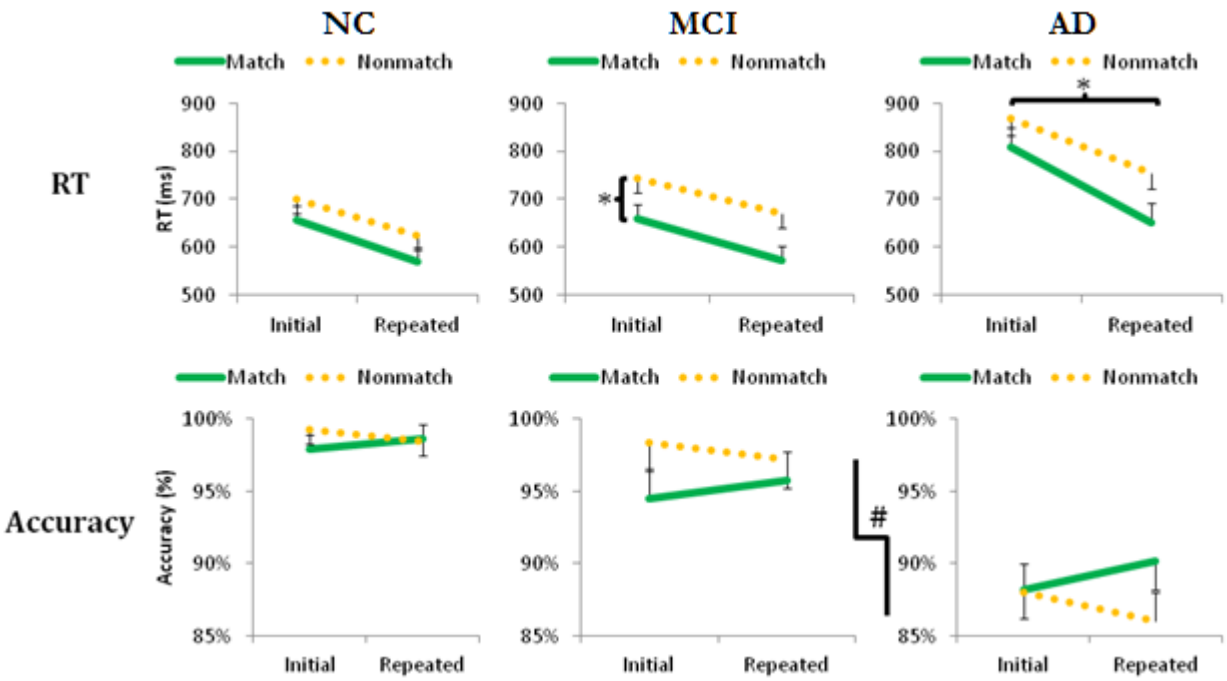

Figure 2.2: Reaction Time and Accuracy in Experiment 1**. I have depicted the untransformed RT and accuracy values for the normal older control (NC), amnestic mild cognitive impairment (MCI), and Alzheimer disease (AD) groups (Table 2.1). The MCI group showed characteristic, slow RTs for nonmatching stimuli (1st row, 2nd column), and the AD group showed greater quickening with repetition (1st row, 3rd column). The AD group also showed uniformly poorer accuracy (2nd row). # indicates the between-group difference between the AD group and both other groups for accuracy, and * indicates the within-group contrasts that drove significant mixed interactions with clinical group for RT.**

First, I tested our hypotheses, specifically that a) the MCI and AD groups would show slower nonmatching stimuli than the NC group and that b) the MCI and AD groups would show stronger RP than NC. 2 x 2 x 3 ANOVAS on retrieval status, repetition, and clinical group for RTs revealed a large WM X Group interaction, F (2, 42) = 4.95, MSE = 0.179, p = 0.006, η_p^2 = 0.19, and a moderate RP X Group interaction, F (2, 42) = 2.923,

MSE = 0.183, p = 0.036, η_p^2 = 0.12. For the WM X Group interaction, simple effects testing found moderate main effects of WM for the NC group, F (1, 42) = 4.38, p = 0.02, η_p^2 = 0.10, and the MCI group, F (1, 42) = 5.46, p = 0.01, η_p^2 = 0.12. For NC, the effect was due to disproportionately fast RTs for nonmatching stimuli, but for MCI, the effect was due to disproportionately slow RTs for nonmatching stimuli (Figure 2.2). For the RP X Group interaction, simple effects testing found a moderate effect of RP for AD such that repetition was associated with faster RTs, F (1, 42) = 3.94, p = 0.025, η_p^2 = 0.09. Other effects were non-significant.

Next, to identify whether the WM or RP effects identified above that distinguished participants were distinguishable from information collected from standard neuropsychological tests conducted with this clinical population, I conducted a series of correlations between the WM and RP effects (i.e., the difference in RT between the levels of each factor) and each of the neuropsychological tests that had been collected with the research participants at the time of clinical evaluation. Because neuropsychological tests values tended to be skewed and kurtotic, Spearman's ϱ was used to evaluate each correlation. To control for potential motor and processing speed confounds implicit in the Trailmaking test (TMT), the Trailmaking test (TMT) difference (i.e., $TMT_B - TMT_A$) was used rather than the raw TMT_A and TMT_B values (Corrigan & Hinkeldey, 1987; Giovagnoli et al., 1996). All non-parametric correlations were non-significant (Table 2.1).

Finally, I conducted an analysis of the accuracy data to identify any potential speed/accuracy trade-off effects (Downing, 2000). 2 x 2 x 3 ANOVAs revealed a main effect of clinical group, F (2, 42) = 10.35, *MSE* = 2.284, $p < 0.001$, η_p^2 = 0.33, such that NC and MCI showed comparable accuracy, but AD was significantly less accurate than both other

groups, $F_{NC\text{-}AD}$ (1, 42) = 20.34, $p < 0.001$, $\eta_p^2 = 0.33$, $F_{MCI\text{-}AD}$ (1, 42) = 11.29 $p = 0.001$, $\eta_p^2 = 0.18$. Other effects were non-significant.

Discussion

Working memory retrieval status differentiated all clinical groups

I found that NC, MCI, and AD groups each showed a unique working memory (WM) retrieval status signature for RT. This effect was driven by two main phenomena: disproportionate RT impairment for nonmatching stimuli in persons with MCI, and relatively uniform RT impairment for both matching and nonmatching stimuli in persons with AD. As noted in the introduction, reports of context-specific cognitive dysfunction in AD are not new, but such findings have rarely been reported in persons with MCI (Economou, Papageorgiou, & Karageorgiou, 2006; Pignatti et al., 2005). Moreover, the particular context-specific dysfunction identified in the research participants with MCI was not found to covary with the measures of the standard neuropsychological tools routinely used during annual clinical assessment. I believe this novel finding in MCI reflects nascent WM dysfunction, consistent with the tendency of these individuals to present with WM complaints (Belleville, Chertkow, & Gauthier, 2007; Kramer et al., 2006; Winblad et al., 2004). It may relate to recent reports of category-specific encoding deficits in persons with MCI (Hudon, Villeneuve, & Belleville, 2011).

The finding in MCI also extends and validates previous reports that healthy older adults show greater impairment with nonmatch stimuli relative to younger adults (Lawson et al., 2007). These findings suggest that the WM aging effect observed in pathological aging in this study may represent an extreme variant of normative cognitive aging in that processing of nonmatch stimuli is disproportionately dysfunctional. The findings also corroborate a

pilot report that frontal ERPs related to nonmatch stimuli are disrupted in MCI (Broster et al., 2011).

I had anticipated observing disproportionate nonmatch impairment in persons with MCI and persons with AD, but persons with AD instead showed a uniform deficit regardless of WM retrieval status. I propose that individuals with advanced neuropathology show impairment with match stimuli secondary to their primary impairment with nonmatch stimuli. Thus, individuals with AD show both match and nonmatch impairment, but persons with MCI show only nonmatch impairment. Consistently, older adults who have experienced cognitive aging show small-magnitude context-dependent attention impairments, but persons with AD show uniform deficits such that involuntary attention-shifting is also affected (Ballesteros, Reales, Mayas, & Heller, 2008; Greenwood, Parasuraman, & Alexander, 1997; Greenwood, Parasuraman, & Haxby, 1993).

Individuals with AD showed greater repetition priming

I found that persons with AD showed the largest benefit from repetition. This finding contributes to the ongoing scientific and clinical effort to characterize the status of nondeclarative memory in AD (Budson, 2009). Similar to the effect of WM, the effect of RP was not associated with performance on standard neuropsychological measures. Reports of increased, stable, and decreased RP in AD have been reported elsewhere in the literature (Chertkow et al., 1994; Klimkowicz-Mrowiec et al., 2008). I propose that the presence of enhanced RP effects in AD in the current study arose from two main sources. First, the RP in our study occurred with very short lag (i.e., 6-10s). Nondeclarative impairment in AD is implicated mainly with longer-lag RP, perhaps due to medial temporal cortical involvement in such effects (Wang, Lazzara, Ranganath, Knight, & Yonelinas, 2010). Second, because the

current task had been made less difficult during protocol development to ensure that persons with AD could complete the task without experiencing undue stress and frustration, relatively few WM cognitive resources were needed to complete the current task. Persons with AD have been reported to show relatively enhanced nondeclarative memory effects when concurrent declarative tasks are minimized (Stark, Gordon, & Stark, 2008). I believe that our results suggest that rapid, short-term repetition has promise for producing positive effects, even in individuals who have already converted to AD. This finding is important because neurocognitive training in AD is normatively limited to persons with MCI based in part on the belief that they are most likely to benefit, and it is rarely prescribed even among such persons (Faucounau, Wu, Boulay, De Rotrou, & Rigaud, 2010; Gates, Sachdev, Fiatarone Singh, & Valenzuela, 2011; Hopper, 2003; Jean et al., 2010; H. Li et al., 2011; Lubinsky, Rich, & Anderson, 2009; Martin et al., 2011; Spector, Woods, & Orrell, 2008; Zanetti et al., 1997). Our result suggests that individuals with AD may also benefit from appropriately-tailored neurocognitive training protocols. The results of the current study, which indicate maintained or enhanced capacity to improve behavioral responses with repetition priming even in persons with AD, may provide the empirical justification for testing priming-based cognitive rehabilitation as a behavioral intervention in persons with MCI or AD.

I feel it necessary to emphasize at this point that I did not observe accuracy changes concurrent with the RT changes resulting from the RP manipulations. Instead, so far as accuracy is concerned, I observed only an overall trend that persons with AD performed more poorly than other participants. In our opinion, the non-significant RP effect on accuracy resulted mainly from a lack of accuracy feedback in the protocol design. I found this protocol design element to be necessary to prevent participants with AD from becoming

frustrated and terminating participation. An important follow-up test will be to devise a non-stressful accuracy feedback mechanism so that the viability of leveraging the RP effect to improve accuracy outcomes in persons with AD may be evaluated. In persons with severe AD, enhanced RP effects have been linked to improved accuracy (Klimkowicz-Mrowiec et al., 2008).

Limitations

The current study contained more women in the AD group, reflective of the epidemiology of AD (Gao, Hendrie, Hall, & Hui, 1998). In our opinion, true gender effects on our data were probably small or absent. Women and men with mild AD do differ in the course of cognitive impairment, but the differences are small and most salient for verbal tasks (Henderson & Buckwalter, 1994; Irvine, Laws, Gale, & Kondel, 2012). Because the current study was a visual memory task rather than a verbal or verbal memory task, these small effects probably had little or no effect on the current findings. Additionally, including gender as a categorical covariate in the statistical analysis did not change the significance of any effects described in this manuscript. Demographic confounds such as age and education produce larger effects, but these effects were matched across groups in the current study (Stern, 2006).

The current study was powered only to detect effects of moderate effect size or greater. In our opinion, effects of smaller than moderate size are unlikely to be of significant clinical interest; however, the current study may have failed to detect smaller effects of theoretical interest. In our opinion, this concern is mitigated by the extremely large RT and accuracy effects observed empirically for individuals with AD. Still, future studies could repeat the current protocol with larger samples to identify small effects of theoretical interest.

The current study used a research participant recruitment technique somewhat different from that which is typical in the neuropsychological literature. For example, rather than the control group coming from the community or from a simple older adult volunteer group, the control participants, like the other participants, were recruited from the Sanders-Brown Memory Clinic, and were part of a group that was evaluated annually for signs of cognitive change. In our opinion, recruiting directly from the memory clinic population in this way may result in a control group that better-resembles the normal older adult control population that presents at memory clinics ecologically relative to traditional recruitment practices; however, the contrast between the control groups should be considered when the results of the current study are compared to those of other studies.

Future directions

An important future direction will be longitudinal follow-up to confirm that the WM retrieval status effect is related to the clinical course of MCI and AD (Collie & Maruff, 2002; Collie, Maruff, & Currie, 2002). Deficits in executive function have been linked to AD conversion from MCI (Rainville, Lepage, Gauthier, Kergoat, & Belleville, 2012). I will also analyze electrophysiological data collected during experimentation to determine the neural mechanisms of the effects presented. Pilot analysis has linked the WM retrieval status effect to frontal cortex, perhaps reflecting compensation for the special difficulty of nonmatch stimuli for MCI (Broster et al., 2011). Pilot quantitative EEG (qEEG) analysis performed with a subset of this cohort has highlighted the potential role of these methods in further differentiating the NC and MCI cohorts (De Bock et al., 2011).

Conclusions

In sum, I have reported that healthy older adults, persons with MCI, and persons with AD show distinct WM performance profiles. Specifically, persons with MCI showed a unique signature where WM retrieval status nonmatch stimuli produced slower RTs, and persons with AD were uniformly slow. This novel effect was consistent with the hypothesis that such stimuli would differentiate persons with MCI from older adults without impairment. Additionally, individuals with AD benefitted disproportionately from RP, perhaps in part due to the short-lags used in the study and to the task's relative simplicity. This effect was consistent with our interpretation that disparate reports of the status of nondeclarative memory effects in AD may be unified by an appreciation that time-latency of repetition manipulation and the influence of complex, concurrent explicit task elements can affect how the nondeclarative memory capacity manifests. These two findings inform efforts for early diagnosis of AD and cognitive interventions for AD, respectively, both of which are crucial for delaying functional AD impairment (Amieva, Letenneur, et al., 2004; Amieva, Rouch-Leroyer, Letenneur, Dartigues, & Fabrigoule, 2004).

Chapter 3: Spared Repetition Effects Linked to an Altered Visual Cortical Mechanism

Adapted from Broster et al., (2015). Altered Neural Repetition Mechanisms during Working Memory Retrieval in Alzheimer's Disease. *Submitted.*

EXECUTIVE SUMMARY

Individuals with dementia of the Alzheimer type (AD) classically show disproportionate impairment in measures of working memory, but repetition learning effects are relatively preserved. As AD affects brain regions implicated in both working memory and repetition effects, the neural basis of this discrepancy is lacking. Participants with AD, amnestic mild cognitive impairment (MCI), and healthy controls performed a working memory task with superimposed repetition effects during retrieval of memory targets and distractors. Participants with AD showed a unique repetition effect at a posteriorly-oriented component. Our results of altered neural repetitions in AD suggest that repetition mechanisms are relatively robust to the course of cognitive aging, but that the repetition effect mechanism manifest at posterior cortex is altered in persons with AD.

Introduction

Repetition Effects and Alzheimer's Disease Pathophysiology

Alzheimer's disease (AD) is associated with deficits in a range of cognitive faculties including explicit memory, language, attention, executive function, and orientation, but some faculties are relatively spared (Baars et al., 2009; Hodges et al., 2006; Wiggs et al., 2006). Among the cognitive capacities relatively spared by Alzheimer's disease are implicit effects such as repetition learning effects, the tendency for the repetition of a stimulus to be associated with altered encoding, processing, and recollection of the subsequent presentation of that stimulus, typically such that the processing becomes more efficient or accurate (Kessels et al., 2011). For example, a repeated stimulus may be processed with more cognitive resources, fewer cognitive resources, different latency of access of cognitive resources, different qualities of cognitive resources, or different behavioral outcomes than upon initial presentation (Gotts, Chow, & Martin, 2012a; Schacter, 1987; Weiner & Grill-Spector, 2012). Distinct types of repetition effects appear differentially sensitive or robust to the progression of AD.

Some types of repetition effects have been reported to be enhanced in AD (Fleischman, Wilson, et al., 2005). Individuals with moderate to severe AD have been reported to have enhanced implicit learning relative to healthy controls in the weather prediction task, where certain apparently-irrelevant symbols with slight correlation to a participant-predicted "weather" outcome unconsciously facilitate participants' subsequent predictions, and their response time (RT) in the delayed-match-to-sample task has been reported to decrease at rates greater than individuals without impairment (Klimkowicz-Mrowiec et al., 2008). Cognitive interventions motivated by purported spared or enhanced

implicit effects in AD have been devised and appear efficacious (Broster et al., 2013; Jean et al., 2010; Mimura & Komatsu, 2010; van Halteren-van Tilborg et al., 2007; Zanetti et al., 1997).

The separability of repetition effects into those that are sensitive to AD and those that are robust to it has been linked to a distinction between anterior and posterior repetition effects, which are believed to process conceptual and perceptual priming capacities, respectively (Fleischman, Wilson, et al., 2005). Conceptual and perceptual priming are impaired relatively early and late, respectively, in the process of AD, consistent with corresponding early and late damage to the cortices believed to implement them (Keane, Gabrieli, Fennema, Growdon, & Corkin, 1991). Understanding the potential mechanism for such sparing may be relevant to developing a neural theory of effective cognitive compensation in AD (Vinogradov, Fisher, & de Villers-Sidani, 2012).

One neural mechanism that may account for such findings is neuroplasticity, the capacity for the function of particular brain regions to change over time, often as a response to damage to a particular region or network. The capacity for this plasticity at the synaptic and neuroanatomical level is intact in persons with MCI or AD (Becker et al., 1996; Belleville et al., 2011; Buckner, 2004). Individuals with a typical presentation of AD or its prodromal clinical state, amnestic mild cognitive impairment (MCI), experience diffuse brain damage beginning at medial temporal cortex before affecting anterior structures and proceeding posteriorly (Lehmann et al., 2011; Scheff et al., 2013). Repetition effects are associated with idiosyncratic modulations in processing throughout cortex both in regions affected early in AD and in regions spared until late in AD pathophysiology. Identifying functional neuroplasticity in regions spared until late in AD pathophysiology relevant to maintained

repetition effects would provide a mechanism for evaluating the extent to which interventions use plasticity to produce a clinical effect.

Characteristics of Neural Repetition Effects

Traditionally, repetition effects were associated with reductions in brain activity or processing speed upon secondary stimulus presentation. However, contemporary models of repetition effects acknowledge that such effects are accompanied by alterations in brain activity that may increase in magnitude, decrease in magnitude, show altered latency, or display some combination of these effects (Gotts et al., 2012a; Gotts, Milleville, & Martin, 2014; Grill-Spector, Henson, & Martin, 2006; Henson, 2012a; Henson & Rugg, 2003; Henson, Rylands, Ross, Vuilleumeir, & Rugg, 2004). The multimodal nature of repetition effects improves the utility of techniques with sufficient resolution in multiple dimensions. Namely, event-related potentials (ERPs) capture temporal and qualitative aspects of repetition effects while maintaining sufficient spatial sensitivity for gross spatial distinctions (e.g., anterior vs. posterior) (Guo et al., 2007; Lawson et al., 2007; Q. Li, Guo, & Jiang, 2008; Race, Badre, & Wagner, 2010).

I assessed repetition effects associated with a delayed-match-to-sample task in healthy controls, individuals with MCI, and individuals with AD. This task has previously been shown to be associated with maintained or enhanced repetition effects in the context of AD (Broster et al., 2013). Because posterior cortex experiences damages relatively late in the clinical course of AD, I hypothesized that the repetition effect manifest in posterior cortex would exhibit neural plasticity in persons with AD such that it would resemble the form of the frontal and temporal repetition effects.

Methods

Participants, Measures and Procedures, and Visual Stimuli

The cohort and procedural methodology in this experiment were equivalent to those previously described in Chapter 2. However, some additional methodological discussion is needed to clarify the processing of the EEG data.

Electrophysiological Data Preprocessing

Electrophysiological data used in this experiment had been partially processed using SCAN 4.5 for reasons unrelated to the current manuscript. This preprocessing consisted of manual artifact rejection, ocular artifact reduction using the NeuroScan regression algorithm, a finite impulse response filter with a band-pass of 0.05 to 40 Hz at 12 dB/octave, epoching at -100 to 1000 ms relative to participant exposure to each stimulus, baseline-correcting to the time-window from -100 to 0 ms relative to stimulus onset, and re-referencing from a midline online reference electrode to an averaged mastoid reference. Then, epochs associated with accurate behavioral responses and electrophysiological activity within ± 75 μV of baseline were averaged for each of the 6 experimental conditions (i.e., the 1st, 2nd, and 3rd presentation of matching or non-matching stimuli).

Those files then underwent bad channel imputation using the ERP PCA Toolkit (EP Toolkit) to prepare the data for temporal PCA (Dien, 2010a). Promax and Infomax rotations were used for the temporal and spatial elements of the procedure, respectively, to permit limited correlation between temporal components, following the recommendation of methodologists (Dien, 2010b). To determine the appropriate number of temporal components to retain, the averaged data was compared to a random dataset, and

components that explained both greater variance than the random dataset and at least 0.5% of variance in the data were retained. Principle components reflecting classical ERP signatures were identified using topographical maps of each component, each component's temporal course, and the effect of the experimental manipulations on each component.

Data Analysis

Behavioral data analysis has been published separately and found that participants with MCI showed greater reaction time (RT) differences between matching and non-matching stimuli and that participants with AD showed a greater difference in RT between initial and repeated stimuli than the other groups (Broster et al., 2013).

For the analysis of the PCA data, the a priori hypothesis was first evaluated. Temporal components were assessed using 2 × 2 × 3 robust ANOVAs on retrieval status (match or non-match), repetition (initial or repeated), and group (NC, MCI, or AD) using the EP Toolkit to identify a posteriorly-oriented component showing a Group × Repetition interaction distinguished by its manifestation in the AD group. Subsequently, post-hoc robust ANOVAs were performed for all principle components using similarly-structured robust ANOVAs. To limit the effect of multiple comparisons on these tests, each ANOVA was conducted only at the peak electrode of the corresponding component, and these tests were supplemented with Bonferroni correction on the number of components tested, where the components to be tested were the components retained as described in *Data Processing*. Uncorrected p value thresholds for each of these analyses are listed in the corresponding section of the online supplemental materials. Simple-effects models were used to interpret interaction effects. All significance values listed are based on two-tailed p values. For the sake

of brevity, results failing to reach one-tailed significance (i.e., $p > 0.1$) have been omitted from the report.

Results

Conventionally-Averaged Waveforms

After processing, the ERP waveforms showed normative characteristics including visual P1, N1, P2, N2, and P3 peaks (Figure 3.1). Upon quick visual gloss, repetition appeared to be associated most clearly with greater P3 mean amplitude (i.e., greater mean amplitude for the positive-going waveform beginning around 300 ms after stimulus onset).

Temporal principal components analysis

To disentangle the effects of visually-overlapping ERP components, I applied temporal PCA to the data to increase the chance that statistical analysis would be conducted on discrete phenomena. Temporal PCA identified 27 temporal components that explained more variance than a random ERP dataset, of which 21 explained at least 0.5% of variance. Of these, the first component to be associated with latency unlikely to be modulated by the experimental manipulations was TF8, which had a latency of earlier than 100 ms. Effects associated with TF8 or lower-order factors were not included in the current analysis, but their temporal peaks have been recorded in Table A1 of the Appendix. The grand averages of the first seven temporal factors at a frontal and posterior electrode have been shown in Figure 3.2.

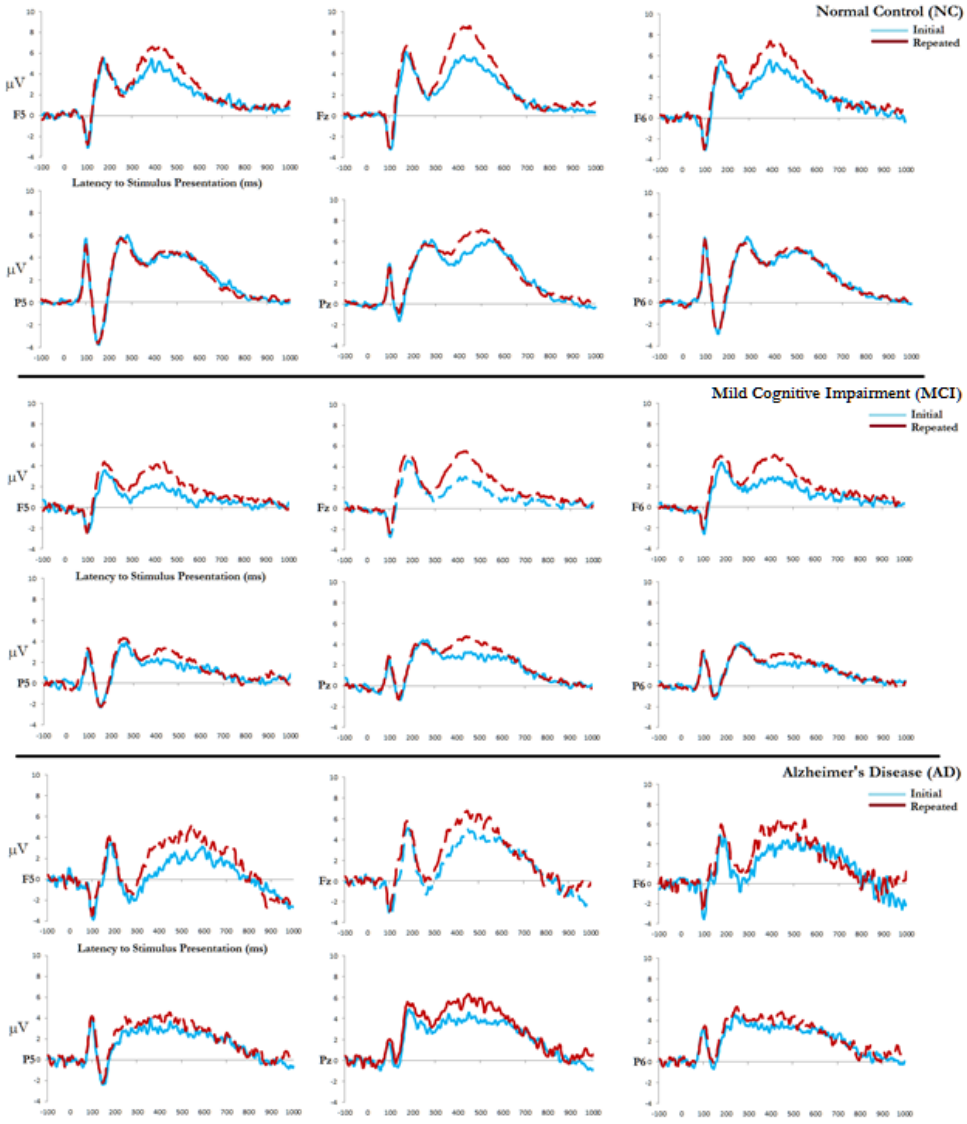

Figure 3.1: Conventional ERPs in Experiment 1. **This figure depicts the grand average waveforms in each clinical group for the initial and repeated instances of visual stimuli at 6 standardized electrodes (i.e., F5, Fz, F6, P5, Pz, and P6). Each set of 6 graphs depicts 6 electrodes: the first row in each set depicts electrodes from the left, middle, and right side of the scalp at frontal sites, and the second row in each set similarly depicts electrodes at posterior sites. The waves show normative features including classical components such as a posterior P1, N1, P2, N2, P3, and LPC; however, some components appear to overlap temporally, suggesting that a temporal principal components analysis approach might be helpful in deconvoluting independent components.**

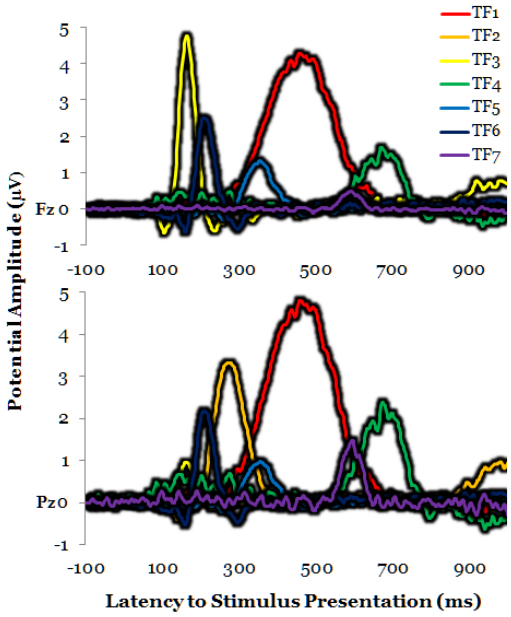

Figure 3.2: Summary of ERP PCA Solution for Experiment 1. This figure shows the grand average of the first seven temporal factors (TF) at Fz (top) and Pz (bottom) across all groups and conditions. Individual factors are color-coded along a warm-cool axis in accordance with their ordinal factor number. In particular, please note the uniquely posterior orientation of the second temporal component (TF2). This component reaches its maximum amplitude of only 0.4 μV at Fz; consequently, it is inscrutable among the noise associated with other temporal factors at the frontal electrode.

A Priori Analysis

First, I assessed the a priori hypothesis that a posterior repetition mechanism would manifest uniquely in the AD group. Statistically, this was assessed by identifying an ERP component estimated as a PCA factor that evidenced a significant interaction between the clinical group and repetition robust ANOVA factors.

Of the first seven temporal factors (i.e., the factors associated with a temporal course plausibly linked to the experimental manipulations), only TF2 was associated with a significant interaction between clinical group and repetition, T_{WJt}/c (2.0, 28.4) = 2.78, p = 0.04. This was a positive-going, posteriorly-oriented component peaking at 272 ms and maximal at PO6 at which individuals without impairment or with MCI showed repetition

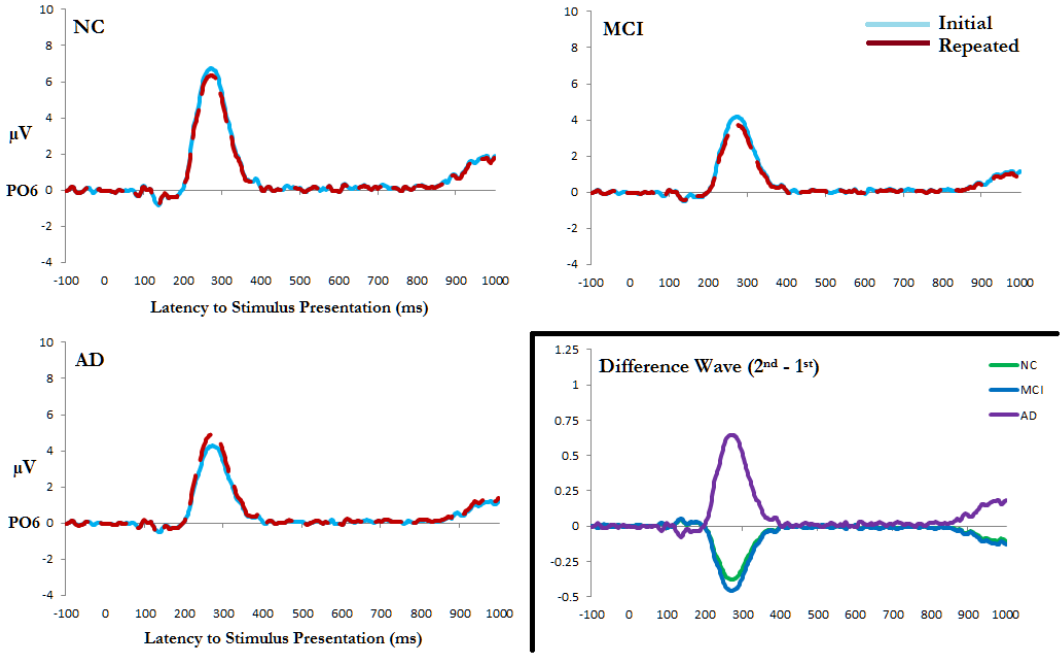

Figure 3.3: Summary of distinguishing Alzheimer's disease repetition effect. This graph summarizes the unique posterior effect in the AD group. The separate event-related potentials to the initial and subsequent presentation of stimuli are graphed for the NC, MCI, and AD groups, and the difference waves between those conditions (subsequent – initial) are shown together in the bottom-right quadrant. Individuals with AD showed a larger subsequent potential.

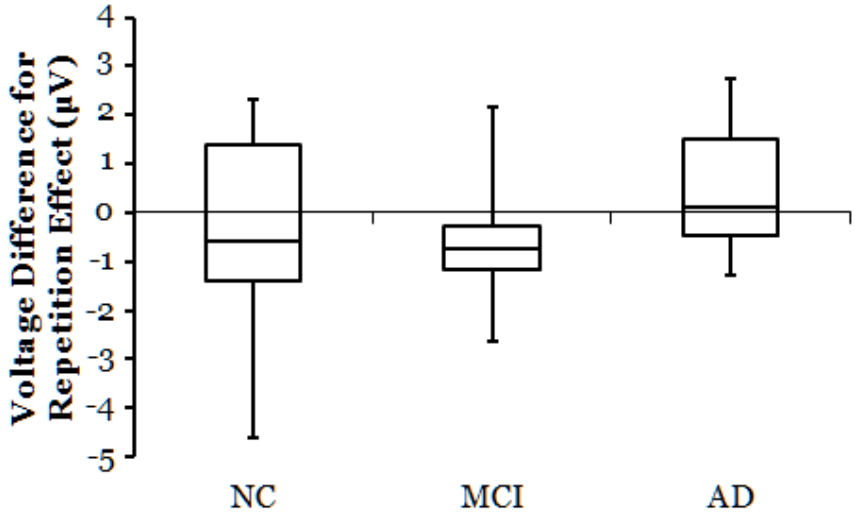

Figure 3.4: Box-plot of distinguishing Alzheimer's disease repetition effect. This box-and-whiskers graph shows the five-point summary of the unique posterior effect. Positive values indicate that the secondary presentations of an image were associated with a larger amplitude than the initial presentation (i.e., 2nd > 1st). The boxes depict the first quartile, median, and third quartile for the NC, MCI, and AD groups, respectively, while the error bars depict the minimum and maximum value for each group. Individuals with AD showed a more positive mean amplitude difference than the other groups.

decrement of about 0.4 - 0.5 μV, but individuals with AD showed repetition enhancement of about 0.7 μV, F (1,43) = 4.37, p = 0.02, η_p^2 = 0.09 (Figures 3.3 and 3.4). This interaction was non-significant for other factors (ps > 0.1).

Post-Hoc Analysis

In addition to testing the a priori hypothesis, atheoretical post-hoc tests were performed by evaluating robust ANOVAs at the peak electrode of each temporal component of higher order than the first component likely to be associated with spurious effects as previously described (i.e., for temporal factors 1 through 7). For these analyses, Bonferroni correction was applied on the number of components evaluated, resulting in a significance threshold of 0.007 for post-hoc tests. Uncorrected p values have been recorded below.

TF1, a positive-going waveform peaking at 458 ms, was associated with main effects of retrieval status, T_{WJt}/c (1.0, 29.1) = 11.47, p = 0.0027, and repetition, T_{WJt}/c (1.0, 33.3) = 40.50, p = 0.00002, such that non-match stimuli and repeated stimuli were associated with a more positive-going waveform. TF2, a positive-going waveform peaking at 272 ms, was not associated with significant effects other than the effect described in the a priori analysis section. TF3, a positive-going waveform peaking at 162 ms, was associated with a main effect of repetition, T_{WJt}/c (1.0, 28.4) = 13.53, p = 0.001, such that repetition was associated with a more positive-going waveform. TF4, a positive-going waveform peaking at 672 ms, was associated with a main effect of retrieval status, T_{WJt}/c (1.0, 42.1) = 35.05, p < 0.00000001, such that distractor stimuli were associated with a more positive-going waveform. TF5, a positive-going waveform peaking at 354 ms, was associated with main effects of retrieval status, T_{WJt}/c (1.0, 29.2) = 18.16, p = 0.00034, and repetition, T_{WJt}/c (1.0,

37.4) = 13.53, p = 0.00062, such that match stimuli and repeated stimuli were associated with a more positive-going waveform. TF6, a positive-going waveform peaking at 208 ms, was associated with a main effect of retrieval status, T_{WJt}/c (1.0, 38.7) = 15.78, p = 0.00064, qualified by a significant retrieval status X repetition interaction, T_{WJt}/c (1.0, 27.9) = 10.39, p = 0.0048, such that upon initial presentation distracter stimuli were associated with a more positive-going waveform, T_{WJt}/c (1.0, 40.2) = 26.67, p < 0.00000001, but upon subsequent presentation this difference was non-significant, T_{WJt}/c (1.0, 31.4) = 2.25, p = 0.14. TF7, a positive-going waveform peaking at 594 ms, was associated with a main effect of retrieval status, T_{WJt}/c (1.0, 37.2) = 9.33, p = 0.0048, such that distracter stimuli were associated with a more positive-going waveform.

Other main effects and interactions were non-significant after Bonferroni correction.

Integrated Data Analyses

The repetition effect identified at temporal factor 2 was correlated with the neuropsychological scores and behavioral repetition effects previous presented in Chapter 2 (Table 2.1). All such correlations were non-significant (ps > 0.1).

Discussion

Our results implicate an AD-related difference in an early, posterior repetition effect mechanism – whereas repetition was associated with a reduced effect at this site in participants without AD, it was associated with an enhanced effect in participants with AD. The repetition enhancement in AD was consistent with the manifestation of this effect for frontally and temporally-oriented components (e.g., TF1, TF3, TF5). The sensitivity of the posterior mechanism to pathological cognitive aging departs somewhat from previous

findings that the posterior repetition effect mechanism is robust to cognitive aging. Consistent with classical descriptions of the posterior mechanism, it was amodal with respect to stimulus retrieval status; that is, whether a stimulus was a working memory match or nonmatch did not significantly modulate the repetition effect waveform (Guo et al., 2007).

This finding mirrors some reports that individuals with AD show unique behavioral capabilities when handling short-lag repetition effects, even relative to individuals with milder impairment. Individuals with AD have been shown to disproportionately improve RT with repetition in this paradigm, and they have similarly been reported to benefit most from implicit learning in a weather prediction paradigm (Broster, Blonder, & Jiang, 2012; Broster et al., 2013; Klimkowicz-Mrowiec et al., 2008). However, to the best of our knowledge, the maintenance or enhancement of these behavioral phenomena had not previously been linked to any particular neural mechanism.

In our opinion, the current finding suggests a solution for this issue. Even though persons with a clinical AD diagnosis have experienced widespread cortical damage, the relative sparing of the posterior cortex in general and the posterior repetition effect in particular during the course of the pathophysiology of AD may have allowed for a plastic response at that mechanism that accounts for behavioral sparing or enhancement of such effects. In other words, enhancement of the posterior repetition effect occurs due to damage to other repetition effects at parts of cortex damaged earlier in the course of AD, and this plasticity accounts for the relative sparing of repetition effects in AD.

To our knowledge, the current report of occipital plasticity in mild AD has not been previously reported in the literature. Instead, to the extent that particular patterns of neural compensation are proposed, prefrontal compensation tends to be linked to maintained

behavioral performance in MCI and mild AD, though the interpretation that this activity reflects compensation is not without controversy (De Vogelaere, Santens, Achten, Boon, & Vingerhoets, 2012; Frantzidis et al., 2014; Jacobs et al., 2015; Liang, Wang, Yang, Jia, & Li, 2011; Qi et al., 2010). The novelty of the current effect in the literature may be due to the uniqueness of the current cohort and experimental design. Most studies that have identified the potential frontal compensatory response have observed it in the context of normal aging or MCI, and studies that have purported to see it in individuals with dementia have been relatively inconsistent. Individuals with mild AD may show secondary cortical damage in frontal cortex relative to individuals with normal aging or MCI, which could account for secondary compensatory mechanisms at occipital cortex, which is relatively spared until individuals have moderate to severe dementia. Further, studies targeting repetition effects in the context of a concurrent memory task have been rare in such groups. The current repetition effect compensatory pattern may be evoked by the need to manage neural resources given concurrent working memory processing demands on frontal resources.

Not all studies have reported that individuals with AD have intact or enhanced repetition effects. In fact, many studies have reported that persons with AD have impaired repetition effects. A major variable differentiating many of the studies of repetition effects in AD is the amount of time-lag between repetitions in the paradigm. In addition to other sources of variation including modality and differences in the EEG topography of interest, studies that have shown repetition effect impairment in AD have tended to involve somewhat longer-lag repetition effects than the 10-12 second repetitions used in the current study, or the implicit task is correlated with an explicit one (Broster et al., 2013; Olichney et al., 2006; Olichney et al., 2002; Olichney et al., 2013; Olichney et al., 2008). In such cases, impairment seen in persons with AD may reflect explicit memory encoding deficits or

primary explicit deficits, respectively, rather than a deficit in repetition effects per se, and those deficits may serve as useful diagnostic tools (Fleischman, Wilson, et al., 2005; Olichney et al., 2008).

In addition to the finding in the posterior repetition effect mechanism, the post-hoc analysis identified multiple independent temporal components capturing variance classically linked to the P2, N2, P3, and LPC that showed unique types of repetition effects depending upon the temporal course of the component. For example, most components were associated with repetition enhancement (i.e., a more positive-going wave following repetition), but TF6 showed a retrieval status-dependent repetition suppression. These findings support the theory that the memory context of a repeated stimulus and the temporal and spatial location of a repetition effect mechanism can produce qualitatively-distinct signatures, as in the difference between models such as Bayesian explaining away, sharpening, or scaling models of repetition effects (Gotts et al., 2012a). Further, the posterior repetition effect mechanism indicates that the cognitive status of an individual can also influence the quality of repetition effects within a given mechanism and stimulus type.

The current results are consistent with the clinical perspective that persons with AD may retain sufficient plasticity and brain function to benefit from appropriately-tailored interventions targeting the relatively intact posterior repetition effect mechanism. Interventions with these characteristics exist and have apparent efficacy, but are not routinely prescribed (Hopper, 2003). This reality has been linked to the early history of failed cognitive interventions in AD that focused on explicit interventions on the theory that the intervention should directly strengthen the impaired memory capacity. The current results

provide a way to understand a potential mechanism for repetition effect-oriented cognitive interventions in AD.

The current cohort included a disproportionate number of women in the AD group. As a result, gender is a potential confound for differences related to the AD group in particular. I are unaware of any theoretical or empirical basis for attributing the current posterior repetition effect finding to gender; most gender differences in the pathophysiological of cognitive aging have been related to verbal capacities not relevant to the current paradigm (Broster et al., 2013). However, replication of the current finding with a gender-balanced cohort will be necessary to help rule-out this potential confound.

In sum, I report that an "amodal" posterior repetition effect mechanism manifests in a qualitatively different fashion in persons with AD, perhaps reflecting plasticity secondary to cortical damage. I suggest that this phenomenon may account for the behavioral sparing or enhancement of repetition effects in the clinical course of AD for many empirical paradigms, including the paradigm used in the current study. I hope that the current results will contribute to a theoretical basis for believing that persons with AD retain a meaningful capacity to benefit from cognitive intervention (Vinogradov et al., 2012).

Chapter 4: Working Memory Restores Emotional Repetition Effects in Persons with Mild Cognitive Impairment

Adapted from a manuscript in preparation

EXECUTIVE SUMMARY

While previous chapters of this dissertation have identified spared repetition effects in MCI and AD along with related cognitive plasticity, other researchers have emphasized that an absence of neural repetition effects is a hallmark of AD that manifests early in its pathophysiological course. I hypothesized that this disconnect might result from manifestation of the neural repetition effect capacity in MCI only in the context of a concurrent working memory task. Participants with and without amnestic mild cognitive impairment performed two emotionally-valenced tasks: one with a working memory task, and one with a distracter content-identification task. Results indicated that the experiments evoked similar neural components, but that repetition effects for the MCI group were present only for the P600 component, which was uniquely evoked by the emotional working memory task. I suggest that cognitive challenge can expose neural capabilities of individuals with MCI that might have appeared extinct.

Keywords: cognitive challenge, event-related potential, Alzheimer's disease, mild cognitive impairment, IAPS, repetition effect, working memory

Introduction

Repetition effects, which encompass unconscious alterations in behavior, memory, or cognitive processing of a phenomenon upon repeated exposure, have been purported to have myriad statuses in the context of dementia due to Alzheimer's disease (AD) and its clinical prodrome, amnestic mild cognitive impairment (MCI) (Fleischman, 2007; Fleischman & Gabrieli, 1998). In the weather prediction task, where individuals unconsciously learn associations between symbols and a "weather" outcome by repetition, people with moderate to severe AD show enhanced implicit effects relative to older adults without impairment, and related implicit effects are spared across a range of domains relative to explicit memory capacities such as working memory, especially for short-term implicit effects (Kessels et al., 2011; Klimkowicz-Mrowiec et al., 2008; Mitchell & Schmitt, 2006). Individuals with AD also appear to show enhanced or spared repetition effects in the context of word-choice, short-term priming, and visual delayed-match-to-sample working memory tasks (Broster et al., 2013; Kazmerski & Friedman, 1997; Schnyer, Allen, Kaszniak, & Forster, 1999), and this sparing has been linked to apparent cognitive plasticity at posterior cortex (Broster et al., 2015).

Sparing of repetition effects or other aspects of implicit memory in AD has been linked to cognitive rehabilitation interventions that proffer benefits to individuals with AD (Jean et al., 2010; Kessels & de Haan, 2003a, 2003b; Lubinsky et al., 2009; Mimura & Komatsu, 2010; van Halteren-van Tilborg et al., 2007; White, Ford, Brown, Peel, & Triebel, 2014; Zanetti et al., 1997). For example, implicit memory-based paradigms such as errorless learning and procedural memory stimulation have shown special promise in clinical contexts, and they have performed better than similar interventions such as effortful learning that included additional concurrent explicit elements (Mimura & Komatsu, 2010). These findings

indicate that the question of the status of repetition effects and implicit effects is more generally relevant to potential untapped clinical impact in persons with AD (Hopper, 2003).

Simultaneous with the considerable evidence of spared behavioral, cognitive, or clinical effects of repetition in AD, an absence of late electrophysiological repetition effects has been proposed as a biomarker of AD (Olichney et al., 2006; Olichney et al., 2002); its preceding clinical stage, MCI (Olichney et al., 2008); and even *its* preceding clinical state, sometimes called pre-Alzheimer's disease (pre-AD) (Olichney et al., 2013). In these studies, individuals without impairment show a marked voltage difference in late event-related potentials (ERPs) evoked by repeated and initially-presented stimuli, but individuals with various stages of AD showed an absent or disrupted difference between ERPs to such stimuli. In these experiments, word stimuli were displayed to participants, participants made a judgment about the content of each word, and individual stimuli were re-tested after a delay ranging from several seconds to about 2 minutes. The effect has proven to be reliable through multiple experiments and cohorts and has been reported to discriminate between pre-AD and individuals without impairment with 84% accuracy (Olichney et al., 2013).

The status of repetition effects in AD and their reliability as a biomarker is an important clinical and experimental question. If these effects are reliably intact to an interesting extent in early AD, they represent an unappreciated clinical opportunity (Hopper, 2003). On the other hand, if the reports of spared or enhanced effects are unreliable for whatever reason (e.g., being apparent only in cohorts with idiosyncratic characteristics), characterizing the source of the sparing to identify the scope of the effect would be valuable from a clinical perspective and direct future experimentation probing the effect.

One potential theme that may account for the discrepancy is that the word repetition paradigms that have found a lack of late repetition effects during AD were concurrent with a

task that required participants to make fact-based content judgments about the current stimulus (Fleischman, 2007). By contrast, the repetition effects implicit in the weather prediction and delayed-match-to-sample tasks were concurrent with explicit tasks requiring participants to speculate about an outcome or recall items held in working memory, respectively (Broster et al., 2011; Broster et al., 2013; Klimkowicz-Mrowiec et al., 2008). In other words, cognitive challenge appears to evoke a neural capacity for which repetition effects are spared.

In evaluating this possibility, it is helpful for the reader to be briefly acquainted with the somewhat complicated nature of "repetition effects" as I are describing them in slightly more detail. While often described as if a monolithic capacity, repetition effects are instantiated through multiple neural mechanisms that may or may not correlate with a traditional "repetition priming" behavioral output (Gotts et al., 2012a; Gotts, Chow, & Martin, 2012b; Grill-Spector et al., 2006; Henson, 2012b). For example, when speaking of how repetition effects manifest in cognitive processing, individual such effects may manifest as increased measurements, decreased measurements, quickened effects, or some combination of these, and, even within a certain individual, multiple discrete repetition effects may be measured depending upon the time and space of the measurement (Grill-Spector et al., 2006). Therefore, even among neural repetition effects, it is necessary to clarify which such effect is meant. Further, even if a particular neural repetition effect occurs in one fashion (e.g., via increased measurements), it does not entail that all neural repetition effects show the same such effect.

These observations are helpful for a few reasons. First, they clarify that I anticipate seeing multiple neural mechanisms be responsive to repetition effects. Second, they clarify I do not anticipate that individual effects will be similar in manifestation (e.g., some may

become larger with repetition while others become smaller with repetition). Finally, to the extent that all neural mechanisms are task-dependent, I do not necessarily anticipate that the same neural mechanisms will be prominent in every experiment that incidentally includes a repetition effect manipulation (Grill-Spector et al., 2006).

In the current experiment, participants performed 2 experiments that incorporated implicit repetition effects: one where participants performed a content-judgment task, and one where participants performed a delayed-match-to-sample working memory task. To assess the possibility that differences in levels of emotional content might interfere with the manifestation of repetition effects in the context of AD (Borg et al., 2011; Kazui et al., 2003; May, Manning, Einstein, Becker, & Owens, 2015), both tasks used stimuli that were differentially emotionally-valenced to further interrogate proposed moderators of differential manifestation of repetition effects in AD (Zhang, Lawson, Guo, & Jiang, 2006).

Methods

Participants

32 older adult participants – 16 with amnestic mild cognitive impairment (MCI), 16 with normal cognitive status (NC) – participated in experimental protocols. All NC participants were the spouse or long-term partner of an individual with amnestic mild cognitive impairment; hence, individual MCI participants were matched with their unaffected spouse for purposes of analysis. Of the participants, 22 were members of the University of Kentucky Alzheimer's Disease Center (UK-ADC) longitudinal clinical cohort while 10 were recruited from the Kentucky Neuroscience Institute (KNI) at the University of Kentucky. Recruiting directly from tertiary care memory clinics reduces the risk that cognitive effects observed result from non-AD memory impairment conditions such as

thyroid or vitamin B_{12} deficiency (Jicha et al., 2008; Luck et al., 2007). Individuals in the UK-ADC cohort are assessed every year (prior to clinical change) or every 6 months (subsequent to clinical change) with a battery of neuropsychological tests including the Uniform Data Set (UDS) and Geriatric Depression Scale, Short Form (GDS15). For participants who were part of the UK-ADC cohort, the UDS scores collected most proximal in time to research participation were consulted as descriptors of the cognitive status of participants; for participants who were recruited directly from KNI, research personnel trained in the administration of the UDS collected the UDS and GDS15 data on-site. One spousal dyad elected not to perform the on-site neuropsychological testing, so those two participants have been omitted from related analyses in this manuscript. Because other missing data were sparse, missing neuropsychological data was handled using the expectation-maximization (EM) algorithm. Summarized neuropsychological findings and associations are included as part of Table 4.1.

In keeping with contemporary clinical criteria (Albert et al., 2011; Arsenault-Lapierre et al., 2011; Lekeu et al., 2010; Reid & Maclullich, 2006), MCI was indicated by A) absence of dementia, B) absence of cognitive, clinical, or behavioral symptoms consistent with sources of non-amnestic cognitive impairment, and C) objective memory impairment evidenced by performance more than 1.5 standard deviations below age-standardized normal values on at least one of several memory measures including Wechsler Memory Scale Logical Memory (WMS-R), the California Verbal Learning Test (CVLT-II), and the Benton Visual Retention Test (BVRT-5, Forms C & D). AD was diagnosed using Alzheimer's Disease Dementia Workgroup criteria, which hold, briefly, that insidious-onset dementia is present in the absence of another psychiatric or neurological condition (McKhann et al., 2011). All participants were recruited directly from the tertiary care setting and had received

comprehensive work-up to rule-out other psychiatric or neurological causes of cognitive impairment. Individuals with MCI had been diagnosed within 12 months of data collection, all research participants had been evaluated clinically within 12 months of data collection, and all research participants were evaluated clinically on an annual basis to check for conversion to MCI. In other words, all participants were clinically evaluated both prior to and subsequent to research participation to confirm their clinical status. All participants were between age 65 and 92 with visual acuity better than 20/50 with corrective lenses in at least one eye. Exclusion criteria included history of stroke; epilepsy; head trauma; CNS infection, chronic infectious disease; psychiatric illness including substance abuse, major depression, or other mood disorder; or other neurological disease (Robert et al., 2006). Participants taking medications known to affect cognitive function, such as sedatives or opiates, were similarly excluded.

During initial screening for recruitment, individuals who reported themselves to be left-handed were excluded to reduce the risk that associated hemispheric ERP effects might be interpreted. However, during subsequent on-site re-screening, it was determined that two participants were actually initially left-handed, but had been forced to learn to write right-handed early in life. Because these individuals were balanced in terms of their cognitive status (i.e., one NC, one MCI), I decided not to exclude their data from the analyses.

Table 4.1: Neuropsychological summary and associated correlations for effects in Chapter 4. NC = normal control, MCI = amnestic mild cognitive impairment, AD = Alzheimer's disease; N = number of participants, Females = number of female participants, Age = age of participant in years, Education = formal education of participants in years; MMSE = mini-mental status examination, LOGIMEMI = Logical Memory Story A, Immediate Recall, LOGIMEMII = Logical Memory Story A, Delayed Recall, DIGIF = Digit Span Forward, DIGIFLEN = Digit Span Forward Length, DIGIB = Digit Span Backward, DIGIBLEN = Digit Span Backward Length, ANIMALS = Category Fluency (Animals), VEG = Category Fluency (Vegetables), TRAILA = Trailmaking A, TRAILB = Trailmaking B, DSYM = Digit Symbol, BOSTON = Boston Naming Task, GDS15 = Geriatric Depression Scale, short-form; df, F/χ2, p, and ϱ indicate statistical summaries for the omnibus tests of group differences for each column. Welch's robust test of means was used for measures showing heterogeneity of variance. Variance displayed is the standard error of the mean (SEM) for each group. Because behavioral and electrophysiological repetition effects were empirically associated with interactions of clinical group, correlations depicted compare within-dyad differences in neuropsychological test scores with within-dyad differences in individual repetition effects. To reduce the impact of differential violations of normality assumptions, Spearman's ϱ was used to assess correlations of each neuropsychological test with the behavioral and primary electrophysiological repetition effect in each experiment. For all neuropsychological tests except for TRAILA, TRAILB, and the GDS15, a larger score indicates better performance, whereas the opposite is true for TRIALA/B and the GDS15. Hence, the signs of correlations of TRAILA/B and GDS15 have been reversed in this chart for ease of interpretation. Positive ϱ values indicate that large differences in the neuropsychological status of individuals in a dyad were related to large differences in the size of the relevant repetition effect; negative ϱ values indicate that large differences in the neuropsychological status of individuals in a dyad were related to small differences in the size of the relevant repetition effect. Because missingness was relatively rare in this dataset, the expectation-maximization (EM) algorithm was used to impute missing variables using existing behavioral and neuropsychological data where actionable. Two individuals (one MCI, one NC) did not participate in neuropsychological testing, so they were excluded from that process and from these analyses. For the analogous correlations with the main behavioral and electrophysiological repetition effect in Experiment 3, all correlations were non-significant (ps > 0.1) apart from a spurious association with GDS15 scores due to zero-inflation in that sample; consequently, for the sake of readability, those correlations have been omitted from this table.

	N	*Females*	*Age*	*Education*	*MMSE*	*LOGIMEMI*	*LOGIMEMII*	*DIGIF*	*DIGIFLEN*	*DIGIB*	*DIGIBLEN*	*ANIMALS*	*VEG*	*TRAILA*	*TRAILB*	*DSYM*	*BOSTON*	*GDS 15*
NC	16	9	76.7 ± 1.4	16.7 ± 0.7	28.8 ± 0.3	14.1 ± 1.0	12.7 ± 1.1	8.0 ± 0.7	6.3 ± 0.3	6.1 ± 0.6	4.7 ± 0.3	19.6 ± 1.2	14.8 ± 0.9	37.5 ± 3.0	82.3 ± 5.5	40.9 ± 2.6	27.0 ± 1.6	1.0 ± 0.4
MCI	16	7	77.2 ± 1.5	17.1 ± 0.9	26.2 ± 0.7	7.4 ± 0.8	6.4 ± 1.0	8.7 ± 0.5	6.9 ± 0.2	5.9 ± 0.5	4.6 ± 0.2	13.6 ± 1.5	9.1 ± 0.8	54.4 ± 6.5	181.2 ± 21.9	32.9 ± 4.1	23.6 ± 1.1	2.0 ± 0.9
df		1	1, 30	1, 30	1, 18.3	1, 28	1, 28	1, 28	1, 28	1, 28	1, 28	1, 28	1, 28	1, 20.6	1, 17.0	1, 28	1, 28	1, 28
F/χ^2		0.5	0.06	0.14	7.76	20.98	20.75	0.94	2.39	0.03	0.10	8.75	18.53	3.45	11.80	0.0003	5.94	2.66
p		0.72	0.81	0.71	0.01	< 0.001	< 0.001	0.34	0.13	0.87	0.76	0.006	< 0.001	0.08	0.003	0.99	0.02	0.11
Correlation:			ϱ		.591	.507	.560	.052	.113	.063	-.030	.735	.405	.580	.658	.576	.764	-.004
Behavioral Repetition Group Difference Experiment 2			*p*		.016*	.045*	.024*	.849	.677	.816	.913	.001**	.120	.019*	.006**	.019*	.001**	.987
Correlation:			ϱ		.454	.611	.523	.254	.278	.396	.266	.257	-.065	.424	.497	.371	.359	.121
LPP Repetition Effect Group Difference			p		.077	.012*	.038*	.343	.297	.128	.319	.337	.810	.102	.050*	.158	.172	.656

Measures and Procedures

All participants performed two tasks: an affective repetition task, and a working memory task. Additionally, all but two participants either made the neuropsychological data from their most proximal UK-ADC visits available to research personnel or agreed to undergo equivalent neuropsychological testing on-site, as actionable.

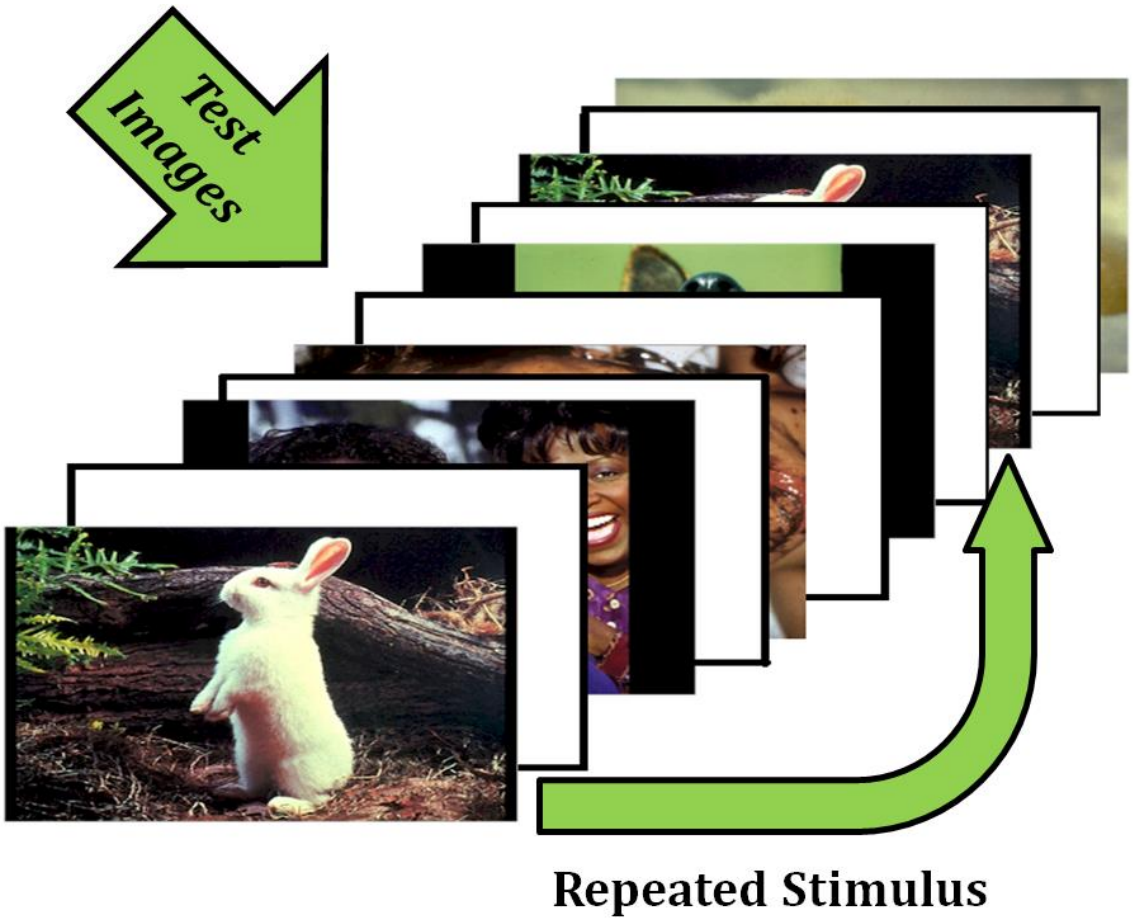

Figure 4.1: Experiment 2 Schematic. This schematic summarizes the typical course of the affective repetition paradigm. Participants indicate whether the content of each image includes humans or human parts, and individual images are all repeated exactly twice after variable lag. Individual images differed in their hedonic valence and arousal levels (i.e., low arousal positive, LAP, or high arousal negative, HAN).

For the first task, participants performed an affective repetition task while electroencephalography was performed. Participants observed images from the International

Affective Picture System (IAPS) and performed a distractor task of judging whether images contained human or human parts (hereafter, "HHP"), and individuals emotional images were tested multiple times with variable image lag (Figure 4.1). Participants pressed the "A" and "L" keys on a keyboard to indicate each response. To reduce the difficulty of the task for participants less familiar with use of keyboards, all other keys on the keyboard had been removed. Incorporating multiple memory faculties into a single paradigm, as in the emotional enhancement effect-repetition paradigm used in the current study, facilitates the interpretation of any interaction effects observed (Kennedy et al., 2009; Voss & Paller, 2008, 2009).

360 trials were performed altogether in 3 blocks of 120 trials each. Each block lasted approximately 7 minutes and included periodic "rest" periods of approximately 10s. Each trial consisted of the presentation of a single image, and each image in the study was tested exactly 3 times. Images were presented with a pseudorandom presentation sequence with respect to stimulus type. The hand used to indicate each HHP response was balanced within-participants, within-dyads, and between-dyads. That is, the hand that participants would use to indicate whether HHP were included in each image were switched between blocks (e.g., if it was "A" during block 1, it would become "L" during block 2); for each dyad of participants, the initial key used to indicate HHP being present was counterbalanced (e.g., if the participant with MCI used "A" during block 1, his or her spouse sued "L" during block 1); and for each alternating dyad of participants, the initial key used by the MCI participant in the dyad was counterbalanced (e.g., if the participant with MCI in the first dyad used "A" during block 1, the participant with MCI in the second dyad used "L" during block 1). Participants took a short, self-paced break between blocks that typically lasted about 60 seconds. During this time research personnel confirmed the comfort of

participants and provided encouragement to participants that included reassurance about the ambiguity and difficulty of the task for some of the stimuli. In this experiment, the ongoing task was intended primarily to ensure that participants remained focused on the content of the images to ensure their affective impact, and the ongoing task was not correlated with the implicit emotional manipulation employed (cf., *Visual Stimuli*). Hence, participants did not receive accuracy feedback.

Because of the relative simplicity of the task and in the interest of participants' time, participants were not required to perform a practice session before participating in this task unless they elected to. No participants elected to participate in a practice session for this task.

For the second task, participants performed an affective delayed-match-to-sample task with repetition while electroencephalography was performed (Figure 4.2). During each trial, participants were first shown two sample images surrounded by a green border and were subsequently directed to indicate whether sequentially-presented images matched a sample image. Participants pressed the "A" and "L" keys on a keyboard to indicate matching or non-matching responses. To reduce the difficulty of the task for participants less familiar with use of keyboards, all other keys on the keyboard had been removed. Incorporating multiple memory faculties into a single paradigm, as in the emotional enhancement effect-repetition paradigm used in the current study, facilitates the interpretation of any interaction effects observed (Kennedy et al., 2009; Voss & Paller, 2008, 2009).

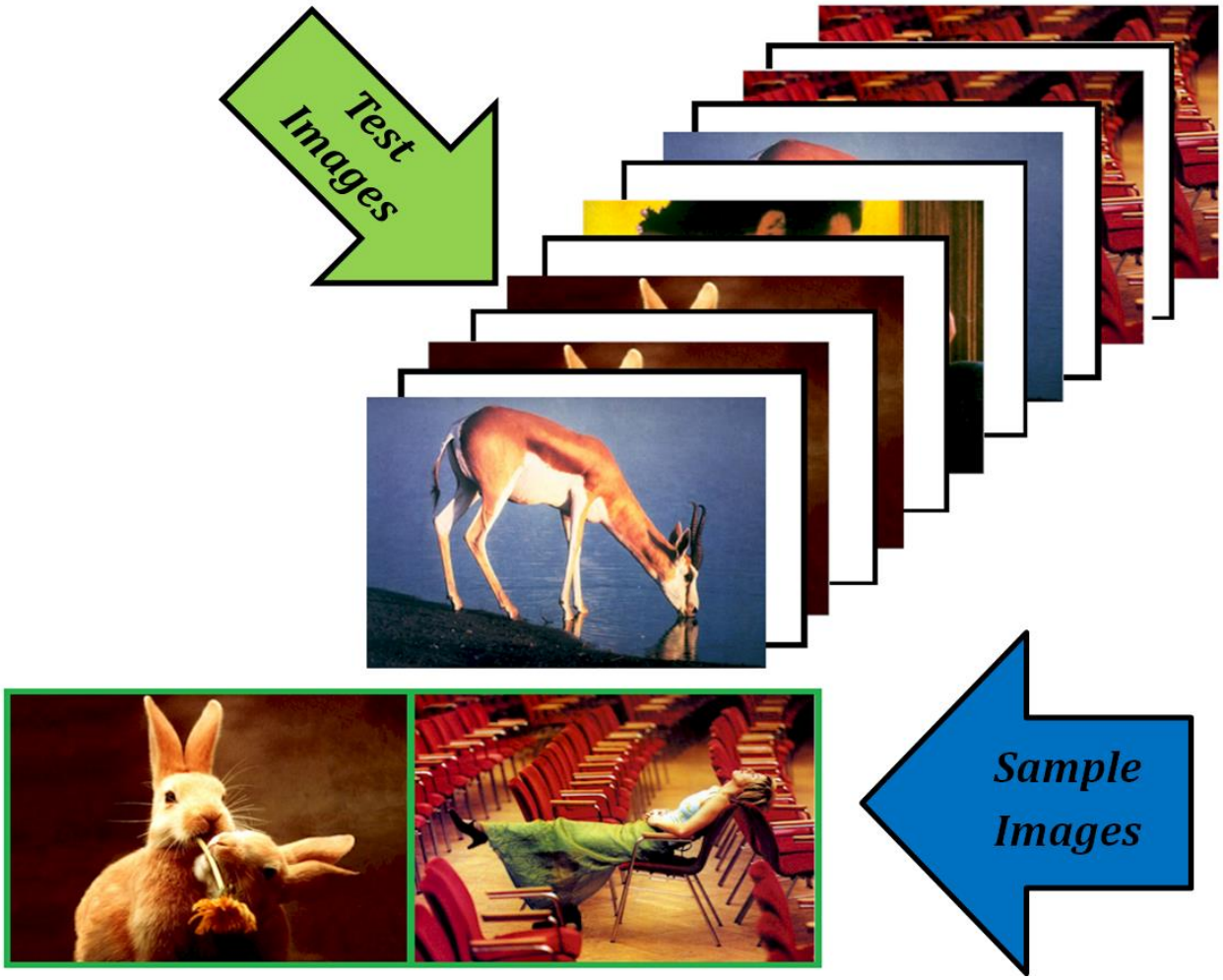

Figure 4.2: Experiment 3 Schematic. **This figure summarizes a typical trial in the current experiment. First, two sample images are displayed with a green border, and participants are directed to commit these images to memory. Then, text images are displayed one-by-one, and participants indicate whether each image was among the sample images from that trial by keyboard press.**

For the second task, participants performed an affective delayed-match-to-sample task with repetition while electroencephalography was performed (Figure 4.2). During each trial, participants were first shown two sample images surrounded by a green border and were subsequently directed to indicate whether sequentially-presented images matched a sample image. Participants pressed the "A" and "L" keys on a keyboard to indicate matching or non-matching responses. To reduce the difficulty of the task for participants less familiar

with use of keyboards, all other keys on the keyboard had been removed. Incorporating multiple memory faculties into a single paradigm, as in the emotional enhancement effect-repetition paradigm used in the current study, facilitates the interpretation of any interaction effects observed (Kennedy et al., 2009; Voss & Paller, 2008, 2009).

384 trials were performed altogether in 4 blocks of 96 trials each. Each block lasted approximately 5.5 minutes and included periodic "rest" periods of approximately 10s. Each image in the study was tested 2-4 times, and images were presented with a pseudorandom presentation sequence. The hand used to indicate a "match" response was balanced within-participants, within-dyads, and between-dyads. That is, the hand that participants would use to indicate a match was switched between blocks (e.g., if it was "A" during block 1, it would become "L" during block 2); for each dyad of participants, the initial key used to indicate a match was counterbalanced (e.g., if the participant with MCI used "A" during block 1, his or her spouse sued "L" during block 1); and for each alternating dyad of participants, the initial key used by the MCI participant to indicate a match in the dyad was counterbalanced (e.g., if the participant with MCI in the first dyad used "A" during block 1, the participant with MCI in the second dyad used "L" during block 1). Participants took a short, self-paced break between blocks that typically lasted about 60 seconds. During this time research personnel confirmed the comfort of participants and provided encouragement to participants that included reassurance about the ambiguity and difficulty of the task for some of the stimuli. Because of previous experience suggesting that negative accuracy feedback was disruptive to individuals with MCI's subsequent performance, participants did not receive accuracy feedback (Broster et al., 2013).

A 5-minute practice period preceded the entire experiment to ensure that participants were comfortable with the cognitive and motor components of the task. This practice period was also designed to reduce or eliminate the influence of motor learning confounds on any repetition effects. During the practice period research personnel remained in the experimental chamber with the participant and provided oral feedback related to performance. As in the 2 blocks of formal experimentation, computerized feedback was not provided.

For all but one dyad, both the participant with MCI and the unaffected spouse or partner came to the laboratory at the same time. In such events, the participant with MCI participated in research protocols first, and the unaffected participant participated subsequently. While the spouse was participating in the task protocol, the participant was re-screened for eligibility and known confounds, and the UDS battery was administered if applicable. One dyad preferred to come to the laboratory separately due to scheduling conflicts, and they were the only exception to this aspect of the protocol.

Visual Stimuli

Stimuli were 120 re-sized two-dimensional 8.3 cm x 5.8 cm IAPS images. All stimuli were presented on a high-resolution color monitor using E-prime software. Sample images were presented with a thick green outline for 3s, and each test stimulus was presented for 1.5s. Both individual images and individual trials were separated by a 1.1-1.4s jitter interval, which was employed to prevent bias in RT measures due to participants anticipating stimulus onset. Stimuli were presented at a 65 cm visual distance at a visual angle of approximately 7°.

IAPS images have been extensively tested and validated for numerous features including hedonic valence and arousal ratings in younger adults (Lang, Bradley, & Cuthbert, 1998; Libkuman, Otani, Kern, Viger, & Novak, 2007). However, the validation of IAPS images in older adults and adults with cognitive impairment is relatively limited (Gruhn & Scheibe, 2008). In particular, in older adults the hedonic valence and arousal dimensions of emotional judgments, which are largely independent in younger adults, become coupled such that high arousal is associated with negative hedonic valence and low arousal is associated with positive hedonic valence (Gruhn & Scheibe, 2008; Keil & Freund, 2009; Porto, Bertolucci, & Bueno, 2011). To account for this association, I used a multiple polynomial regression imputation algorithm to estimate the hedonic valence and arousal of IAPS images of older adults based on 4 unpublished rating sessions of various subsets of the IAPS images in older adults. Image rating was conducted according to the standards associated with the stimulus resource (Mikels, Fredrickson, et al., 2005). Younger adults' ratings of images' arousal and hedonic valence, the interaction between the two dimensions, and quadratic or cubic trends in the ratings of arousal and hedonic valence were used to predict older adults' arousal and hedonic valence ratings of the IAPS images. Consistent with previous reports, empirical arousal and hedonic valence values were non-independent in older adults (Figure 4.3). Hence, I interpolated new adjusted arousal and hedonic valence scores for all IAPS images using a regression imputation algorithm based on the prediction model described above to establish relatively appropriate arousal and hedonic valence scores for the entire set of IAPS images.

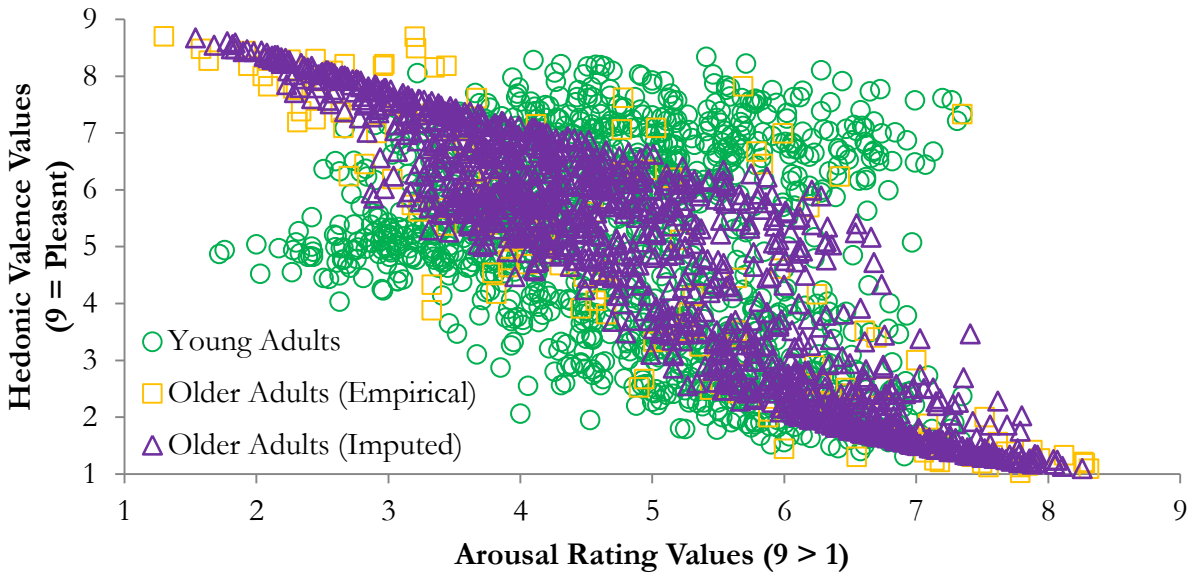

Figure 4.3: Scatterplot of distribution of hedonic valence and arousal scores of IAPS images. This graph depicts younger and older adults' ratings of IAPS images hedonic valence and arousal. In younger adults (green circles), these dimensions are relatively uncorrelated, but the correlation between these dimensions is stronger in older adults (orange squares). The results of applying a polynomial ordinary least squares regression algorithm to generate estimated older adult hedonic valence and arousal ratings for all IAPS images (purple triangles) further clarifies this dependent relationship. This dependence led us to encode the emotional enhancement effect levels of the experimental stimuli unidimensionally.

Based on this finding and a desire for a parsimonious design, IAPS image content was interpreted in a unidimensional fashion to ensure validity with our older adult cohort. Initially, I had planned for 3 levels along this single dimension – low arousal positive (LAP), high arousal negative (HAN), and neutral. To identify images belonging to each group, I collected images that scored within 2 points of the most extreme relevant values for LAP or HAN (i.e., images scored 1-3 or 7-9, as applicable) or that scored within 2 points of the middle value on both dimensions for neutral images (i.e., images scoring 4-6). However, upon examination of the exemplars of each class, I determined subjectively that the neutral stimulus set showed poor face validity in terms of the types of content it encompassed, so I elected to use only 2 levels: LAP and HAN, as previously formalized.

Having selected the LAP and HAN images via the empirical methodology previously described, I next worked to ensure that our distractor task was not confounded with the emotional enhancement effect categories. Initially, I had planned to use a classical "man-made/not man-made" image content decision paradigm as the distractor task in this experiment. However, a X^2 test suggested that such a task would be correlated with emotional enhancement effects for our LAP and HAN image sets. The HHP task was selected for its lack of association with the hedonic valence/arousal category of stimuli.

Electrophysiological Data Preprocessing

First, electrophysiological data were averaged according to normative protocols. Specifically, electrophysiological data were partially preprocessed using SCAN 4.5. This preprocessing consisted of manual artifact rejection, a finite impulse response filter with a band-pass of 0.05 to 40 Hz at 12 dB/octave, and epoching at -200 to 1000 ms relative to participant exposure to each stimulus. These epoched data were subsequently processed further using the ERP PCA Toolkit (EP Toolkit), consisting of ocular artifact reduction using independent components analysis (ICA), motor artifact reduction, bad channel imputation, baseline-correction, and re-referencing to the average of the mastoid electrodes. Then, epochs associated with behavioral responses and electrophysiological activity within ± 75 μV of baseline were averaged for each of the 4 experimental conditions (i.e., the initial or repeated presentation of LAP or HAN stimuli).

Then, temporospatial principal components analysis (PCA) was applied to the data to dissociate overlapping components present in the conventionally-averaged ERPs. In our opinion, this step was necessary in the current experiment and preferable to difference waves on the grounds that individual stimuli varied on more than only psychological conditions

(e.g., the LAP and HAN stimuli were not identical to one another). Promax and Infomax rotations were used for the temporal and spatial elements of the procedure, respectively, to permit limited correlation between temporal components, following the recommendation of methodologists (Dien, 2010b). To determine the appropriate number of temporal components to retain, the averaged data were compared to a random dataset, and components that explained both greater variance than the random dataset and at least 0.5% of variance in the data were retained. Principle components reflecting classical ERP signatures were identified using topographical maps of each component, each component's temporal course, and the effect of the experimental manipulations on each component.

Data Analysis

Data were analyzed as 2 × (2 × 2) mixed robust ANOVAs on cognitive status (NC or MCI), emotional enhancement effect stimulus type (LAP or HAN), or repetition effect stimulus type (initial or repeated) or as 2 × (2 × 2 × 2) mixed robust ANOVAs (i.e., including a factor for stimulus working memory status in the relevant experiment) using the EP Toolkit's robust ANOVA plug-in. Effects relevant to a priori hypotheses were first evaluated, and then post-hoc robust ANOVAs were performed for all principle components using similarly-structured robust ANOVAs. To limit the effect of multiple comparisons on these tests, each ANOVA was conducted only at the peak electrode of the corresponding component, and these tests were supplemented with Bonferroni correction on the number of components tested, where the components to be tested were the components retained as described in *Data Processing*. Uncorrected *p* value thresholds for each of these analyses are listed in the corresponding section of the online supplemental materials. Simple-effects models were used to interpret interaction effects. All significance values listed are based on

two-tailed *p* values except for directional a priori hypotheses, for which one-tailed *p* values were used. For the sake of brevity, results failing to reach one-tailed significance (i.e., $p > 0.1$) have been omitted from the report

Additionally, to improve power to detect lower-order effects involving clinical group, data were analyzed as 16 dyad pairs to take advantage of shared variance attributable to similarities correlated with spousehood. Hence, behavioral data and processed ERP data were analyzed as 2 × 2 × 2 within-dyad robust ANOVAs on cognitive status (NC or MCI), emotional enhancement effect stimulus type (LAP or HAN), or repetition effect stimulus type (initial or repeated) or as 2 × 2 × 2 × 2 within-dyad robust ANOVAs (i.e., including a factor for stimulus working memory status in the relevant experiment) using the EP Toolkit's robust ANOVA plug-in. Ultimately, while this analysis did increase the ability to detect certain effects, the analysis was not associated with any categorical changes in the significance of lower-order effects in these experiments, so the analysis will not be discussed further.

Results

Behavioral Analysis

For both Experiment 2 & 3, ANOVAs on reaction time (RT) identified significant Group × Repetition interactions, $F(1, 28) = 7.70$, $p = 0.010$, $\eta_p^2 = 0.22$, $F(1, 28) = 5.79$ $p = 0.023$, $\eta_p^2 = 0.17$, respectively. For both experiments, this interaction resulted from a larger decrease in RT with repetition in NC than in persons with MCI (80 ms vs. 40 ms for Experiment 2, 120 ms vs. 80 ms for Experiment 3). Both clinical groups showed a change in RT in the same direction with repetition.

Table 4.2: Behavioral Results for Experiments 2 and 3. Group-averaged reaction time and performance accuracy and standard error values for each empirical condition have been summarized. Reaction time values are reaction times associated with accurate responses only. Accuracy values are the proportion of total trials of each type to which an accurate response was given. Both experiments were associated with group differences in the manifestation of repetition effects. NC = normal control; MCI = mild cognitive impairment; LAP = low arousal positive stimuli; HAN = high arousal negative stimuli; 1st = initial presentation; 2nd = subsequent presentations

Clinical Group	Presentation	Emotional Repetition (Experiment 2)		Emotional Repeated Retrieval (Experiment 3)							
		Reaction Time (ms)		Reaction Time (ms)				Accuracy (%)			
				Match		Nonmatch		Match		Nonmatch	
		LAP	HAN	LAP	HAN	LAP	HAN	LAP	HAN	LAP	HAN
NC	1st	985 ± 21	1072 ± 19	829 ± 22	859 ± 23	839 ± 21	890 ± 20	88 ± 2	87 ± 2	92 ± 1	91 ± 2
	2nd	890 ± 19	960 ± 19	713 ± 19	746 ± 17	735 ± 19	760 ± 16	91 ± 2	92 ± 2	94 ± 1	91 ± 2
MCI	1st	993 ± 29	1074 ± 29	918 ± 45	918 ± 38	924 ± 35	963 ± 39	64 ± 6	60 ± 7	64 ± 7	66 ± 7
	2nd	917 ± 30	1000 ± 32	814 ± 35	848 ± 41	849 ± 39	881 ± 34	70 ± 5	65 ± 6	66 ± 7	65 ± 7

Behavioral accuracy results for Experiment 2 were not interpreted as accuracy was near ceiling and inaccuracies tended to be associated with images with ambiguous human figures or human organs. Behavioral accuracy results for Experiment 3 were not associated with significant effects or interactions involving repetition.

Conventionally-Averaged Waveforms

The conventionally-averaged waveforms showed classical components including a P3, frontal N400, posterior P2, and late positive component (LPC) (Figure 4.4). The experiments differed considerably in the apparent evoked potentials, particularly at the posterior P3 and frontal LPC. Respective components in the emotional delayed-match-to-sample task were shifted somewhat earlier in time, perhaps owing to the greater stringent time-pressure in that task. Individuals with MCI appeared to have smaller-amplitude ERPs, especially at frontal electrodes.

Difference waves of repetition effects (2^{nd} - 1^{st}) indicated that the simple emotional repetition task (Experiment 2) was apparently associated mainly with a single repetition effect in the late time-window whereas the emotional task that involved repeated working memory retrieval was associated with both a later repetition effect and one earlier effect. However, even when observing difference waves, the independence of components was unclear. Further, neural repetition effects are theorized to be multiple and independent in style of manifestation, so overlapping components could produce a misleading impression of how individual components manifest. Consequently, to identify relatively independent electrophysiological components and to disentangle effects of temporally-adjacent components, temporal PCA was applied to the data.

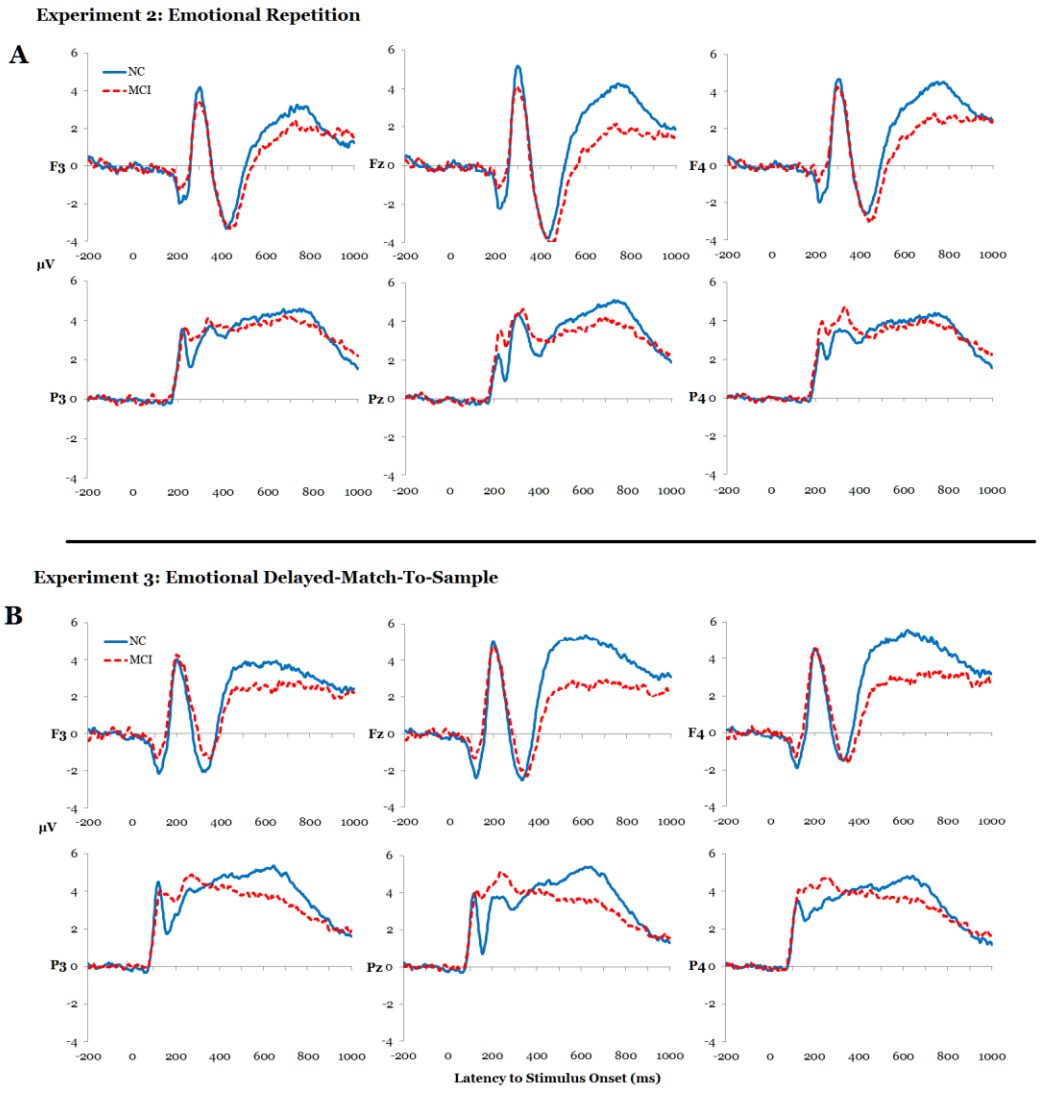

Figure 4.4: Conventional ERPs separated by clinical group for Experiments 2 & 3. The grand average waveforms of all experimental conditions and participants by group have been displayed at 6 electrodes for each experiment. Waveforms relevant to Experiments 2 & 3 are depicted in sections A and B, respectively. Note that the latency of Experiment 3 is shifted 100 ms earlier than that of Experiment 2, consistent with the similarly increased performance time in that experiment (Table 4.2).

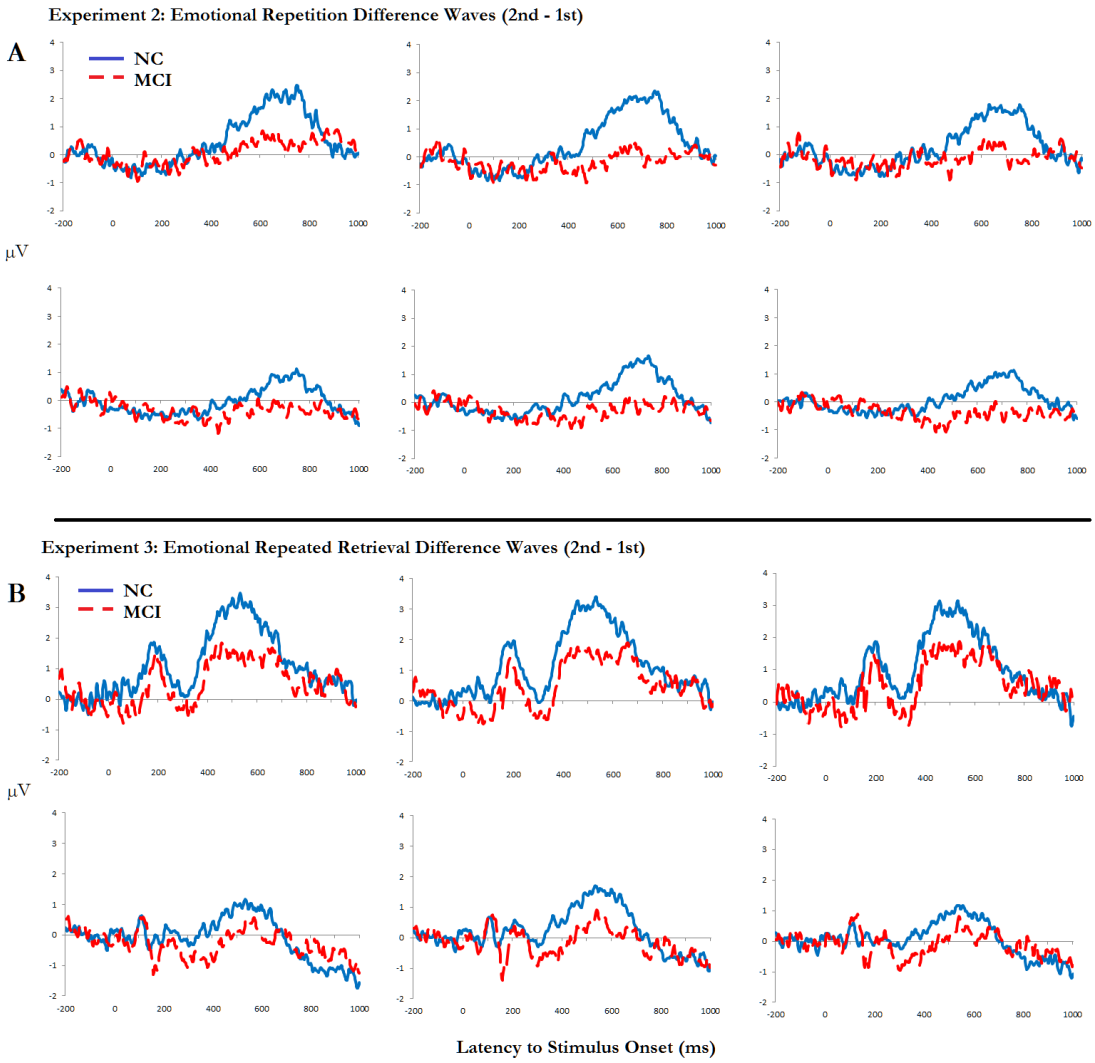

Figure 4.5: Repetition Effect Difference Waves separated by clinical group for Experiments 2 & 3. Difference waves suggested that the simple emotional repetition paradigm (A) was associated with a repetition effect in the late time-window whereas the emotional repeated retrieval paradigm (B) was potentially associated with discrete earlier and later effects.

Temporal Principal Components Analysis

The primary principal components associated with the experiments corresponded to classical ERP components, including the P2, P3, frontal N400, P600, and late positive potential (LPP) (Figure 4.6A). One clear contrast between experiments was that the P600 was severely attenuated in the pure emotional repetition paradigm, but it was the largest

temporal component in the emotional repeated retrieval paradigm. Further, the PCA solution suggested that the apparent monolithic late repetition effect apparent in both experiments was actually composed of discrete overlapping phenomena: one peaking near 600 ms, and one peaking near the end of the epoched time-window. Because of the evidence that the late repetition effects might represent discrete effects rather than a monolith, statistical evaluation of the experimental data was restricted to analysis of the individual temporal components of the PCA solution. Refer to the Appendix for a detailed summary of the temporal factors of the PCA solution (Table A1).

A Priori Analysis

For Experiment 2, the LPP was associated with a Group × Repetition interaction, T_{WJt}/c (1.0,22.4) = 3.18, p = 0.10, resulting from a repetition effect being present for individuals without impairment, F (1,30) = 10.21, p = 0.003, but no such effect being present for individuals with MCI (Figure 4.6B, first column). For Experiment 3, the P600 was associated with a Group × Repetition interaction T_{WJt}/c (1.0,26.2) = 5.78, p = 0.025, resulting from the repetition effect being larger in persons without impairment T_{WJt}/c (1.0,15.0) = 22.32, p = 0.0029, than in persons with MCI, T_{WJt}/c (1.0,15.0) = 7.47, p = 0.031, despite being present in both groups (Figure 4.6B, second column).

Post-Hoc Electrophysiological Analyses

In this chapter, post-hoc analyses were focused on effects related to repetition effects (i.e., main effects of repetition or statistical interactions in which repetition was implicated), so other effects will not be discussed here. After Bonferroni correction, no such effects reached significance for either experiment.

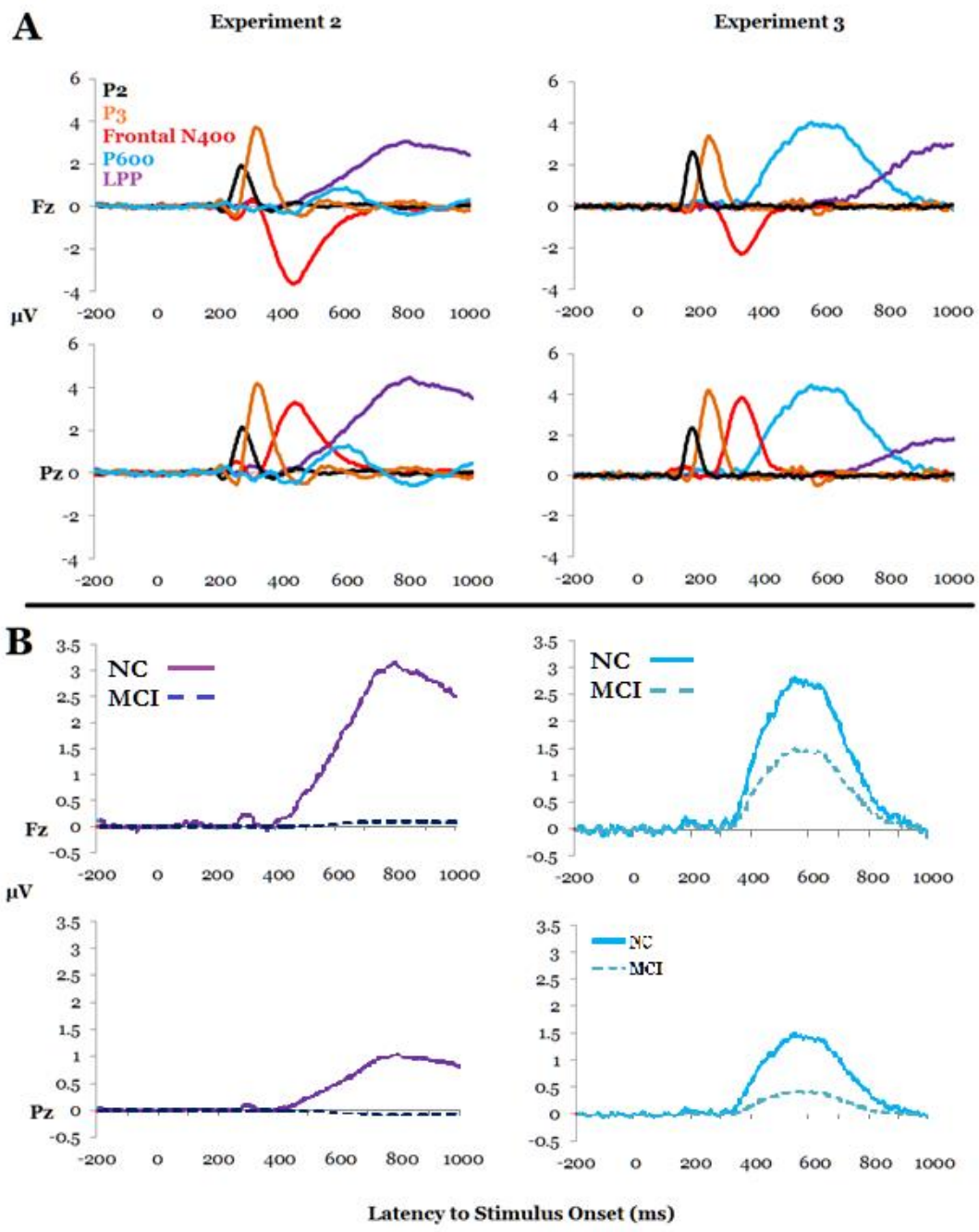

Figure 4.6: Components in Experiments 2 & 3 and repetition effect difference waves. A) These graphs depict the temporal PCA solution of Experiment 2 (first column) and Experiment 3 (second column) at a frontal (first row) and posterior (second row) electrode. Notable is the stark contrast in the size of the P600 between experiments; the component is prominent for the working memory task, but almost negligible in the simple repetition task. Note that although the waveforms have been colored to highlight correspondence between experiments, the components' differed in ordinal variance contribution between experiments. These discrepancies can be scrutinized in the Appendix. B) These graphs show difference waves between the 1st and 2nd presentations of stimuli (2nd minus 1st; positive values indicate larger amplitudes with repetition). Individuals with MCI did not show a repetition effect at the LPP (first column), but at the large P600 that was only apparent in the working memory study, persons with MCI showed a repetition effect, albeit an attenuated one (second column). The first and second rows show the effect at a frontal (Fz) and posterior (Pz) electrode, respectively. LPP = late positive potential

Integrated Analyses

The behavioral and electrophysiological repetition effects previously identified were compared to the Uniform Data Set (UDS) neuropsychological scores associated with each participant. Because each repetition effect expressed itself differently in each clinical groups (i.e., reflected in the significant Group × Repetition interactions), it would be necessary to perform correlations for each clinical group if the data were organized as monads. As a result, for these correlational analyses, the data were organized into spousal dyads. First, the difference between the 2nd and 1st instance of an RT or mean ERP component voltage value was computed for each participant (2nd - 1st). Then, the difference in those resultant values between the dyad member with MCI and the member without impairment was computed. These values were correlated with the difference in neuropsychological scores between dyad members. For the sake of ease of interpretation, individual difference scores were subtracted such that larger degrees of relative impairment were associated with larger difference values (e.g., for neuropsychological tests where low raw scores were associated with superior performance, scores of the spouse without impairment were subtracted from those of the spouse with MCI; the opposite was performed for neuropsychological tests where high raw scores indicated superior performance). For the sake of relative parsimony, only the largest component associated with a significant repetition effect for each experiment was tested in this way (i.e., the LPP for Experiment 2, and the P600 for Experiment 3).

Noteworthy results included that larger MMSE score differences within a dyad (i.e., caused mostly by the degree of impairment of the individual with MCI) indicated larger differences in behavioral RT repetition effects in the simple emotional repetition task (Experiment 2), but to smaller differences in behavioral RT repetition effects in the

emotional working memory task (Experiment 3) (Table 4.2). Additionally, the LPP repetition effect in the simple emotional repetition task was associated with many of the same neuropsychological scores as its associated behavioral RT repetition effects, but the P600 repetition effect was not associated with any neuropsychological scores other than the geriatric depression scale, short-form, an effect which appeared to be driven by a small number of participants with non-floor scores on this test. For a complete correlational summary, please refer to Table 4.1.

Owing to the observation that the behavioral and electrophysiological repetition effects of the simple emotional repetition task appeared to uniquely have a similar correlational profile with regard to the neuropsychological scores of participants, the behavioral and primary electrophysiological repetition effects were similarly correlated. The respective scores for the simple emotional repetition task were correlated, Spearman's ϱ = 0.68, p = 0.004, but the scores for the emotional working memory task were non-significantly correlated, Spearman's ϱ = -0.32, p = 0.23.

Discussion

I found that persons with MCI and persons without impairment showed a late positive potential (LPP) repetition effect difference that mirrored the findings of Olichney and colleagues for the task involving content evaluation (Olichney et al., 2006), but a repetition effect remained in a distinct but temporally-overlapping component (P600) for the task that required participants to use working memory. Interestingly, the relevant late neural component was of very small magnitude in the experiment that did not include a concurrent working memory task, and the two components were difficult to distinguish visually without the benefit of PCA. In our opinion, these findings indicate that a neural mechanism evoked

by working memory is sensitive to repetition effects and maintains relative normalcy in terms of how that effect manifests in MCI. This finding that a neural mechanism with spared electrophysiological repetition effects manifests only in a working memory context may help to explain why repetition effects in stages of AD have appeared to produce disparate stories in different experimental contexts.

Behaviorally, both tasks were actually associated with more improvement in RT for individuals without impairment. This departed from a previous study that showed that individuals with AD showed more RT improvement than persons with MCI or those without impairment in the context of a non-emotional delayed-match-to-sample working memory task (Broster et al., 2013). These two experiments differed methodologically in a few ways that may account for this discrepancy. First, the stimuli in the two experiments differed dramatically in complexity, luminance, coloration, and emotional content. Additional resources needed to process the characteristics of these stimuli may have revealed relative impairment in the MCI group that was not apparent in the previous experiment (Chakor, Bertone, McKerral, Faubert, & Lachapelle, 2005; Hansen, Johnson, & Ellemberg, 2012). Second, the current experiments did not include a cohort that had received an AD diagnosis, so the clinical group that showed RT enhancement in the previous experiment was not present in the second experiment. Since behavioral *enhancement* has been linked to only individuals with more advanced disease, it may be that the current cohort was simply not sufficiently advanced pathophysiologically for repetition effects to manifest (Klimkowicz-Mrowiec et al., 2008).

Of note, in the current delayed-match-to-sample task, individuals with MCI did show a smaller repetition effect at the P600 than individuals without impairment, though both groups showed an effect that was larger than zero. This similarly departed from the previous

study, which did not show such a contrast. In that study, the magnitude of repetition effects in MCI was similar to those of persons without impairment. Similar to our discussion of the behavioral results, this discrepancy may have resulted in differences in the experimental stimuli or the patient population. In our opinion, the remaining presence of a repetition effect in persons with MCI in the presence of working memory, even if validly attenuated, should be appreciated as a leveragable cognitive rehabilitation target (B. Boller, Jennings, Dieudonne, Verny, & Ergis, 2012).

Additionally, I suggest that the current results emphasize the importance of ecological validity in psychological experiments, especially in the context of characterizing the cognitive capabilities of patient populations. In the current experiments, the residual late repetition effect capacity was visible only when evoked by cognitive challenge associated with working memory, and it was almost completely masked in the experiment with a simpler content-evaluation task.

The current experiments also included a replication and partial extension of Olichney and colleagues' extensive work on the use of repetition effects of late ERP components, which I have identified with the LPP component in the current experiments, as biomarkers for AD, MCI, or pre-AD (Olichney et al., 2006; Olichney et al., 2002; Olichney et al., 2013; Olichney et al., 2008). In a repeated visual content-evaluation task similar to Olichney's repeated word content-evaluation task, I found that the LPP repetition effect was attenuated to the point of extinction in persons with MCI, similar to his related findings. The current results extend Olichney's observation to complex visual stimuli and to emotional stimuli. These findings suggest that Olichney's candidate biomarker may be more robust than previously appreciated, which may reduce theoretical disruptive effects on the biomarker in a more complex clinical setting. Consistent with this possibility, a milder form of the late

repetition effect reduction observed in this study and in Olichney and colleagues' work has been identified in comparing repetition effects linked to content evaluation in healthy older relative to younger adults, and passive viewing of images without evaluation has been linked to an absence of repetition effects at the LPP in younger adults (Schupp et al., 2006; Zhou, Li, Broster, Niu, & Wang, 2015). However, I would like to emphasize that the existence of a candidate repetition effect biomarker does not preclude functional maintenance of behavioral repetition effects in this context.

In these experiments, ERPs associated with emotional repeated retrieval were not correlated with neuropsychological or behavioral outcomes, but ERPs associated with simple emotional repetition were correlated with both neuropsychological and behavioral outcomes. This finding replicates previous findings that the traditional correlation between particular later ERP components and behavioral outcomes such as reaction time breaks down when coupled with cognitive tasks that engage multiple memory systems (Kutas, McCarthy, & Donchin, 1977; McCarthy & Donchin, 1981).

Owing to the limited spatial resolution of pure ERP/EEG methods, I did not attempt source localization using the current data. However, studies of working memory, emotion, and repetition have been employed in fMRI experiments (Bentley, Vuilleumier, Thiel, Driver, & Dolan, 2003; Migo et al., 2015; Narumoto, Okada, Sadato, Fukui, & Yonekura, 2001). The results generally support a spatial narrative characterized by complex interactions between cognitive-emotional systems that modulate one another's behavior including regions such as temporal and intraparietal sulci, inferior frontal gyri, inferior occipital gyri, lateral fusiform gyri, cingulate cortex, and the amygdala (Pessoa, 2008). However, because the studies that have implicated various brain regions in methods similar to those of the current results tend to involve only individual subsets of the concepts

explored in this manuscript (e.g., repetition in the context of emotion, but not working memory; or repetition outside the context of Alzheimer's disease), the connection between any individual region and a particular ERP component requires further investigation. In our opinion, the current results, which identify discrete repetition effects at latency differences unable to be discriminated with fMRI alone, indicate that simultaneous fMRI and ERP/EEG paradigms could be employed to link the phenomena in the current study to the neuroanatomic literature.

This experiment excluded individuals taking certain categories of psychoactive drugs, but individuals with mild cognitive impairment were uniformly taking donepezil or rivastigmine as part of their regular medical regimen as treatment for their cognitive change (Kumar, Singh, & Ekavali, 2015). These medications have known effects on ERP waveforms, so a subset of group differences identified in this study could be attributable to such differences (Guillem et al., 2006; Reeves, Struve, & Patrick, 2002). Because the differences in ERPs in this experiment were associated with interactions between experimental conditions and groups, the relevance of this issue to the main findings of this manuscript is limited. However, care should be exercised in the interpretation of apparent simple group differences in the conventionally-averaged data.

The current experiments identified discrete late repetition effects, one of which was only evoked to an appreciable degree by a concurrent working memory task. In the absence of a working memory task, I replicated Olichney's candidate AD biomarker, which was an absence of repetition effects at a late ERP component in persons with MCI. In the presence of the task, another late repetition effect manifested that was present in both groups, though it was attenuated in persons with MCI. These results suggest that persons with MCI maintain

some typical repetition effects, but that they can only be observed in task-specific contexts (Grill-Spector et al., 2006).

Chapter 5: High Arousal Negative Emotional Stimuli Evoke Altered Working Memory Processing in Persons with Mild Cognitive Impairment

Adapted from a manuscript in preparation

EXECUTIVE SUMMARY

Emotional enhancement effects have been proposed to be robust to the pathophysiology of Alzheimer's disease. Others have suggested that such effects are dysfunctional in this context, especially when other memory faculties are simultaneously engaged. Participants with and without amnestic mild cognitive impairment performed an emotionally-valenced delayed-match-to-sample repetition task while encephalography was performed to assess alterations in synaptic activity linked to discrete memory faculties in these groups. Results indicated that for persons with MCI, high arousal negative stimuli led to working memory processing patterns previously associated with AD, but this pattern did not exist for low arousal positive stimuli. I suggest that high arousal negative stimuli acutely exacerbate cognitive symptoms of MCI while low arousal positive stimuli may be protective.

Keywords: event-related potentials, mild cognitive impairment, Alzheimer's disease, emotional enhancement effects, working memory, affective cognition

Introduction

Alzheimer's disease (AD) is associated with severe deficits in multiple memory capacities including working memory, but emotional enhancement effects, the ability for arousing, pleasant, or unsettling memories to improve encoding or subsequent retrieval of memories, appear spared in AD relative to other forms of dementia (Balconi et al., 2015; Bertoux et al., 2014; Fernandez-Duque & Black, 2005; Joshi et al., 2014; Kumfor, Irish, Hodges, & Piguet, 2014; Lavenu, Pasquier, Lebert, Petit, & Van der Linden, 1999; L. A. Miller et al., 2012)

Despite the apparent relative robustness of emotional enhancement effects in persons with AD, the emotional realm does change in AD. Anterior and medial temporal structures such as the amygdalae subserve emotional processing, and they experience pathophysiological change early in the course of AD (Braak, Alafuzoff, Arzberger, Kretzschmar, & Del Tredici, 2006; Braak & Braak, 1991). Further, the function of such limbic structures has been validated in functional imaging studies, which generally report lower-magnitude signals following emotional stimuli for individuals of advanced age or who are experiencing a stage of AD (Budson et al., 2006; E A Kensinger, 2008; E. A. Kensinger, Anderson, Growdon, & Corkin, 2004; E. A. Kensinger et al., 2002; Leclerc & Kensinger, 2011; Waring, Seiger, Solomon, Budson, & Kensinger, 2014). Further, emotional effects have been linked to impaired inhibition of inappropriate responses due to prioritization of emotional phenomena, even when they are irrelevant to the task at-hand (S. Yang et al., 2014).

Emotional effects have also been proposed to have idiosyncratic effects on working memory processing, including that its specific effects on working memory appeared spared in the process of healthy aging (Broster et al., 2012; Freeman et al., 2013; E. A. Kensinger &

Corkin, 2003a; Kerestes et al., 2012; Waring, Payne, Schacter, & Kensinger, 2010). In particular, while certain emotional enhancement effects are attenuated over the course of aging, the influence of emotional effects on working memory appear to be relatively spared (Mikels, Larkin, et al., 2005). In other words, emotional enhancement effects in the context of working memory in particular may have unique preservation patterns relative to emotional enhancement effects in general.

The clinical ramifications of this question merit investigation. The relevance of residual emotional enhancement effects in AD is of significant practical and clinical importance. If arousing, pleasant, or unsettling stimuli or environments ameliorate or harshen the symptoms of dementia related to AD, informing clinicians or caregivers about those circumstances could help patients to experience their illness in as unobtrusive a manner as possible.

One theory of emotional enhancement effects in AD holds that in aging and dementia, emotional enhancement effects retain their normative benefits to the extent that they do not co-occur with functions that subserve executive functions such as working memory and attention (Borg et al., 2011; Broster et al., 2012). For example, Borg and colleagues (2011) found that relative to young adult control participants, older individuals without dementia and older adults with dementia similarly benefited from emotional enhancement effects in a simple visual recognition task, but showed no benefit or impairment, respectively, when emotional enhancement effects co-occurred with a task that superimposed a visuospatial binding task on the visual recognition task. In other words, increased competition for domain-general neural resources led emotional enhancement effects to be replaced by emotional decrement effects (Broster et al., 2012).

Given this theory, I suggest that stressful, arousing emotional circumstances are likely to exacerbate the AD cognitive phenotype whereas pleasant, calm circumstances are likely to ameliorate it. This theory is consistent with reports that aging, MCI, and AD are all associated with maintained benefits from stimuli of positive hedonic valence, but show disordered process of stimuli of negative hedonic valence (F. Boller et al., 2002; Hamann et al., 2002; Ikeda et al., 1998; Kazui et al., 2003; Kazui et al., 2000; LaBar et al., 2005; Sava et al., 2015). It may also help contextualize the mechanism for the well-demonstrated utility of implicit cognitive interventions such as errorless learning, a cognitive intervention strategy in persons with early AD that limits the stressful emotional consequences of negative feedback to maximize the benefit of the intervention (Jean et al., 2010; Kessels & de Haan, 2003b; Lee, Yip, Yu, & Man, 2013; White et al., 2014).

When assessing on-line forms of cognition such as working memory, electrophysiological methods including event-related potentials (ERP/EEG) can provide information directly based on neural activity to clarify whether differences in cognitive processing may occur even in the absence of differences in behavioral output (Guo et al., 2008). Previous work has identified a reversal in processing differences between matching and nonmatching stimuli in the P300 to P600 range of ERPs evoked by the delayed-match-to-sample task as a hallmark of AD (Broster et al., 2011; Broster et al., 2013). Further, while limited somewhat by the great variety in interpretations of what constitutes "emotional" stimuli, ERP/EEG research in the previous decades has characterized how ERPs are modulated by emotionally valenced or arousing stimuli (Feng et al., 2014; Foti, Hajcak, & Dien, 2009; Mendez-Bertolo, Pozo, & Hinojosa, 2011; Rozenkrants, Olofsson, & Polich, 2008; Schupp, Junghofer, Weike, & Hamm, 2003; Schupp et al., 2006).

In the current protocol, participants with and without MCI performed a delayed-match-to-sample task with emotionally-valenced stimuli to test the status of emotional enhancement effects in the context of working memory. I hypothesized that individuals with MCI would show an AD-like working memory effect in the electrophysiological data, and that this effect would be exacerbated in stimuli at higher levels of emotional enhancement.

Methods

Results discussed in this chapter are based on the protocols previously outlined in Chapter 4 and will not be reproduced here. Please refer to Chapter 4 for details on participant characteristics, protocol structure, stimuli characteristics, and electrophysiological processing techniques. For the sake of ease of reference, some of these data have been reproduced in Table 5.1 along with correlational results involving major behavioral and electrophysiological effects subsequently discussed in the Results section.

Results

Behavioral Analyses

Mixed ANOVAs on behavioral effects revealed an unqualified main effect of group, $F(1, 28) = 5.34$, $p = 0.028$, $\eta_p^2 = 0.16$, such that individuals with MCI were slower than individuals without impairment (Table 4.2).

Mixed ANOVAs on accuracy revealed a main effect of group, $F(1, 28) = 16.38$, $p < 0.001$, $\eta_p^2 = 0.37$, such that individuals with MCI were less accurate than individuals without impairment, and an Emotion × Working Memory interaction, $F(1, 28) = 4.41$, $p = 0.047$, $\eta_p^2 = 0.14$, and. The interaction resulted from a larger accuracy difference between working

memory conditions for high arousal negative stimuli than for low arousal positive stimuli (2.5% vs. 0.1%). Other effects were non-significant.

Table 5.1: Neuropsychological summary for cohort of experiments discussed in Chapters 4 and 5. NC = normal older control, MCI = amnestic mild cognitive impairment, AD = Alzheimer's disease; N = number of participants, Females = number of female participants, Age = age of participant in years, Education = formal education of participants in years; MMSE = mini-mental status examination, LOGIMEMI = Logical Memory Story A, Immediate Recall, LOGIMEMII = Logical Memory Story A, Delayed Recall, DIGIF = Digit Span Forward, DIGIFLEN = Digit Span Forward Length, DIGIB = Digit Span Backward, DIGIBLEN = Digit Span Backward Length, ANIMALS = Category Fluency (Animals), VEG = Category Fluency (Vegetables), TRAILA = Trailmaking A, TRAILB = Trailmaking B, DSYM = Digit Symbol, BOSTON = Boston Naming Task, GDS15 = Geriatric Depression Scale, short-form; df, F/χ^2, p, and ϱ indicate statistical summaries for the omnibus tests of group differences for each column. Welch's robust test of means was used for measures showing heterogeneity of variance. Variance displayed is the standard error of the mean (SEM) for each group. Because behavioral and electrophysiological repetition effects were empirically associated with interactions of clinical group, correlations depicted compare within-dyad differences in neuropsychological test scores with within-dyad differences in individual repetition effects. To reduce the impact of differential violations of normality assumptions, spearman's ϱ was used to assess correlations of each neuropsychological test with the behavioral and primary electrophysiological repetition effect in each experiment. For all neuropsychological tests except for TRAILA, TRAILB, and the GDS15, a larger score indicates better performance, whereas the opposite is true for TRIALA/B and the GDS15. Hence, the signs of correlations of TRAILA/B and GDS15 have been reversed in this chart for ease of interpretation. Positive ϱ values indicate that large differences in the neuropsychological status of individuals in a dyad were related to large differences in the size of the relevant repetition effect; negative ϱ values indicate that large differences in the neuropsychological status of individuals in a dyad were related to small differences in the size of the relevant repetition effect. Because missingness was relatively rare in this dataset, the expectation-maximization (EM) algorithm was used to impute missing variables using existing behavioral and neuropsychological data where actionable. Two individuals (one MCI, one NC) did not participate in neuropsychological testing, so they were excluded from that process and from these analyses.

	N	*Females*	*Age*	*Education*	*MMSE*	*LOGIMEMI*	*LOGIMEMII*	*DIGIF*	*DIGIFLEN*	*DIGIB*	*DIGIBLEN*	*ANIMALS*	*VEG*	*TRAILA*	*TRAILB*	*DSYM*	*BOSTON*	*GDS 15*
NC	16	9	76.7 ± 1.4	16.7 ± 0.7	28.8 ± 0.3	14.1 ± 1.0	12.7 ± 1.1	8.0 ± 0.7	6.3 ± 0.3	6.1 ± 0.6	4.7 ± 0.3	19.6 ± 1.2	14.8 ± 0.9	37.5 ± 3.0	82.3 ± 5.5	40.9 ± 2.6	27.0 ± 1.6	1.0 ± 0.4
MCI	16	7	77.2 ± 1.5	17.1 ± 0.9	26.2 ± 0.7	7.4 ± 0.8	6.4 ± 1.0	8.7 ± 0.5	6.9 ± 0.2	5.9 ± 0.5	4.6 ± 0.2	13.6 ± 1.5	9.1 ± 0.8	54.4 ± 6.5	181.2 ± 21.9	32.9 ± 4.1	23.6 ± 1.1	2.0 ± 0.9
df		1	1, 30	1, 30	1, 18.3	1, 28	1, 28	1, 28	1, 28	1, 28	1, 28	1, 28	1, 28	1, 20.6	1, 17.0	1, 28	1, 28	1, 28
F/χ^2		0.5	0.06	0.14	7.76	20.98	20.75	0.94	2.39	0.03	0.10	8.75	18.53	3.45	11.80	0.0003	5.94	2.66
p		0.72	0.81	0.71	0.01	< 0.001	< 0.001	0.34	0.13	0.87	0.76	0.006	< 0.001	0.08	0.003	0.99	0.02	0.11
Correlation:				ϱ	.209	-.018	-.302	-.040	-.003	.097	-.025	.326	.434	.269	.288	.621	.209	-.180
Behavioral Working Memory Group Difference				*p*	.436	.948	.256	.883	.991	.720	.926	.218	.093	.313	.279	.010**	.437	.505
Correlation:				ϱ	-.248	-.157	.085	.289	.225	.081	.249	.283	.405	.215	.074	-.053	.125	-.284
P600 Working Memory Group Difference				*p*	.355	.561	.753	.277	.403	.765	.353	.287	.120	.424	.787	.846	.644	.286

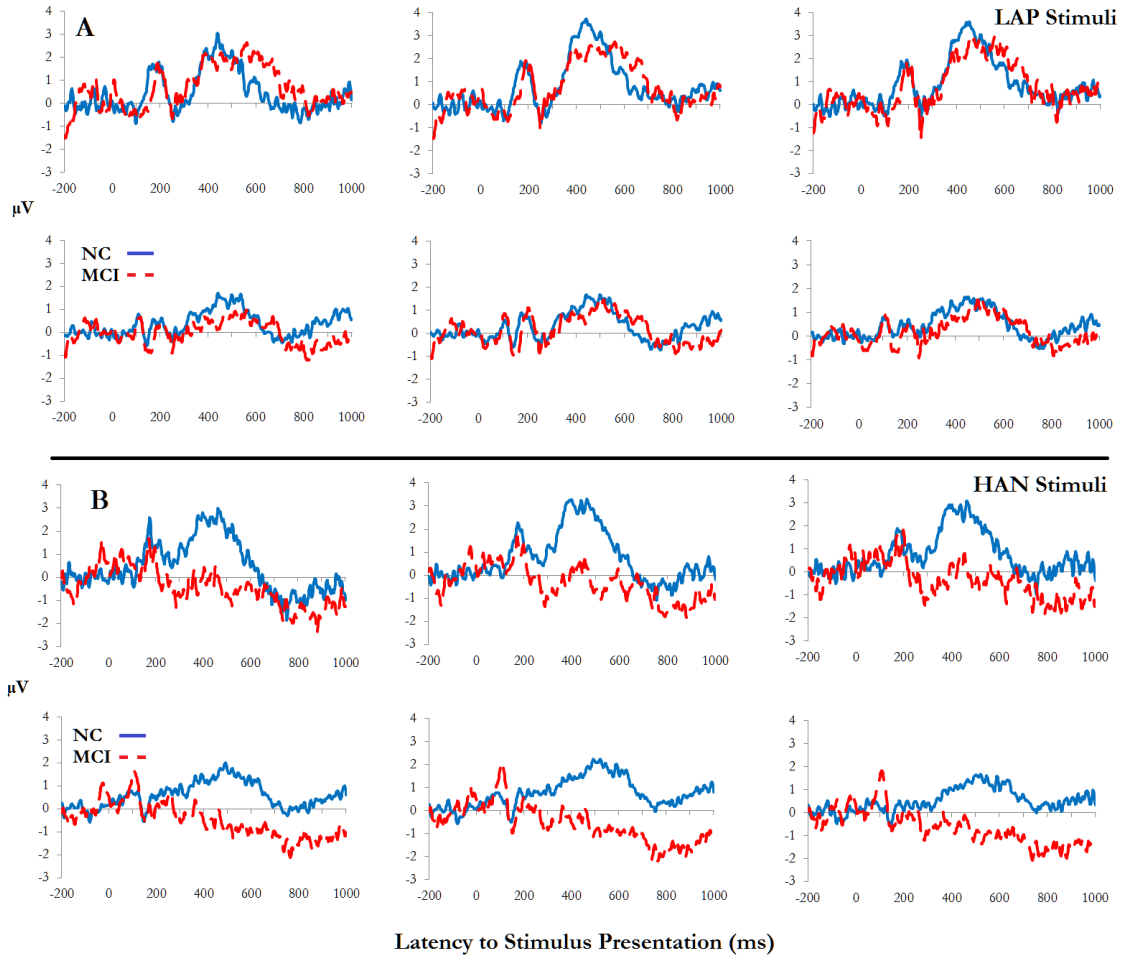

Figure 5.1: Working memory difference waves for LAP and HAN stimuli. Averaged ERPs for persons without impairment (NC) and persons with MCI (MCI) for low arousal positive stimuli (A) and high arousal negative stimuli (B). Differences between groups appeared most obvious for high arousal negative stimuli and appeared to be mostly confined to the later ERP time-window.

C*onventionally-Averaged Waveform and Temporal Principal Components Analysis Solution*

In general, the experiment produced ERPs with normative characteristics, including prominent P3 and late positive components. Please refer to Chapter 4 for additional details about these materials (Figure 4.4).

To test the primary hypothesis that working memory and emotional enhancement effects would show an idiosyncratic signature in MCI, I also produced difference waves of working memory effects (Match - Nonmatch) for LAP and HAN stimuli for each clinical

group (Figure 5.1). For LAP stimuli, despite some potentially increased variability in late ERP effect onset in persons with MCI, overall differences between groups were relatively small, especially when taking into account the amount of noise present in the baseline. However, for HAN stimuli, working memory differences between groups were salient in the later ERP components. Because the individual components primarily responsible for this contrast were not clear, temporal principal components analysis (PCA) was performed to discriminate discrete components. Refer to the Appendix for details of the PCA solution (Table A1).

A Priori Analysis

The P600 was associated with a significant Group × Emotion × Match three-way interaction, T_{WJt}/c (1.0,23.3) = 8.95, p = 0.011, resulting from an Emotion × Match interaction for individuals with MCI, T_{WJt}/c (1.0,15.0) = 7.54, p = 0.027, but not for individuals without impairment. In individuals without impairment, matching stimuli were associated with a larger P600 than were nonmatching stimuli regardless of emotional content of stimuli, T_{WJt}/c (1.0,15.0) = 18.39, p = 0.0032 , but in individuals with MCI, this pattern was present for positive stimuli, T_{WJt}/c (1.0,15.0) = 10.41, p = 0.0079 , but it was absent for negative stimuli, T_{WJt}/c (1.0,15.0) = 1.26, p = 0.28, and the direction of this effect trended in the opposite direction for negative stimuli in this group (Figure 5.2).

Post-Hoc Electrophysiological Analyses

The frontal N400 component was associated with a main effect of emotion, $T_{WJt}/c(1.0,30.0)=10.17$, p=0.0059, such that the component was larger for negative stimuli, and a main effect of repetition, $T_{WJt}/c(1.0,22.3)=7.05$, p=0.010, such that the component

was more negative upon repetition. Other effects were non-significant after Bonferroni correction.

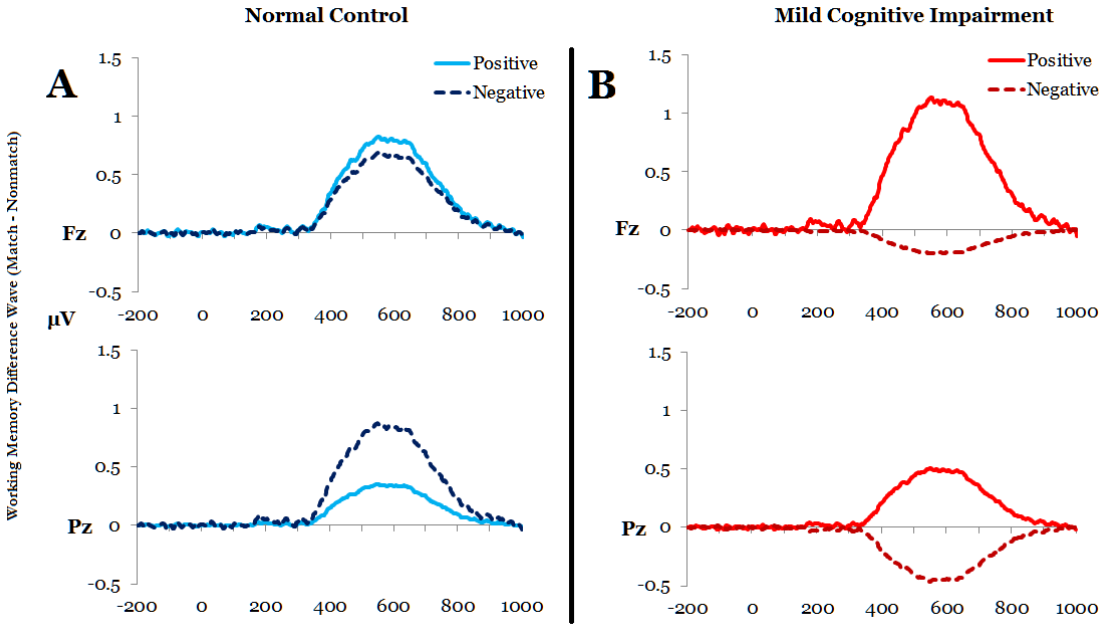

Figure 5.2: Summary of the group differences at the P600 as difference waves. Each line depicts the difference in P600 activity between matching and non-matching stimuli for stimuli that were either positive (purple) or negative (tan). Individuals without impairment (A) and individuals with MCI (B) showed similar brain responses for positive stimuli, but very different responses for negative stimuli. Data have been graphed at a frontal (Fz) and posterior (Pz) electrode in the first and second rows, respectively, to provide a general sense of differences in this effect at frontal and posterior sites.

Integrated Analyses

Individual neuropsychological data were not significantly correlated with behavioral working memory reaction time effects or with the electrophysiological working memory effects at the P600 after accounting for multiple comparisons (Table 5.1, bottom rows). Additionally, behavioral working memory effects were not significantly correlated with the corresponding electrophysiological P600 working memory effects.

Discussion

I found that persons with MCI showed AD-like ERPs when performing working memory with high arousal negative (HAN) emotional stimuli, but showed ERPs similar to persons without impairment for low arousal positive (LAP) stimuli. Persons with MCI were also slower and less accurate than persons without impairment. These findings suggest that HAN stimuli, and, by extension, HAN environments, exacerbate the effects of AD on working memory processing.

When exposed to LAP stimuli, participants with MCI showed working memory processing patterns similar to those of persons without impairment. While I did hypothesis that such images would evoke a processing profile more similar to those of younger adults, I would not anticipate that persons with MCI would show a profile more similar to that of persons with NC than even for simple line-drawing images without appreciable hedonic valence or arousal (Broster et al., 2011). This may suggest that, rather than merely being associated with a milder degree of dysregulation, LAP stimuli may normalize working memory processing in persons with MCI even for complex stimuli.

In other words, these findings support the theory that stressful circumstances disrupt the normal effects of emotional enhancement on working memory, but stop short of suggesting that emotional enhancement effects disrupt cognition in the context of MCI in general. Instead, based on the contrast of the current results with similar studies that used simpler stimuli that were non-emotional, the current results suggest that LAP environments maintain the ability to facilitate normal working memory processing in persons with MCI. By extension, LAP environments likely also maintain the ability to facilitate normal processing in aspects of cognition subserved by working memory. Future work should evaluate the

extent to which LAP environments or stimuli have beneficial effects in contexts beyond working memory to confirm this possibility.

The current results may support a neural basis for recent investigations of the impact of mindfulness training in persons with cognitive change due to AD (Larouche, Hudon, & Goulet, 2015; Quintana Hernandez et al., 2014; Quintana Hernandez et al., 2015; van Boxtel & Speckens, 2014; Wells et al., 2013). Specifically, therapeutic effects of mindfulness may be attributable in part to the generation of a mental status relatively similar to that evoked by the low arousal positive stimuli utilized in the current experiment.

In this study, stimuli were selected along a bimodal, unidimensional hedonic valence-arousal axis due to data suggesting that these features became more and more closely correlated over the course of aging. Consequently, I cannot differentiate effects of negative hedonic valence and high arousal in the current study. Some have suggested that despite the apparent collinearity of hedonic valence and arousal judgments by older adults, physiological effects of these dimensions remain distinct (Gavazzeni, Wiens, & Fischer, 2008). Consequently, I suggest that follow-up research might attempt to disentangle the influence of the arousal and hedonic valence dimensions of stimuli on the presence of the AD-like cognitive signature replicated in the current study (Broster et al., 2011). In our opinion, given the effects of arousal on neural substrates subserving attention, the arousal dimension of the stimuli may have been the primary driver of the effect observed (Borg et al., 2011; Garcia-Rodriguez, Vincent, Casares-Guillen, Ellgring, & Frank, 2012). However, because the physiological or cognitive effects of differences in subjective hedonic valence relative to neutral stimuli are not necessarily rectilinear, empirical data are necessary to confirm this inference.

Some studies of ERPs evoked by emotional stimuli have reported emotional effects at latencies as early as the P1, which would be an earlier latency than the latencies found in the current study (Foti et al., 2009). However, such studies differed in design by the inclusion of neutral stimuli, and it was typically only in contrasts with non-emotional, neutral stimuli that the earliest latency emotional effects were observed, though some later latency effects were similarly constrained to contrasts between emotional and non-emotionally stimuli (Foti et al., 2009; Schupp et al., 2003). In this experiment, such stimuli were excluded because of perceived poor face validity among stimuli rated neutrally on both hedonic valence and arousal, and hedonic valence and arousal were not treated dimensionally because of evidence that those factors were collinear in older adults and persons with MCI. However, since other physiological correlates of the dimensional independence of hedonic valence and arousal appear intact despite correlation in the self-reported ratings of emotional images, ERPs associated with hedonic valence and arousal may likewise remain independent. Future studies should test this possibility as a way to assess the neural mechanisms of apparent burgeoning collinearity between these factors (Porto et al., 2011).

In the current study, the working memory effects of interest manifested primarily at a later component called the P600, but in a similar study that used non-emotional effects, the effect occurred somewhat earlier, during the classical P300 (Broster et al., 2011). Multiple differences between the two studies could account for this discrepancy. First, the use of emotional stimuli classically evokes a prominent late component called the late positive potential (LPP), which is absent or subtle in experiments without emotional effects. Therefore, differences in stimulus characteristics could account for the discrepancy. Second, the current study used PCA to disentangle overlapping components, but the previous study

used a conventional analysis approach. The PCA approach may have identified the true source of the apparent variance in the working memory effect more accurately.

ERPs associated with working memory were not correlated with neuropsychological or behavioral outcomes in the current study. This finding replicates previous findings that the traditional correlation between particular later ERP components and behavioral outcomes such as reaction time breaks down when coupled with cognitive tasks that engage multiple memory systems (Kutas et al., 1977; McCarthy & Donchin, 1981). Consistent with this interpretation, a previous study using the current cohort that did not engage working memory systems evoked ERPs that were associated with significant correlations with both neuropsychological measures and behavioral outcomes (Chapter 4).

The post-hoc finding that the N400 was associated with more negative values for HAN stimuli replicates some similar findings in the affective priming literature (Zhang et al., 2006). N400 effects are classically evoked by semantic violations in the context of language-based semantic priming paradigms, but have also been linked to other cognitive domains that researchers have analogized to language semantics, especially processes that denote violation of systematic rules, including phenomena that evoke moral disgust (Featherstone, Morrison, Waterman, & MacGregor, 2013; James, Cereghetti, Roullet Tribes, & Oechslin, 2015; Koelsch, Gunter, Wittfoth, & Sammler, 2005; Luo et al., 2013). As such, the larger N400 identified in the current study may represent a complex evaluation of inexcusable moral circumstances depicted in a HAN stimulus rather than a mere categorization of the stimulus on the dimensions of arousal and hedonic valence. This possibility may help contextualize why repetition was associated with larger N400 amplitudes rather than the smaller N400 amplitudes that generally accompany repetition of N400-relevant semantic

violations. Whereas repeating a semantic violation may normalize it, reducing the perceived magnitude of the violation and the accompanying N400 magnitude, the repetition of circumstances that promote moral outrage may rouse increased scrutiny. Future studies could attempt to modulate the sense of moral outrage evoked by some HAN stimuli while controlling for subjective arousal and hedonic valence to assess the true determinant of N400 magnitude in such stimuli.

Participants in this experiment were screened for depressive symptoms, and individuals with current depressive symptoms were not enrolled in the study. Because the rate of depression in the general population with cognitive change due to Alzheimer's disease is high and some evidence suggests that individuals with depression or remitted depression show a visual attention bias toward negative stimuli, this may suggest that the current results may be limited in the extent to which they are externally valid to the patient population with cognitive change due to Alzheimer's disease (Chi et al., 2015; Drijgers, Verhey, Leentjens, Kohler, & Aalten, 2011; Korczyn & Halperin, 2009). Future studies could investigate any moderating effects of individual depressive states on the current results.

This experiment excluded individuals taking certain categories of psychoactive drugs, but individuals with mild cognitive impairment were uniformly taking donepezil or rivastigmine as part of their regular medical regimen as treatment for the changes to their memory and thinking (Kumar et al., 2015). These medications have known effects on ERP waveforms, so a subset of group differences identified in this study could be attributable to such differences (Guillem et al., 2006; Reeves et al., 2002). Because the differences in ERPs in this experiment were associated with interactions between experimental conditions and groups, the relevance of this issue to the main findings of this manuscript is limited.

However, care should be exercised in the interpretation of apparent simple group differences in the conventionally-averaged data.

I report evidence that individuals with MCI show relatively normal working memory processing of low arousal positive stimuli, but they show disordered working memory processing of high arousal negative stimuli. I suggest that these findings are relevant to ongoing disputes in the literature regarding the status and viability of emotional enhancement effects in MCI and AD. Further, I suggest that endeavoring to reduce stressors and negative environmental factors may reduce the functional impact of the early stages of AD on patients' lives.

Appendix

Table A1: Principal Components Analysis Summary for Event-Related Potential Data. The approximate temporal peak of the temporal components in each experiment and, if applicable, the classical ERP component it most resembles have been listed for each experiment included in this dissertation. For each experiment, a vertical line separates the components that were retained for a priori or post-hoc analyses from those that were not. Exp 1 = Experiment 1; Exp 2 = Experiment 2; Exp 3 = Experiment 3; TF = temporal factor; ms = milliseconds.

	TF1	*TF2*	*TF3*	*TF4*	*TF5*	*TF6*	*TF7*	*TF8*	*TF9*	*TF10*	*TF11*	*TF12*	*TF13*	*TF14*	*TF15*	*TF16*	*TF17*	*TF18*	*TF19*	*TF20*	*TF21*
Exp 1																					
Approximate Temporal Peak (ms)	458	272	162	672	354	208	594	94	120	836	794	548	874	-70	138	502	564	736	924	696	242
Classical Approximant	P3	N2	P2	LPC	P3	P2	P3														
Exp 2																					
Approximate Temporal Peak (ms)	800	434	268	314	604	220	1000	142	504	-12	-202										
Classical Approximant	LPP	N400	P2	P3	P600																
Exp 3																					
Approximate Temporal Peak (ms)	550	998	328	226	174	440	714	116	142	276	382	980	38	198	-194	738	-90	-58	-62		
Classical Approximant	P600	LPP	N400	P3	P2																

References

1 Abner, E. L., Kryscio, R. J., Cooper, G. E., Fardo, D. W., Jicha, G. A., Mendiondo, M. S., . . . Schmitt, F. A. (2012). Mild cognitive impairment: statistical models of transition using longitudinal clinical data. *Int J Alzheimers Dis, 2012*, 291920. doi: 10.1155/2012/291920

2 Abrisqueta-Gomez, J., Bueno, O. F., Oliveira, M. G., & Bertolucci, P. H. (2002). Recognition memory for emotional pictures in Alzheimer's patients. *Acta Neurol Scand, 105*(1), 51-54.

3 Aizpurua, A., Garcia-Bajos, E., & Migueles, M. (2011). False recognition and source attribution for actions of an emotional event in older and younger adults. *Exp Aging Res, 37*(3), 310-329. doi: 10.1080/0361073X.2011.568829

4 Albert, M. S., DeKosky, S. T., Dickson, D., Dubois, B., Feldman, H. H., Fox, N. C., . . . Phelps, C. H. (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement, 7*(3), 270-279. doi: 10.1016/j.jalz.2011.03.008

5 Amieva, H., Letenneur, L., Dartigues, J. F., Rouch-Leroyer, I., Sourgen, C., D'Alchee-Biree, F., . . . Fabrigoule, C. (2004). Annual rate and predictors of conversion to dementia in subjects presenting mild cognitive impairment criteria defined according to a population-based study. *Dement Geriatr Cogn Disord, 18*(1), 87-93. doi: 10.1159/000077815

6 Amieva, H., Rouch-Leroyer, I., Letenneur, L., Dartigues, J. F., & Fabrigoule, C. (2004). Cognitive slowing and learning of target detection skills in pre-demented subjects. *Brain Cogn, 54*(3), 212-214. doi: 10.1016/j.bandc.2004.02.003

7 Arsenault-Lapierre, G., Whitehead, V., Belleville, S., Massoud, F., Bergman, H., & Chertkow, H. (2011). Mild cognitive impairment subcategories depend on the source of norms. *J Clin Exp Neuropsychol, 33*(5), 596-603. doi: 10.1080/13803395.2010.547459

8 Baars, M. A., van Boxtel, M. P., Dijkstra, J. B., Visser, P. J., van den Akker, M., Verhey, F. R., & Jolles, J. (2009). Predictive value of mild cognitive impairment for dementia. The influence of case definition and age. *Dement Geriatr Cogn Disord, 27*(2), 173-181. doi: 10.1159/000200465

9 Baddeley, A. D., Bressi, S., Della Sala, S., Logie, R., & Spinnler, H. (1991). The decline of working memory in Alzheimer's disease. A longitudinal study. *Brain, 114 (Pt 6)*, 2521-2542.

10 Balconi, M., Cotelli, M., Brambilla, M., Manenti, R., Cosseddu, M., Premi, E., . . . Borroni, B. (2015). Understanding Emotions in Frontotemporal Dementia: The Explicit and Implicit Emotional Cue Mismatch. *J Alzheimers Dis*. doi: 10.3233/JAD-142826

11 Ballesteros, S., Reales, J. M., Mayas, J., & Heller, M. A. (2008). Selective attention modulates visual and haptic repetition priming: effects in aging and Alzheimer's disease. *Exp Brain Res, 189*(4), 473-483. doi: 10.1007/s00221-008-1441-6

12 Becker, J. T., Mintun, M. A., Aleva, K., Wiseman, M. B., Nichols, T., & DeKosky, S. T. (1996). Compensatory reallocation of brain resources supporting verbal episodic memory in Alzheimer's disease. *Neurology, 46*(3), 692-700.

13 Belleville, S., Chertkow, H., & Gauthier, S. (2007). Working memory and control of attention in persons with Alzheimer's disease and mild cognitive impairment. *Neuropsychology, 21*(4), 458-469. doi: 10.1037/0894-4105.21.4.458

14 Belleville, S., Clement, F., Mellah, S., Gilbert, B., Fontaine, F., & Gauthier, S. (2011). Training-related brain plasticity in subjects at risk of developing Alzheimer's disease. *Brain, 134*(Pt 6), 1623-1634. doi: 10.1093/brain/awr037

15 Belleville, S., Gilbert, B., Fontaine, F., Gagnon, L., Menard, E., & Gauthier, S. (2006). Improvement of episodic memory in persons with mild cognitive impairment and healthy older adults: evidence from a cognitive intervention program. *Dement Geriatr Cogn Disord, 22*(5-6), 486-499. doi: 10.1159/000096316

16 Belleville, S., Peretz, I., & Malenfant, D. (1996). Examination of the working memory components in normal aging and in dementia of the Alzheimer type. *Neuropsychologia, 34*(3), 195-207.

17 Belleville, S., Sylvain-Roy, S., de Boysson, C., & Menard, M. C. (2008). Characterizing the memory changes in persons with mild cognitive impairment. *Prog Brain Res, 169*, 365-375. doi: 10.1016/S0079-6123(07)00023-4

18 Bentley, P., Vuilleumier, P., Thiel, C. M., Driver, J., & Dolan, R. J. (2003). Effects of attention and emotion on repetition priming and their modulation by cholinergic enhancement. *J Neurophysiol, 90*(2), 1171-1181. doi: 10.1152/jn.00776.2002

19 Bertoux, M., de Souza, L. C., Sarazin, M., Funkiewiez, A., Dubois, B., & Hornberger, M. (2014). How Preserved is Emotion Recognition in Alzheimer Disease Compared With Behavioral Variant Frontotemporal Dementia? *Alzheimer Dis Assoc Disord.* doi: 10.1097/WAD.0000000000000023

20 Bisiacchi, P. S., Tarantino, V., & Ciccola, A. (2008). Aging and prospective memory: the role of working memory and monitoring processes. *Aging Clin Exp Res, 20*(6), 569-577.

21 Boller, B., Jennings, J. M., Dieudonne, B., Verny, M., & Ergis, A. M. (2012). Recollection training and transfer effects in Alzheimer's disease: effectiveness of the repetition-lag procedure. *Brain Cogn, 78*(2), 169-177. doi: 10.1016/j.bandc.2011.10.011

22 Boller, F., El Massioui, F., Devouche, E., Traykov, L., Pomati, S., & Starkstein, S. E. (2002). Processing emotional information in Alzheimer's disease: effects on memory performance and neurophysiological correlates. *Dement Geriatr Cogn Disord, 14*(2), 104-112. doi: 64932

23 Borella, E., Carretti, B., & De Beni, R. (2008). Working memory and inhibition across the adult life-span. *Acta Psychol (Amst), 128*(1), 33-44. doi: 10.1016/j.actpsy.2007.09.008

24 Borg, C., Leroy, N., Favre, E., Laurent, B., & Thomas-Anterion, C. (2011). How emotional pictures influence visuospatial binding in short-term memory in ageing and Alzheimer's disease? *Brain Cogn, 76*(1), 20-25. doi: 10.1016/j.bandc.2011.03.008

25 Braak, H., Alafuzoff, I., Arzberger, T., Kretzschmar, H., & Del Tredici, K. (2006). Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry. *Acta Neuropathol, 112*(4), 389-404. doi: 10.1007/s00401-006-0127-z

26 Braak, H., & Braak, E. (1991). Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathol, 82*(4), 239-259.

27 Broster, L. S., Blonder, L. X., & Jiang, Y. (2012). Does emotional memory enhancement assist the memory-impaired? *Front Aging Neurosci, 4*, 2. doi: 10.3389/fnagi.2012.00002

28 Broster, L. S., Li, J., Jenkins, S. L., Tarrant, S. D., Jicha, G. A., & Jiang, Y. (2015). *Altered Neural Responses to Affective Repetition in Persons with Mild Cognitive Impairment*. Paper presented at the Association for Clinical and Translational Science, Washington, D.C.

29 Broster, L. S., Li, J., Smith, C., Jicha, G. A., Munro, N., Hively, L., & Jiang, Y. (2011). Left frontal potentials differentiate mild cognitive impairment from normal aging during a working memory task *Annual Meeting of the Society for Neuroscience*. Washington, DC.

30 Broster, L. S., Li, J., Smith, C. D., Jicha, G. A., Schmitt, F. A., & Jiang, Y. (2013). Repeated retrieval during working memory is sensitive to amnestic mild cognitive impairment. *J Clin Exp Neuropsychol, 35*(9), 946-959. doi: 10.1080/13803395.2013.838942

31 Buckner, R. L. (2004). Memory and executive function in aging and AD: multiple factors that cause decline and reserve factors that compensate. *Neuron, 44*(1), 195-208. doi: 10.1016/j.neuron.2004.09.006

32 Buckner, R. L., Sepulcre, J., Talukdar, T., Krienen, F. M., Liu, H., Hedden, T., . . . Johnson, K. A. (2009). Cortical hubs revealed by intrinsic functional connectivity: mapping, assessment of stability, and relation to Alzheimer's disease. *J Neurosci, 29*(6), 1860-1873. doi: 10.1523/JNEUROSCI.5062-08.2009

33 Budson, A. E. (2009). Understanding memory dysfunction. *Neurologist, 15*(2), 71-79. doi: 10.1097/NRL.0b013e318188040d

34 Budson, A. E., Simons, J. S., Sullivan, A. L., Beier, J. S., Solomon, P. R., Scinto, L. F., . . . Schacter, D. L. (2004). Memory and emotions for the september 11, 2001, terrorist attacks in patients with Alzheimer's disease, patients with mild cognitive impairment, and healthy older adults. *Neuropsychology, 18*(2), 315-327. doi: 10.1037/0894-4105.18.2.315

35 Budson, A. E., Todman, R. W., Chong, H., Adams, E. H., Kensinger, E. A., Krangel, T. S., & Wright, C. I. (2006). False recognition of emotional word lists in aging and Alzheimer disease. *Cogn Behav Neurol, 19*(2), 71-78. doi: 10.1097/01.wnn.0000213905.49525.d0

36 Burt, D. B., Zembar, M. J., & Niederehe, G. (1995). Depression and memory impairment: a meta-analysis of the association, its pattern, and specificity. *Psychol Bull, 117*(2), 285-305.

37 Caggiano, D. M., Jiang, Y., & Parasuraman, R. (2006). Aging and repetition priming for targets and distracters in a working memory task. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn, 13*(3-4), 552-573. doi: 10.1080/138255890969555

38 Carlesimo, G. A., Mauri, M., Graceffa, A. M., Fadda, L., Loasses, A., Lorusso, S., & Caltagirone, C. (1998). Memory performances in young, elderly, and very old healthy individuals versus patients with Alzheimer's disease: evidence for discontinuity between normal and pathological aging. *J Clin Exp Neuropsychol, 20*(1), 14-29. doi: 10.1076/jcen.20.1.14.1482

39 Carstensen, L. L., Pasupathi, M., Mayr, U., & Nesselroade, J. R. (2000). Emotional experience in everyday life across the adult life span. *J Pers Soc Psychol, 79*(4), 644-655.

40 Celone, K. A., Calhoun, V. D., Dickerson, B. C., Atri, A., Chua, E. F., Miller, S. L., . . . Sperling, R. A. (2006). Alterations in memory networks in mild cognitive

impairment and Alzheimer's disease: an independent component analysis. *J Neurosci, 26*(40), 10222-10231. doi: 10.1523/JNEUROSCI.2250-06.2006

41 Chakor, H., Bertone, A., McKerral, M., Faubert, J., & Lachapelle, P. (2005). Visual evoked potentials and reaction time measurements to motion-reversal luminance- and texture-defined stimuli. *Doc Ophthalmol, 110*(2-3), 163-172. doi: 10.1007/s10633-005-3694-8

42 Charles, S. T., Mather, M., & Carstensen, L. L. (2003). Aging and emotional memory: the forgettable nature of negative images for older adults. *J Exp Psychol Gen, 132*(2), 310-324.

43 Charles, S. T., & Piazza, J. R. (2007). Memories of social interactions: age differences in emotional intensity. *Psychol Aging, 22*(2), 300-309. doi: 10.1037/0882-7974.22.2.300

44 Chertkow, H., Bub, D., Bergman, H., Bruemmer, A., Merling, A., & Rothfleisch, J. (1994). Increased semantic priming in patients with dementia of the Alzheimer's type. *J Clin Exp Neuropsychol, 16*(4), 608-622. doi: 10.1080/01688639408402672

45 Chi, S., Wang, C., Jiang, T., Zhu, X. C., Yu, J. T., & Tan, L. (2015). The prevalence of depression in Alzheimer's disease: a systematic review and meta-analysis. *Curr Alzheimer Res, 12*(2), 189-198.

46 Cohen, J. D. (1988). *Statistical Power Analysis for the Behavioral Sciences* (Second ed.): Lawrence Erlbaum Associates.

47 Collette, F., Van der Linden, M., & Salmon, E. (1999). Executive dysfunction in Alzheimer's disease. *Cortex, 35*(1), 57-72.

48 Collie, A., & Maruff, P. (2002). An analysis of systems of classifying mild cognitive impairment in older people. *Aust N Z J Psychiatry, 36*(1), 133-140.

49 Collie, A., Maruff, P., & Currie, J. (2002). Behavioral characterization of mild cognitive impairment. *J Clin Exp Neuropsychol, 24*(6), 720-733. doi: 10.1076/jcen.24.6.720.8397

50 Corrigan, J. D., & Hinkeldey, N. S. (1987). Relationships between parts A and B of the Trail Making Test. *J Clin Psychol, 43*(4), 402-409.

51 De Bock, T. J., Das, S., Mohsin, M., Munro, N. B., Hively, L., Jiang, Y., . . . Black, C. (2011). Early detection of Alzheimer's disease using nonlinear analysis of EEG via Tsallis entropy. *IEEE Security and Privacy*, 1-4. doi: 10.1109/BSEC.2010.5510813

52 de Gelder, B., van Honk, J., & Tamietto, M. (2011). Emotion in the brain: of low roads, high roads and roads less travelled. *Nat Rev Neurosci, 12*(7), 425; author reply 425. doi: 10.1038/nrn2920-c1

53 De Vogelaere, F., Santens, P., Achten, E., Boon, P., & Vingerhoets, G. (2012). Altered default-mode network activation in mild cognitive impairment compared with healthy aging. *Neuroradiology, 54*(11), 1195-1206. doi: 10.1007/s00234-012-1036-6

54 Dien, J. (2010a). The ERP PCA Toolkit: an open source program for advanced statistical analysis of event-related potential data. *J Neurosci Methods, 187*(1), 138-145. doi: 10.1016/j.jneumeth.2009.12.009

55 Dien, J. (2010b). Evaluating two-step PCA of ERP data with Geomin, Infomax, Oblimin, Promax, and Varimax rotations. *Psychophysiology, 47*(1), 170-183. doi: 10.1111/j.1469-8986.2009.00885.x

56 Drijgers, R. L., Verhey, F. R., Leentjens, A. F., Kohler, S., & Aalten, P. (2011). Neuropsychological correlates of apathy in mild cognitive impairment and Alzheimer's disease: the role of executive functioning. *Int Psychogeriatr, 23*(8), 1327-1333. doi: 10.1017/S1041610211001037

57 Economou, A., Papageorgiou, S., & Karageorgiou, C. (2006). Working-delayed memory difference detects mild cognitive impairment without being affected by age and education. *J Clin Exp Neuropsychol, 28*(4), 528-535. doi: 10.1080/13803390590949340

58 Evans-Roberts, C. E., & Turnbull, O. H. (2011). Remembering relationships: preserved emotion-based learning in Alzheimer's disease. *Exp Aging Res, 37*(1), 1-16. doi: 10.1080/0361073X.2011.536750

59 Faucounau, V., Wu, Y. H., Boulay, M., De Rotrou, J., & Rigaud, A. S. (2010). Cognitive intervention programmes on patients affected by Mild Cognitive Impairment: a promising intervention tool for MCI? *J Nutr Health Aging, 14*(1), 31-35.

60 Faul, F., Erdfelder, E., Buchner, A., & Lang, A. G. (2009). Statistical power analyses using G*Power 3.1: tests for correlation and regression analyses. *Behav Res Methods, 41*(4), 1149-1160. doi: 10.3758/BRM.41.4.1149

61 Faul, F., Erdfelder, E., Lang, A. G., & Buchner, A. (2007). G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods, 39*(2), 175-191.

62 Faust, M. E., Balota, D. A., Spieler, D. H., & Ferraro, F. R. (1999). Individual differences in information-processing rate and amount: implications for group differences in response latency. *Psychol Bull, 125*(6), 777-799.

63 Featherstone, C. R., Morrison, C. M., Waterman, M. G., & MacGregor, L. J. (2013). Semantics, syntax or neither? A case for resolution in the interpretation of N500 and P600 responses to harmonic incongruities. *PLoS One, 8*(11), e76600. doi: 10.1371/journal.pone.0076600

64 Feng, C., Li, W., Tian, T., Luo, Y., Gu, R., Zhou, C., & Luo, Y. J. (2014). Arousal modulates valence effects on both early and late stages of affective picture processing in a passive viewing task. *Soc Neurosci, 9*(4), 364-377. doi: 10.1080/17470919.2014.896827

65 Fernandez-Duque, D., & Black, S. E. (2005). Impaired recognition of negative facial emotions in patients with frontotemporal dementia. *Neuropsychologia, 43*(11), 1673-1687. doi: 10.1016/j.neuropsychologia.2005.01.005

66 Ferraro, F. R., Balota, D. A., & Connor, L. T. (1993). Implicit memory and the formation of new associations in nondemented Parkinson's disease individuals and individuals with senile dementia of the Alzheimer type: a serial reaction time (SRT) investigation. *Brain Cogn, 21*(2), 163-180. doi: 10.1006/brcg.1993.1013

67 Fleischman, D. A. (2007). Repetition priming in aging and Alzheimer's disease: an integrative review and future directions. *Cortex, 43*(7), 889-897.

68 Fleischman, D. A., & Gabrieli, J. D. (1998). Repetition priming in normal aging and Alzheimer's disease: a review of findings and theories. *Psychol Aging, 13*(1), 88-119.

69 Fleischman, D. A., Gabrieli, J. D., Wilson, R. S., Moro, T. T., & Bennett, D. A. (2005). Repetition priming and recognition memory in younger and older persons: temporal stability and performance. *Neuropsychology, 19*(6), 750-759. doi: 10.1037/0894-4105.19.6.750

70 Fleischman, D. A., Wilson, R. S., Gabrieli, J. D., Schneider, J. A., Bienias, J. L., & Bennett, D. A. (2005). Implicit memory and Alzheimer's disease neuropathology. *Brain, 128*(Pt 9), 2006-2015. doi: 10.1093/brain/awh559

71 Foti, D., Hajcak, G., & Dien, J. (2009). Differentiating neural responses to emotional pictures: evidence from temporal-spatial PCA. *Psychophysiology, 46*(3), 521-530.

72 Frantzidis, C. A., Vivas, A. B., Tsolaki, A., Klados, M. A., Tsolaki, M., & Bamidis, P. D. (2014). Functional disorganization of small-world brain networks in mild Alzheimer's Disease and amnestic Mild Cognitive Impairment: an EEG study using Relative Wavelet Entropy (RWE). *Front Aging Neurosci, 6*, 224. doi: 10.3389/fnagi.2014.00224

73 Freeman, D., Startup, H., Dunn, G., Cernis, E., Wingham, G., Pugh, K., . . . Kingdon, D. (2013). The interaction of affective with psychotic processes: a test of the effects of worrying on working memory, jumping to conclusions, and anomalies of experience in patients with persecutory delusions. *J Psychiatr Res, 47*(12), 1837-1842. doi: 10.1016/j.jpsychires.2013.06.016

74 Gabrieli, J. D., Corkin, S., Mickel, S. F., & Growdon, J. H. (1993). Intact acquisition and long-term retention of mirror-tracing skill in Alzheimer's disease and in global amnesia. *Behav Neurosci, 107*(6), 899-910.

75 Gao, S., Hendrie, H. C., Hall, K. S., & Hui, S. (1998). The relationships between age, sex, and the incidence of dementia and Alzheimer disease: a meta-analysis. *Arch Gen Psychiatry, 55*(9), 809-815.

76 Garcia-Rodriguez, B., Vincent, C., Casares-Guillen, C., Ellgring, H., & Frank, A. (2012). The effects of different attentional demands in the identification of emotional facial expressions in Alzheimer's disease. *Am J Alzheimers Dis Other Demen, 27*(7), 530-536. doi: 10.1177/1533317512459797

77 Gates, N. J., Sachdev, P. S., Fiatarone Singh, M. A., & Valenzuela, M. (2011). Cognitive and memory training in adults at risk of dementia: a systematic review. *BMC Geriatr, 11*, 55. doi: 10.1186/1471-2318-11-55

78 Gavazzeni, J., Wiens, S., & Fischer, H. (2008). Age effects to negative arousal differ for self-report and electrodermal activity. *Psychophysiology, 45*(1), 148-151. doi: 10.1111/j.1469-8986.2007.00596.x

79 Ghashghaei, H. T., & Barbas, H. (2002). Pathways for emotion: interactions of prefrontal and anterior temporal pathways in the amygdala of the rhesus monkey. *Neuroscience, 115*(4), 1261-1279.

80 Giovagnoli, A. R., Del Pesce, M., Mascheroni, S., Simoncelli, M., Laiacona, M., & Capitani, E. (1996). Trail making test: normative values from 287 normal adult controls. *Ital J Neurol Sci, 17*(4), 305-309.

81 Gotts, S. J., Chow, C. C., & Martin, A. (2012a). Repetition Priming and Repetition Suppression: A Case for Enhanced Efficiency Through Neural Synchronization. *Cogn Neurosci, 3*(3-4), 227-237. doi: 10.1080/17588928.2012.670617

82 Gotts, S. J., Chow, C. C., & Martin, A. (2012b). Repetition priming and repetition suppression: Multiple mechanisms in need of testing. *Cogn Neurosci, 3*(3-4), 250-259. doi: 10.1080/17588928.2012.697054

83 Gotts, S. J., Milleville, S. C., & Martin, A. (2014). Object identification leads to a conceptual broadening of object representations in lateral prefrontal cortex. *Neuropsychologia*. doi: 10.1016/j.neuropsychologia.2014.10.041

84 Greenwood, P. M., Parasuraman, R., & Alexander, G. E. (1997). Controlling the focus of spatial attention during visual search: effects of advanced aging and Alzheimer disease. *Neuropsychology, 11*(1), 3-12.

85 Greenwood, P. M., Parasuraman, R., & Haxby, J. V. (1993). Changes in visuospatial attention over the adult lifespan. *Neuropsychologia, 31*(5), 471-485.

86 Greicius, M. D., Krasnow, B., Reiss, A. L., & Menon, V. (2003). Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *Proc Natl Acad Sci U S A, 100*(1), 253-258. doi: 10.1073/pnas.0135058100

87 Grill-Spector, K., Henson, R., & Martin, A. (2006). Repetition and the brain: neural models of stimulus-specific effects. *Trends Cogn Sci, 10*(1), 14-23. doi: 10.1016/j.tics.2005.11.006

88 Gruhn, D., & Scheibe, S. (2008). Age-related differences in valence and arousal ratings of pictures from the International Affective Picture System (IAPS): do ratings become more extreme with age? *Behav Res Methods, 40*(2), 512-521.

89 Gruhn, D., Scheibe, S., & Baltes, P. B. (2007). Reduced negativity effect in older adults' memory for emotional pictures: the heterogeneity-homogeneity list paradigm. *Psychol Aging, 22*(3), 644-649. doi: 10.1037/0882-7974.22.3.644

90 Guillem, F., Chouinard, S., Poulin, J., Godbout, R., Lalonde, P., Melun, P., . . . Stip, E. (2006). Are cholinergic enhancers beneficial for memory in schizophrenia? An event-related potentials (ERPs) study of rivastigmine add-on therapy in a crossover trial. *Prog Neuropsychopharmacol Biol Psychiatry, 30*(5), 934-945. doi: 10.1016/j.pnpbp.2006.02.009

91 Guo, C., Lawson, A. L., & Jiang, Y. (2007). Distinct neural mechanisms for repetition effects of visual objects. *Neuroscience, 149*(4), 747-759. doi: 10.1016/j.neuroscience.2007.07.060

92 Guo, C., Lawson, A. L., Zhang, Q., & Jiang, Y. (2008). Brain potentials distinguish new and studied objects during working memory. *Hum Brain Mapp, 29*(4), 441-452. doi: 10.1002/hbm.20409

93 Hamann, S., Monarch, E. S., & Goldstein, F. C. (2002). Impaired fear conditioning in Alzheimer's disease. *Neuropsychologia, 40*(8), 1187-1195.

94 Hampson, M., Driesen, N. R., Skudlarski, P., Gore, J. C., & Constable, R. T. (2006). Brain connectivity related to working memory performance. *J Neurosci, 26*(51), 13338-13343. doi: 10.1523/JNEUROSCI.3408-06.2006

95 Hansen, B. C., Johnson, A. P., & Ellemberg, D. (2012). Different spatial frequency bands selectively signal for natural image statistics in the early visual system. *J Neurophysiol, 108*(8), 2160-2172. doi: 10.1152/jn.00288.2012

96 Henderson, V. W., & Buckwalter, J. G. (1994). Cognitive deficits of men and women with Alzheimer's disease. *Neurology, 44*(1), 90-96.

97 Henke, K. (2010). A model for memory systems based on processing modes rather than consciousness. *Nat Rev Neurosci, 11*(7), 523-532. doi: 10.1038/nrn2850

98 Henson, R. N. (2012a). Repetition accelerates neural dynamics: in defense of facilitation models. *Cognitive Neuroscience, 3*(3-4), 240-241.

99 Henson, R. N. (2012b). Repetition accelerates neural dynamics: In defense of facilitation models. *Cogn Neurosci, 3*(3-4), 240-241. doi: 10.1080/17588928.2012.689962

100 Henson, R. N., & Rugg, M. D. (2003). Neural response suppression, haemodynamic repetition effects, and behavioural priming. *Neuropsychologia, 41*(3), 263-270.

101 Henson, R. N., Rylands, A., Ross, E., Vuilleumeir, P., & Rugg, M. D. (2004). The effect of repetition lag on electrophysiological and haemodynamic correlates of visual object priming. *Neuroimage, 21*(4), 1674-1689. doi: 10.1016/j.neuroimage.2003.12.020

102 Hodges, J. R., Erzinclioglu, S., & Patterson, K. (2006). Evolution of cognitive deficits and conversion to dementia in patients with mild cognitive impairment: a very-long-

term follow-up study. *Dement Geriatr Cogn Disord, 21*(5-6), 380-391. doi: 10.1159/000092534

103 Hopper, T. L. (2003). "They're just going to get worse anyway": perspectives on rehabilitation for nursing home residents with dementia. *J Commun Disord, 36*(5), 345-359.

104 Howard, J. H., Howard, D. V., Dennis, N. A., & Kelly, A. J. (2008). Implicit learning of predictive relationships in three-element visual sequences by young and old adults. *J Exp Psychol Learn Mem Cogn, 34*(5), 1139-1157. doi: 10.1037/a0012797

105 Hudon, C., Villeneuve, S., & Belleville, S. (2011). The effect of semantic orientation at encoding on free-recall performance in amnestic mild cognitive impairment and probable Alzheimer's disease. *J Clin Exp Neuropsychol, 33*(6), 631-638. doi: 10.1080/13803395.2010.547663

106 Ikeda, M., Mori, E., Hirono, N., Imamura, T., Shimomura, T., Ikejiri, Y., & Yamashita, H. (1998). Amnestic people with Alzheimer's disease who remembered the Kobe earthquake. *Br J Psychiatry, 172*, 425-428.

107 Irvine, K., Laws, K. R., Gale, T. M., & Kondel, T. K. (2012). Greater cognitive deterioration in women than men with Alzheimer's disease: a meta analysis. *J Clin Exp Neuropsychol, 34*(9), 989-998. doi: 10.1080/13803395.2012.712676

108 Isaacowitz, D. M., Allard, E. S., Murphy, N. A., & Schlangel, M. (2009). The time course of age-related preferences toward positive and negative stimuli. *J Gerontol B Psychol Sci Soc Sci, 64*(2), 188-192. doi: 10.1093/geronb/gbn036

109 Isaacowitz, D. M., Toner, K., & Neupert, S. D. (2009). Use of gaze for real-time mood regulation: effects of age and attentional functioning. *Psychol Aging, 24*(4), 989-994. doi: 10.1037/a0017706

110 Jacobs, H. I., Gronenschild, E. H., Evers, E. A., Ramakers, I. H., Hofman, P. A., Backes, W. H., . . . Van Boxtel, M. P. (2015). Visuospatial processing in early Alzheimer's disease: a multimodal neuroimaging study. *Cortex, 64*, 394-406. doi: 10.1016/j.cortex.2012.01.005

111 James, C. E., Cereghetti, D. M., Roullet Tribes, E., & Oechslin, M. S. (2015). Electrophysiological evidence for a specific neural correlate of musical violation expectation in primary-school children. *Neuroimage, 104*, 386-397. doi: 10.1016/j.neuroimage.2014.09.047

112 Jean, L., Simard, M., Wiederkehr, S., Bergeron, M. E., Turgeon, Y., Hudon, C., . . . van Reekum, R. (2010). Efficacy of a cognitive training programme for mild cognitive impairment: results of a randomised controlled study. *Neuropsychol Rehabil, 20*(3), 377-405. doi: 10.1080/09602010903343012

113 Jiang, Y., Haxby, J. V., Martin, A., Ungerleider, L. G., & Parasuraman, R. (2000). Complementary neural mechanisms for tracking items in human working memory. *Science, 287*(5453), 643-646.

114 Jicha, G. A., Abner, E., Schmitt, F. A., Cooper, G. E., Stiles, N., Hamon, R., . . . Markesbery, W. R. (2008). Clinical features of mild cognitive impairment differ in the research and tertiary clinic settings. *Dement Geriatr Cogn Disord, 26*(2), 187-192. doi: 10.1159/000151635

115 Joshi, A., Barsuglia, J. P., Mather, M. J., Jimenez, E. E., Shapira, J., & Mendez, M. F. (2014). Evaluation of emotional blunting in behavioral variant frontotemporal dementia compared to Alzheimer's disease. *Dement Geriatr Cogn Disord, 38*(1-2), 79-88. doi: 10.1159/000357838

116 Kazmerski, V. A., & Friedman, D. (1997). Effect of multiple presentations of words on event-related potential and reaction time repetition effects in Alzheimer's patients and young and older controls. *Neuropsychiatry Neuropsychol Behav Neurol, 10*(1), 32-47.
117 Kazui, H., Mori, E., Hashimoto, M., & Hirono, N. (2003). Enhancement of declarative memory by emotional arousal and visual memory function in Alzheimer's disease. *J Neuropsychiatry Clin Neurosci, 15*(2), 221-226.
118 Kazui, H., Mori, E., Hashimoto, M., Hirono, N., Imamura, T., Tanimukai, S., . . . Cahill, L. (2000). Impact of emotion on memory. Controlled study of the influence of emotionally charged material on declarative memory in Alzheimer's disease. *Br J Psychiatry, 177*, 343-347.
119 Keane, M. M., Gabrieli, J. D., Fennema, A. C., Growdon, J. H., & Corkin, S. (1991). Evidence for a dissociation between perceptual and conceptual priming in Alzheimer's disease. *Behav Neurosci, 105*(2), 326-342.
120 Keil, A., & Freund, A. M. (2009). Changes in the sensitivity to appetitive and aversive arousal across adulthood. *Psychol Aging, 24*(3), 668-680. doi: 10.1037/a0016969
121 Kennedy, K. M., Rodrigue, K. M., Head, D., Gunning-Dixon, F., & Raz, N. (2009). Neuroanatomical and cognitive mediators of age-related differences in perceptual priming and learning. *Neuropsychology, 23*(4), 475-491. doi: 10.1037/a0015377
122 Kensinger, E. A. (2008). *Emotional Memory across the Adult Lifespan*: Psychology Press.
123 Kensinger, E. A., Anderson, A., Growdon, J. H., & Corkin, S. (2004). Effects of Alzheimer disease on memory for verbal emotional information. *Neuropsychologia, 42*(6), 791-800. doi: 10.1016/j.neuropsychologia.2003.11.011
124 Kensinger, E. A., Brierley, B., Medford, N., Growdon, J. H., & Corkin, S. (2002). Effects of normal aging and Alzheimer's disease on emotional memory. *Emotion, 2*(2), 118-134.
125 Kensinger, E. A., & Corkin, S. (2003a). Effect of negative emotional content on working memory and long-term memory. *Emotion, 3*(4), 378-393. doi: 10.1037/1528-3542.3.4.378
126 Kensinger, E. A., & Corkin, S. (2003b). Memory enhancement for emotional words: are emotional words more vividly remembered than neutral words? *Mem Cognit, 31*(8), 1169-1180.
127 Kensinger, E. A., Krendl, A. C., & Corkin, S. (2006). Memories of an emotional and a nonemotional event: effects of aging and delay interval. *Exp Aging Res, 32*(1), 23-45. doi: 10.1080/01902140500325031
128 Kerestes, R., Ladouceur, C. D., Meda, S., Nathan, P. J., Blumberg, H. P., Maloney, K., . . . Phillips, M. L. (2012). Abnormal prefrontal activity subserving attentional control of emotion in remitted depressed patients during a working memory task with emotional distracters. *Psychol Med, 42*(1), 29-40. doi: 10.1017/S0033291711001097
129 Kessels, R. P., & de Haan, E. H. (2003a). Implicit learning in memory rehabilitation: a meta-analysis on errorless learning and vanishing cues methods. *J Clin Exp Neuropsychol, 25*(6), 805-814. doi: 10.1076/jcen.25.6.805.16474
130 Kessels, R. P., & de Haan, E. H. (2003b). Mnemonic strategies in older people: a comparison of errorless and errorful learning. *Age Ageing, 32*(5), 529-533.
131 Kessels, R. P., Remmerswaal, M., & Wilson, B. A. (2011). Assessment of nondeclarative learning in severe Alzheimer dementia: the Implicit Memory Test (IMT). *Alzheimer Dis Assoc Disord, 25*(2), 179-183. doi: 10.1097/WAD.0b013e318203f3ab

132 Kim, D. I., Manoach, D. S., Mathalon, D. H., Turner, J. A., Mannell, M., Brown, G. G., . . . Calhoun, V. D. (2009). Dysregulation of working memory and default-mode networks in schizophrenia using independent component analysis, an fBIRN and MCIC study. *Hum Brain Mapp, 30*(11), 3795-3811. doi: 10.1002/hbm.20807

133 Klimkowicz-Mrowiec, A., Slowik, A., Krzywoszanski, L., Herzog-Krzywoszanska, R., & Szczudlik, A. (2008). Severity of explicit memory impairment due to Alzheimer's disease improves effectiveness of implicit learning. *J Neurol, 255*(4), 502-509. doi: 10.1007/s00415-008-0717-x

134 Knight, M., Seymour, T. L., Gaunt, J. T., Baker, C., Nesmith, K., & Mather, M. (2007). Aging and goal-directed emotional attention: distraction reverses emotional biases. *Emotion, 7*(4), 705-714. doi: 10.1037/1528-3542.7.4.705

135 Koelsch, S., Gunter, T. C., Wittfoth, M., & Sammler, D. (2005). Interaction between syntax processing in language and in music: an ERP Study. *J Cogn Neurosci, 17*(10), 1565-1577. doi: 10.1162/089892905774597290

136 Koenig, P., Smith, E. E., Troiani, V., Anderson, C., Moore, P., & Grossman, M. (2008). Medial temporal lobe involvement in an implicit memory task: evidence of collaborating implicit and explicit memory systems from FMRI and Alzheimer's disease. *Cereb Cortex, 18*(12), 2831-2843. doi: 10.1093/cercor/bhn043

137 Korczyn, A. D., & Halperin, I. (2009). Depression and dementia. *J Neurol Sci, 283*(1-2), 139-142. doi: 10.1016/j.jns.2009.02.346

138 Kramer, J. H., Nelson, A., Johnson, J. K., Yaffe, K., Glenn, S., Rosen, H. J., & Miller, B. L. (2006). Multiple cognitive deficits in amnestic mild cognitive impairment. *Dement Geriatr Cogn Disord, 22*(4), 306-311. doi: 10.1159/000095303

139 Kumar, A., Singh, A., & Ekavali. (2015). A review on Alzheimer's disease pathophysiology and its management: an update. *Pharmacol Rep, 67*(2), 195-203. doi: 10.1016/j.pharep.2014.09.004

140 Kumfor, F., Irish, M., Hodges, J. R., & Piguet, O. (2014). Frontal and temporal lobe contributions to emotional enhancement of memory in behavioral-variant frontotemporal dementia and Alzheimer's disease. *Front Behav Neurosci, 8*, 225. doi: 10.3389/fnbeh.2014.00225

141 Kutas, M., McCarthy, G., & Donchin, E. (1977). Augmenting mental chronometry: the P300 as a measure of stimulus evaluation time. *Science, 197*(4305), 792-795.

142 LaBar, K. S., Torpey, D. C., Cook, C. A., Johnson, S. R., Warren, L. H., Burke, J. R., & Welsh-Bohmer, K. A. (2005). Emotional enhancement of perceptual priming is preserved in aging and early-stage Alzheimer's disease. *Neuropsychologia, 43*(12), 1824-1837. doi: 10.1016/j.neuropsychologia.2005.01.018

143 Labouvie-Vief, G., Diehl, M., Jain, E., & Zhang, F. (2007). Six-year change in affect optimization and affect complexity across the adult life span: a further examination. *Psychol Aging, 22*(4), 738-751. doi: 10.1037/0882-7974.22.4.738

144 Labouvie-Vief, G., Lumley, M. A., Jain, E., & Heinze, H. (2003). Age and gender differences in cardiac reactivity and subjective emotion responses to emotional autobiographical memories. *Emotion, 3*(2), 115-126.

145 Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (1998). Emotion, motivation, and anxiety: brain mechanisms and psychophysiology. *Biol Psychiatry, 44*(12), 1248-1263.

146 Larouche, E., Hudon, C., & Goulet, S. (2015). Potential benefits of mindfulness-based interventions in mild cognitive impairment and Alzheimer's disease: an interdisciplinary perspective. *Behav Brain Res, 276*, 199-212. doi: 10.1016/j.bbr.2014.05.058

147 Lavenu, I., Pasquier, F., Lebert, F., Petit, H., & Van der Linden, M. (1999). Perception of emotion in frontotemporal dementia and Alzheimer disease. *Alzheimer Dis Assoc Disord, 13*(2), 96-101.
148 Lawson, A. L., Guo, C., & Jiang, Y. (2007). Age effects on brain activity during repetition priming of targets and distracters. *Neuropsychologia, 45*(6), 1223-1231. doi: 10.1016/j.neuropsychologia.2006.10.014
149 Leclerc, C. M., & Kensinger, E. A. (2011). Neural processing of emotional pictures and words: a comparison of young and older adults. *Dev Neuropsychol, 36*(4), 519-538. doi: 10.1080/87565641.2010.549864
150 Lee, G. Y., Yip, C. C., Yu, E. C., & Man, D. W. (2013). Evaluation of a computer-assisted errorless learning-based memory training program for patients with early Alzheimer's disease in Hong Kong: a pilot study. *Clin Interv Aging, 8*, 623-633. doi: 10.2147/CIA.S45726
151 Lehmann, M., Crutch, S. J., Ridgway, G. R., Ridha, B. H., Barnes, J., Warrington, E. K., . . . Fox, N. C. (2011). Cortical thickness and voxel-based morphometry in posterior cortical atrophy and typical Alzheimer's disease. *Neurobiol Aging, 32*(8), 1466-1476. doi: 10.1016/j.neurobiolaging.2009.08.017
152 Lekeu, F., Magis, D., Marique, P., Delbeuck, X., Bechet, S., Guillaume, B., . . . Salmon, E. (2010). The California Verbal Learning Test and other standard clinical neuropsychological tests to predict conversion from mild memory impairment to dementia. *J Clin Exp Neuropsychol, 32*(2), 164-173. doi: 10.1080/13803390902889606
153 Li, H., Li, J., Li, N., Li, B., Wang, P., & Zhou, T. (2011). Cognitive intervention for persons with mild cognitive impairment: A meta-analysis. *Ageing Res Rev, 10*(2), 285-296. doi: 10.1016/j.arr.2010.11.003
154 Li, Q., Guo, C., & Jiang, Y. (2008). Brain potentials and repetition effects during encoding and retrieval of words. *Neuroreport, 19*(14), 1365-1368. doi: 10.1097/WNR.0b013e32830c8dda
155 Liang, P., Wang, Z., Yang, Y., Jia, X., & Li, K. (2011). Functional disconnection and compensation in mild cognitive impairment: evidence from DLPFC connectivity using resting-state fMRI. *PLoS One, 6*(7), e22153. doi: 10.1371/journal.pone.0022153
156 Libkuman, T. M., Otani, H., Kern, R., Viger, S. G., & Novak, N. (2007). Multidimensional normative ratings for the International Affective Picture System. *Behav Res Methods, 39*(2), 326-334.
157 Lockenhoff, C. E., & Carstensen, L. L. (2007). Aging, emotion, and health-related decision strategies: motivational manipulations can reduce age differences. *Psychol Aging, 22*(1), 134-146. doi: 10.1037/0882-7974.22.1.134
158 Lubinsky, T., Rich, J. B., & Anderson, N. D. (2009). Errorless learning and elaborative self-generation in healthy older adults and individuals with amnestic mild cognitive impairment: mnemonic benefits and mechanisms. *J Int Neuropsychol Soc, 15*(5), 704-716. doi: 10.1017/S1355617709990270
159 Luck, T., Riedel-Heller, S. G., Kaduszkiewicz, H., Bickel, H., Jessen, F., Pentzek, M., . . . AgeCoDe, g. (2007). Mild cognitive impairment in general practice: age-specific prevalence and correlate results from the German study on ageing, cognition and dementia in primary care patients (AgeCoDe). *Dement Geriatr Cogn Disord, 24*(4), 307-316. doi: 10.1159/000108099
160 Luo, Y., Shen, W., Zhang, Y., Feng, T. Y., Huang, H., & Li, H. (2013). Core disgust and moral disgust are related to distinct spatiotemporal patterns of neural processing:

an event-related potential study. *Biol Psychol, 94*(2), 242-248. doi: 10.1016/j.biopsycho.2013.06.005

161 Martin, M., Clare, L., Altgassen, A. M., Cameron, M. H., & Zehnder, F. (2011). Cognition-based interventions for healthy older people and people with mild cognitive impairment. *Cochrane Database Syst Rev*(1), CD006220. doi: 10.1002/14651858.CD006220.pub2

162 Mather, M., & Knight, M. (2005). Goal-directed memory: the role of cognitive control in older adults' emotional memory. *Psychol Aging, 20*(4), 554-570. doi: 10.1037/0882-7974.20.4.554

163 Mather, M., & Knight, M. R. (2006). Angry faces get noticed quickly: threat detection is not impaired among older adults. *J Gerontol B Psychol Sci Soc Sci, 61*(1), P54-57.

164 Matsuda, O., & Saito, M. (2009). Multiple cognitive deficits in patients during the mild cognitive impairment stage of Alzheimer's disease: how are cognitive domains other than episodic memory impaired? *Int Psychogeriatr, 21*(5), 970-976. doi: 10.1017/S1041610209990330

165 May, C. P., Manning, M., Einstein, G. O., Becker, L., & Owens, M. (2015). The best of both worlds: emotional cues improve prospective memory execution and reduce repetition errors. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn, 22*(3), 357-375. doi: 10.1080/13825585.2014.952263

166 McCarthy, G., & Donchin, E. (1981). A metric for thought: a comparison of P300 latency and reaction time. *Science, 211*(4477), 77-80.

167 McGaugh, J. L., Cahill, L., & Roozendaal, B. (1996). Involvement of the amygdala in memory storage: interaction with other brain systems. *Proc Natl Acad Sci U S A, 93*(24), 13508-13514.

168 McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack, C. R., Jr., Kawas, C. H., . . . Phelps, C. H. (2011). The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement, 7*(3), 263-269. doi: 10.1016/j.jalz.2011.03.005

169 Mendez-Bertolo, C., Pozo, M. A., & Hinojosa, J. A. (2011). Early effects of emotion on word immediate repetition priming: electrophysiological and source localization evidence. *Cogn Affect Behav Neurosci, 11*(4), 652-665. doi: 10.3758/s13415-011-0059-5

170 Migo, E. M., Mitterschiffthaler, M., O'Daly, O., Dawson, G. R., Dourish, C. T., Craig, K. J., . . . Morris, R. G. (2015). Alterations in working memory networks in amnestic mild cognitive impairment. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn, 22*(1), 106-127. doi: 10.1080/13825585.2014.894958

171 Mikels, J. A., Fredrickson, B. L., Larkin, G. R., Lindberg, C. M., Maglio, S. J., & Reuter-Lorenz, P. A. (2005). Emotional category data on images from the International Affective Picture System. *Behav Res Methods, 37*(4), 626-630.

172 Mikels, J. A., Larkin, G. R., Reuter-Lorenz, P. A., & Cartensen, L. L. (2005). Divergent trajectories in the aging mind: changes in working memory for affective versus visual information with age. *Psychol Aging, 20*(4), 542-553. doi: 10.1037/0882-7974.20.4.542

173 Miller, E. K., Erickson, C. A., & Desimone, R. (1996). Neural mechanisms of visual working memory in prefrontal cortex of the macaque. *J Neurosci, 16*(16), 5154-5167.

174 Miller, L. A., Hsieh, S., Lah, S., Savage, S., Hodges, J. R., & Piguet, O. (2012). One size does not fit all: face emotion processing impairments in semantic dementia, behavioural-variant frontotemporal dementia and Alzheimer's disease are mediated

by distinct cognitive deficits. *Behav Neurol, 25*(1), 53-60. doi: 10.3233/BEN-2012-0349

175 Mimura, M., & Komatsu, S. (2007). Cognitive rehabilitation and cognitive training for mild dementia. *Psychogeriatrics, 7*, 137–143. doi: 10.1111/j.1479-8301.2007.00212.x

176 Mimura, M., & Komatsu, S. (2010). Factors of error and effort in memory intervention for patients with Alzheimer's disease and amnesic syndrome. *Psychogeriatrics, 10*(4), 179-186. doi: 10.1111/j.1479-8301.2010.00339.x

177 Missonnier, P., Deiber, M. P., Gold, G., Herrmann, F. R., Millet, P., Michon, A., . . . Giannakopoulos, P. (2007). Working memory load-related electroencephalographic parameters can differentiate progressive from stable mild cognitive impairment. *Neuroscience, 150*(2), 346-356. doi: 10.1016/j.neuroscience.2007.09.009

178 Missonnier, P., Deiber, M. P., Gold, G., Millet, P., Gex-Fabry Pun, M., Fazio-Costa, L., . . . Ibanez, V. (2006). Frontal theta event-related synchronization: comparison of directed attention and working memory load effects. *J Neural Transm, 113*(10), 1477-1486. doi: 10.1007/s00702-005-0443-9

179 Mitchell, D. B., & Schmitt, F. A. (2006). Short- and long-term implicit memory in aging and Alzheimer's disease. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn, 13*(3-4), 611-635. doi: 10.1080/13825580600697616

180 Moayeri, S. E., Cahill, L., Jin, Y., & Potkin, S. G. (2000). Relative sparing of emotionally influenced memory in Alzheimer's disease. *Neuroreport, 11*(4), 653-655.

181 Mori, E., Ikeda, M., Hirono, N., Kitagaki, H., Imamura, T., & Shimomura, T. (1999). Amygdalar volume and emotional memory in Alzheimer's disease. *Am J Psychiatry, 156*(2), 216-222.

182 Moulin, C. J., James, N., Freeman, J. E., & Jones, R. W. (2004). Deficient acquisition and consolidation: intertrial free recall performance in Alzheimer's disease and mild cognitive impairment. *J Clin Exp Neuropsychol, 26*(1), 1-10. doi: 10.1076/jcen.26.1.1.23940

183 Mowszowski, L., Batchelor, J., & Naismith, S. L. (2010). Early intervention for cognitive decline: can cognitive training be used as a selective prevention technique? *Int Psychogeriatr, 22*(4), 537-548. doi: 10.1017/S1041610209991748

184 Murphy, N. A., & Isaacowitz, D. M. (2008). Preferences for emotional information in older and younger adults: a meta-analysis of memory and attention tasks. *Psychol Aging, 23*(2), 263-286. doi: 10.1037/0882-7974.23.2.263

185 Narumoto, J., Okada, T., Sadato, N., Fukui, K., & Yonekura, Y. (2001). Attention to emotion modulates fMRI activity in human right superior temporal sulcus. *Brain Res Cogn Brain Res, 12*(2), 225-231.

186 Nashiro, K., & Mather, M. (2011a). Effects of emotional arousal on memory binding in normal aging and Alzheimer's disease. *Am J Psychol, 124*(3), 301-312.

187 Nashiro, K., & Mather, M. (2011b). How arousal affects younger and older adults' memory binding. *Exp Aging Res, 37*(1), 108-128. doi: 10.1080/0361073X.2011.536746

188 Nashiro, K., Mather, M., Gorlick, M. A., & Nga, L. (2011). Negative emotional outcomes impair older adults' reversal learning. *Cogn Emot, 25*(6), 1014-1028. doi: 10.1080/02699931.2010.542999

189 Nieuwenhuis-Mark, R. E., Schalk, K., & de Graaf, N. (2009). Free recall and learning of emotional word lists in very elderly people with and without dementia. *Am J Alzheimers Dis Other Demen, 24*(2), 155-162. doi: 10.1177/1533317508330561

190 Olichney, J. M., Iragui, V. J., Salmon, D. P., Riggins, B. R., Morris, S. K., & Kutas, M. (2006). Absent event-related potential (ERP) word repetition effects in mild Alzheimer's disease. *Clin Neurophysiol, 117*(6), 1319-1330. doi: 10.1016/j.clinph.2006.02.022

191 Olichney, J. M., Morris, S. K., Ochoa, C., Salmon, D. P., Thal, L. J., Kutas, M., & Iragui, V. J. (2002). Abnormal verbal event related potentials in mild cognitive impairment and incipient Alzheimer's disease. *J Neurol Neurosurg Psychiatry, 73*(4), 377-384.

192 Olichney, J. M., Pak, J., Salmon, D. P., Yang, J. C., Gahagan, T., Nowacki, R., . . . Iragui-Madoz, V. J. (2013). Abnormal P600 word repetition effect in elderly persons with preclinical Alzheimer's disease. *Cogn Neurosci, 4*(3-4), 143-151. doi: 10.1080/17588928.2013.838945

193 Olichney, J. M., Taylor, J. R., Gatherwright, J., Salmon, D. P., Bressler, A. J., Kutas, M., & Iragui-Madoz, V. J. (2008). Patients with MCI and N400 or P600 abnormalities are at very high risk for conversion to dementia. *Neurology, 70*(19 Pt 2), 1763-1770. doi: 10.1212/01.wnl.0000281689.28759.ab

194 Orgeta, V. (2011a). Avoiding threat in late adulthood: testing two life span theories of emotion. *Exp Aging Res, 37*(4), 449-472. doi: 10.1080/0361073X.2011.590759

195 Orgeta, V. (2011b). Emotion dysregulation and anxiety in late adulthood. *J Anxiety Disord, 25*(8), 1019-1023. doi: 10.1016/j.janxdis.2011.06.010

196 Oztekin, I., McElree, B., Staresina, B. P., & Davachi, L. (2009). Working memory retrieval: contributions of the left prefrontal cortex, the left posterior parietal cortex, and the hippocampus. *J Cogn Neurosci, 21*(3), 581-593. doi: 10.1162/jocn.2008.21016

197 Padovan, C., Versace, R., Thomas-Anterion, C., & Laurent, B. (2002). Evidence for a selective deficit in automatic activation of positive information in patients with Alzheimer's disease in an affective priming paradigm. *Neuropsychologia, 40*(3), 335-339.

198 Parasuraman, R., Greenwood, P. M., Haxby, J. V., & Grady, C. L. (1992). Visuospatial attention in dementia of the Alzheimer type. *Brain, 115 (Pt 3)*, 711-733.

199 Pessoa, L. (2008). On the relationship between emotion and cognition. *Nat Rev Neurosci, 9*(2), 148-158. doi: 10.1038/nrn2317

200 Pessoa, L. (2009). How do emotion and motivation direct executive control? *Trends Cogn Sci, 13*(4), 160-166. doi: 10.1016/j.tics.2009.01.006

201 Pessoa, L. (2010). Emergent processes in cognitive-emotional interactions. *Dialogues Clin Neurosci, 12*(4), 433-448.

202 Pessoa, L., & Adolphs, R. (2010). Emotion processing and the amygdala: from a 'low road' to 'many roads' of evaluating biological significance. *Nat Rev Neurosci, 11*(11), 773-783. doi: 10.1038/nrn2920

203 Phelps, E. A. (2004). Human emotion and memory: interactions of the amygdala and hippocampal complex. *Curr Opin Neurobiol, 14*(2), 198-202. doi: 10.1016/j.conb.2004.03.015

204 Phelps, E. A., Delgado, M. R., Nearing, K. I., & LeDoux, J. E. (2004). Extinction learning in humans: role of the amygdala and vmPFC. *Neuron, 43*(6), 897-905. doi: 10.1016/j.neuron.2004.08.042

205 Pignatti, R., Rabuffetti, M., Imbornone, E., Mantovani, F., Alberoni, M., Farina, E., & Canal, N. (2005). Specific impairments of selective attention in mild Alzheimer's disease. *J Clin Exp Neuropsychol, 27*(4), 436-448. doi: 10.1080/13803390490520427

206 Pihlajamaki, M., O'Keefe, K., O'Brien, J., Blacker, D., & Sperling, R. A. (2011). Failure of repetition suppression and memory encoding in aging and Alzheimer's disease. *Brain Imaging Behav, 5*(1), 36-44. doi: 10.1007/s11682-010-9110-3

207 Porto, W. G., Bertolucci, P. H., & Bueno, O. F. (2011). The paradox of age: an analysis of responses by aging Brazilians to International Affective Picture System (IAPS). *Rev Bras Psiquiatr, 33*(1), 10-15.

208 Qi, Z., Wu, X., Wang, Z., Zhang, N., Dong, H., Yao, L., & Li, K. (2010). Impairment and compensation coexist in amnestic MCI default mode network. *Neuroimage, 50*(1), 48-55. doi: 10.1016/j.neuroimage.2009.12.025

209 Quintana Hernandez, D. J., Miro Barrachina, M. T., Ibanez Fernandez, I., del Pino, A. S., Garcia, R., Jr., & Hernandez, J. R. (2014). [Effects of a neuropsychology program based on mindfulness on Alzheimer's disease: randomized double-blind clinical study]. *Rev Esp Geriatr Gerontol, 49*(4), 165-172. doi: 10.1016/j.regg.2014.03.002

210 Quintana Hernandez, D. J., Miro Barrachina, M. T., Ibanez Fernandez, I., Santana Del Pino, A., Rojas Hernandez, J., Rodriguez Garcia, J., & Quintana Montesdeoca Mdel, P. (2015). [Mindfulness-based stimulation in advanced Alzheimer's disease: A comparative, non-inferiority, clinical pilot study]. *Rev Esp Geriatr Gerontol, 50*(4), 168-173. doi: 10.1016/j.regg.2014.11.010

211 Quirk, G. J., & Beer, J. S. (2006). Prefrontal involvement in the regulation of emotion: convergence of rat and human studies. *Curr Opin Neurobiol, 16*(6), 723-727. doi: 10.1016/j.conb.2006.07.004

212 Race, E. A., Badre, D., & Wagner, A. D. (2010). Multiple forms of learning yield temporally distinct electrophysiological repetition effects. *Cerebral Cortex, 20*(7), 1726-1738. doi: 10.1093/cercor/bhp233

213 Rainville, C., Lepage, E., Gauthier, S., Kergoat, M. J., & Belleville, S. (2012). Executive function deficits in persons with mild cognitive impairment: a study with a Tower of London task. *J Clin Exp Neuropsychol, 34*(3), 306-324. doi: 10.1080/13803395.2011.639298

214 Ranganath, C., Cohen, M. X., Dam, C., & D'Esposito, M. (2004). Inferior temporal, prefrontal, and hippocampal contributions to visual working memory maintenance and associative memory retrieval. *J Neurosci, 24*(16), 3917-3925. doi: 10.1523/JNEUROSCI.5053-03.2004

215 Reeves, R. R., Struve, F. A., & Patrick, G. (2002). The effects of donepezil on quantitative EEG in patients with Alzheimer's disease. *Clin Electroencephalogr, 33*(2), 93-96.

216 Reid, L. M., & Maclullich, A. M. (2006). Subjective memory complaints and cognitive impairment in older people. *Dement Geriatr Cogn Disord, 22*(5-6), 471-485. doi: 10.1159/000096295

217 Ribeiro, F., Guerreiro, M., & De Mendonca, A. (2007). Verbal learning and memory deficits in Mild Cognitive Impairment. *J Clin Exp Neuropsychol, 29*(2), 187-197. doi: 10.1080/13803390600629775

218 Robert, P. H., Berr, C., Volteau, M., Bertogliati, C., Benoit, M., Mahieux, F., . . . Pre, A. L. S. (2006). Neuropsychological performance in mild cognitive impairment with and without apathy. *Dement Geriatr Cogn Disord, 21*(3), 192-197. doi: 10.1159/000090766

219 Rochon, E., Waters, G. S., & Caplan, D. (2000). The relationship between measures of working memory and sentence comprehension in patients with Alzheimer's disease. *J Speech Lang Hear Res, 43*(2), 395-413.
220 Rosenbaum, R. S., Furey, M. L., Horwitz, B., & Grady, C. L. (2010). Altered connectivity among emotion-related brain regions during short-term memory in Alzheimer's disease. *Neurobiol Aging, 31*(5), 780-786. doi: 10.1016/j.neurobiolaging.2008.06.002
221 Rozenkrants, B., Olofsson, J. K., & Polich, J. (2008). Affective visual event-related potentials: arousal, valence, and repetition effects for normal and distorted pictures. *Int J Psychophysiol, 67*(2), 114-123. doi: 10.1016/j.ijpsycho.2007.10.010
222 Sambataro, F., Murty, V. P., Callicott, J. H., Tan, H. Y., Das, S., Weinberger, D. R., & Mattay, V. S. (2010). Age-related alterations in default mode network: impact on working memory performance. *Neurobiol Aging, 31*(5), 839-852. doi: 10.1016/j.neurobiolaging.2008.05.022
223 Saunders, N. L., & Summers, M. J. (2010). Attention and working memory deficits in mild cognitive impairment. *J Clin Exp Neuropsychol, 32*(4), 350-357. doi: 10.1080/13803390903042379
224 Saunders, N. L., & Summers, M. J. (2011). Longitudinal deficits to attention, executive, and working memory in subtypes of mild cognitive impairment. *Neuropsychology, 25*(2), 237-248. doi: 10.1037/a0021134
225 Sava, A. A., Paquet, C., Krolak-Salmon, P., Dumurgier, J., Hugon, J., & Chainay, H. (2015). Emotional memory enhancement in respect of positive visual stimuli in Alzheimer's disease emerges after rich and deep encoding. *Cortex, 65*, 89-101. doi: 10.1016/j.cortex.2015.01.002
226 Schacter, D. L. (1987). Implicit expressions of memory in organic amnesia: learning of new facts and associations. *Hum Neurobiol, 6*(2), 107-118.
227 Scheff, S. W., Price, D. A., Schmitt, F. A., Roberts, K. N., Ikonomovic, M. D., & Mufson, E. J. (2013). Synapse stability in the precuneus early in the progression of Alzheimer's disease. *J Alzheimers Dis, 35*(3), 599-609. doi: 10.3233/JAD-122353
228 Scheibe, S., & Carstensen, L. L. (2010). Emotional aging: recent findings and future trends. *J Gerontol B Psychol Sci Soc Sci, 65B*(2), 135-144. doi: 10.1093/geronb/gbp132
229 Schmitt, F. A., Nelson, P. T., Abner, E., Scheff, S., Jicha, G. A., Smith, C., . . . Kryscio, R. J. (2012). University of Kentucky Sanders-Brown healthy brain aging volunteers: donor characteristics, procedures and neuropathology. *Curr Alzheimer Res, 9*(6), 724-733.
230 Schnyer, D. M., Allen, J. J., Kaszniak, A. W., & Forster, K. I. (1999). An event-related potential examination of masked and unmasked repetition priming in Alzheimer's disease: implications for theories of implicit memory. *Neuropsychology, 13*(3), 323-337.
231 Schrijnemaekers, A. M., de Jager, C. A., Hogervorst, E., & Budge, M. M. (2006). Cases with mild cognitive impairment and Alzheimer's disease fail to benefit from repeated exposure to episodic memory tests as compared with controls. *J Clin Exp Neuropsychol, 28*(3), 438-455. doi: 10.1080/13803390590935462
232 Schupp, H. T., Junghofer, M., Weike, A. I., & Hamm, A. O. (2003). Attention and emotion: an ERP analysis of facilitated emotional stimulus processing. *Neuroreport, 14*(8), 1107-1110. doi: 10.1097/01.wnr.0000075416.59944.49
233 Schupp, H. T., Stockburger, J., Codispoti, M., Junghofer, M., Weike, A. I., & Hamm, A. O. (2006). Stimulus novelty and emotion perception: the near absence of

habituation in the visual cortex. *Neuroreport, 17*(4), 365-369. doi: 10.1097/01.wnr.0000203355.88061.c6

234 Seelye, A. M., Schmitter-Edgecombe, M., & Flores, J. (2010). Episodic memory predictions in persons with amnestic and nonamnestic mild cognitive impairment. *J Clin Exp Neuropsychol, 32*(4), 433-441. doi: 10.1080/13803390903201751

235 Snodgrass, J. G., & Vanderwart, M. (1980). A standardized set of 260 pictures: norms for name agreement, image agreement, familiarity, and visual complexity. *J Exp Psychol Hum Learn, 6*(2), 174-215.

236 Spector, A., Woods, B., & Orrell, M. (2008). Cognitive stimulation for the treatment of Alzheimer's disease. *Expert Rev Neurother, 8*(5), 751-757. doi: 10.1586/14737175.8.5.751

237 Sperling, R. (2007). Functional MRI studies of associative encoding in normal aging, mild cognitive impairment, and Alzheimer's disease. *Ann N Y Acad Sci, 1097*, 146-155. doi: 10.1196/annals.1379.009

238 Stark, S. M., Gordon, B., & Stark, C. E. (2008). Does the presence of priming hinder subsequent recognition or recall performance? *Memory, 16*(2), 157-173. doi: 10.1080/09658210701872807

239 Stern, Y. (2006). Cognitive reserve and Alzheimer disease. *Alzheimer Dis Assoc Disord, 20*(3 Suppl 2), S69-74.

240 van Boxtel, M. P., & Speckens, A. E. (2014). [Mindfulness, cognitive function and 'successful ageing']. *Tijdschr Gerontol Geriatr, 45*(3), 137-143. doi: 10.1007/s12439-013-0055-z

241 van Halteren-van Tilborg, I. A., Scherder, E. J., & Hulstijn, W. (2007). Motor-skill learning in Alzheimer's disease: a review with an eye to the clinical practice. *Neuropsychol Rev, 17*(3), 203-212. doi: 10.1007/s11065-007-9030-1

242 Vinogradov, S., Fisher, M., & de Villers-Sidani, E. (2012). Cognitive training for impaired neural systems in neuropsychiatric illness. *Neuropsychopharmacology, 37*(1), 43-76. doi: 10.1038/npp.2011.251

243 Voss, J. L., & Paller, K. A. (2008). Brain substrates of implicit and explicit memory: the importance of concurrently acquired neural signals of both memory types. *Neuropsychologia, 46*(13), 3021-3029. doi: 10.1016/j.neuropsychologia.2008.07.010

244 Voss, J. L., & Paller, K. A. (2009). An electrophysiological signature of unconscious recognition memory. *Nat Neurosci, 12*(3), 349-355. doi: 10.1038/nn.2260

245 Wang, W. C., Lazzara, M. M., Ranganath, C., Knight, R. T., & Yonelinas, A. P. (2010). The medial temporal lobe supports conceptual implicit memory. *Neuron, 68*(5), 835-842. doi: 10.1016/j.neuron.2010.11.009

246 Waring, J. D., Payne, J. D., Schacter, D. L., & Kensinger, E. A. (2010). Impact of individual differences upon emotion-induced memory trade-offs. *Cogn Emot, 24*(1), 150-167. doi: 10.1080/02699930802618918

247 Waring, J. D., Seiger, A. N., Solomon, P. R., Budson, A. E., & Kensinger, E. A. (2014). Memory for the 2008 presidential election in healthy ageing and mild cognitive impairment. *Cogn Emot, 28*(8), 1407-1421. doi: 10.1080/02699931.2014.886558

248 Weiner, K. S., & Grill-Spector, K. (2012). Synchrony upon repetition: One or multiple neural mechanisms? *Cognitive Neuroscience, 3*(3-4), 243-244.

249 Wells, R. E., Yeh, G. Y., Kerr, C. E., Wolkin, J., Davis, R. B., Tan, Y., . . . Kong, J. (2013). Meditation's impact on default mode network and hippocampus in mild

cognitive impairment: a pilot study. *Neurosci Lett, 556*, 15-19. doi: 10.1016/j.neulet.2013.10.001

250 White, L., Ford, M. P., Brown, C. J., Peel, C., & Triebel, K. L. (2014). Facilitating the use of implicit memory and learning in the physical therapy management of individuals with Alzheimer disease: a case series. *J Geriatr Phys Ther, 37*(1), 35-44. doi: 10.1519/JPT.0b013e3182862d2c

251 Wiggs, C. L., Weisberg, J., & Martin, A. (2006). Repetition priming across the adult lifespan--the long and short of it. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn, 13*(3-4), 308-325. doi: 10.1080/138255890968718

252 Wilkinson, A. J., & Yang, L. (2012). Plasticity of inhibition in older adults: retest practice and transfer effects. *Psychol Aging, 27*(3), 606-615. doi: 10.1037/a0025926

253 Winblad, B., Palmer, K., Kivipelto, M., Jelic, V., Fratiglioni, L., Wahlund, L. O., . . . Petersen, R. C. (2004). Mild cognitive impairment--beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *J Intern Med, 256*(3), 240-246. doi: 10.1111/j.1365-2796.2004.01380.x

254 Yang, L., & Hasher, L. (2011). Age differences in the automatic accessibility of emotional words from semantic memory. *Cogn Emot, 25*(1), 3-9. doi: 10.1080/02699930903523348

255 Yang, L., & Krampe, R. T. (2009). Long-term maintenance of retest learning in young old and oldest old adults. *J Gerontol B Psychol Sci Soc Sci, 64*(5), 608-611. doi: 10.1093/geronb/gbp063

256 Yang, S., Luo, W., Zhu, X., Broster, L. S., Chen, T., Li, J., & Luo, Y. (2014). Emotional content modulates response inhibition and perceptual processing. *Psychophysiology, 51*(11), 1139-1146. doi: 10.1111/psyp.12255

257 Zanetti, O., Binetti, G., Magni, E., Rozzini, L., Bianchetti, A., & Trabucchi, M. (1997). Procedural memory stimulation in Alzheimer's disease: impact of a training programme. *Acta Neurol Scand, 95*(3), 152-157.

258 Zhang, Q., Lawson, A., Guo, C., & Jiang, Y. (2006). Electrophysiological correlates of visual affective priming. *Brain Res Bull, 71*(1-3), 316-323. doi: 10.1016/j.brainresbull.2006.09.023

259 Zhou, T., Li, J., Broster, L. S., Niu, Y., & Wang, P. (2015). Reduced late positivity in younger adults, but not older adults, during short-term repetition. *Brain Res, 1594*, 223-232. doi: 10.1016/j.brainres.2014.10.042

Lucas S Broster

Biographical Information

Place of Birth: Columbia, MO

Education

Graduate Certificate, Applied Statistics, University of Kentucky, Lexington, KY, January 2014
Graduate Certificate, Clinical & Translational Science, University of Kentucky, Lexington, KY, January 2013
B.A., Cognitive Science, Yale University, New Haven, CT, May 2009

Professional Positions Held

American Medical Association, 2009 - present
American Medical Student Association, 2009 – present
Post-hoc Abstract Reviewer, Annual Meeting of Organization of Human Brain Mapping, 2011-2015
AOA/MD/PhD Research Day Program Committee, University of Kentucky, Member, 2011-2013
Internal Advisory Board, University of Kentucky MD/PhD Program, 2012-2013
University of Kentucky Health Occupation Professionals for Equality (UKHOPE), 2009-2015
Secretary, 2013-2014
Vice-President, 2011-2012, 2014-
Coordinator for Gender, Sex, & Love: a lecture by visiting physician Dr. Marci Bowers, 2011
Psychiatry Medical Student Interest Group, Vice-President, 2011-2012
Student-Faculty Liaison for Pharmacology, University of Kentucky College of Medicine, 2010-2011
Institutional Review Board Student Representative, Department of Psychology, Yale University, New Haven, CT, 2006

Honors

Poster Award: "Altered Emotional Enhancement Effects in Persons with Mild Cognitive Impairment," *Annual Clinical & Translational Science Symposium*, Lexington, KY, 2015
NIMH UC Davis ERP Boot Camp Fellow, July 2014
Poster Award: "Altered Emotional Enhancement Effects in Persons with Mild Cognitive Impairment," *Annual Clinical & Translational Science Symposium*, Lexington, KY, 2014
TL1 Scholar, UL1RR033173/UL1TR000117, "Clinical & translational science training grant," 2012-2015
T32 Scholar, 5T32 AG242-18, "Molecular and cellular mechanisms of brain aging," 2011-2012
Travel Award: *Organization for Human Brain Mapping*, Seattle, WA, 2013
Poster Award: "Unique Electrophysiological Signatures of Mild Cognitive Impairment and Alzheimer's Disease," *Annual Clinical & Translational Science Symposium*, Lexington KY, 2013
Travel Award: *Cognitive Aging Conference 2012*, Atlanta, GA, 2012
Poster Award: "Alterations of brain function during working memory in military veterans with mild brain injury or posttraumatic stress disorder," *Spring Neuroscience Day*, Lexington KY, 2012
Periodical review: "DC: Do measurable changes in brain function herald dementia?" *Alzheimer Disease Forum,* 2011

"Hot Topic" highlight: "Left frontal brain potentials differentiate mild cognitive impairment from normal aging during a working memory task," *Annual Meeting of the Society for Neuroscience*, Washington DC, 2011
Travel Award: *Annual Meeting for the Society for Neuroscience,* Washington, DC, 2011
Departmental Travel Award: *Chinese Academy of Sciences Institute of Psychology,* Beijing, China, 2011
Poster Award: "Early Alzheimer's patients benefit from repetition in a working memory paradigm," *Cognitive Science Symposium*, Lexington, KY, 2011
Hokkaido International Foundation Graduate, 2008
Richard U Light Fellow, New Haven, CT, 2008

Publications

Zhou T, Li J, **Broster LS**, Niu Y, Wang P (2015). Reduced late positivity in younger adults, but not older adults, during short-term repetition. *Brain Research* 1594, 223-232.

Zheng Z, Li J, Xiao F, **Broster LS**, Jiang Y, Xi M (2015). The effects of unitization on the contribution of familiarity and recollection processes to associative recognition memory: Evidence from event-related potentials. *International Journal of Psychophysiology*

Yang S, Luo W, Zhu X, **Broster LS**, Chen T, Li J, Luo Y (2014). Emotional content modulates response inhibitions and perceptual processing. *Psychophysiology* 51 (11), 1139-1146.

Luo Y, Wu T, **Broster LS**, Feng C, Zhang D, Gu R, Luo YJ (2014). The temporal course of the influence of anxiety on fairness considerations. *Psychophysiology* 51 (9), 834-842.

Zhang D, Gu R, **Broster LS**, Jiang Y, Luo W, Zhang J, Luo Y (2014). Linking brain electrical signals elicited by current outcomes with future risk decision-making. *Frontiers in Behavioral Neuroscience* 8.

McBride J, Zhao X, Munro N, Smith CD, Jicha GA, Hively L, **Broster LS**, Schmitt FA, Kryscio RJ, Jiang Y (2014). Spectral and Complexity Analysis of Scalp EEG Characteristics for Mild Cognitive Impairment and Early Alzheimer's Disease. Computer Methods and Programs in Biomedicine, 114:2, 153-163.

Xu P, Gu R, **Broster LS**, Wu R, Van Dam NT, Jiang Y, Fan J, Luo Y-J (2013). Neural Basis of Emotional Decision Making in Trait Anxiety. *The Journal of Neuroscience* 33:47, 18641-18653.

Broster LS, Li J, Smith CD, Jicha GA, Schmitt FA, Jiang Y (2013). Repeated retrieval during working memory is sensitive to amnestic mild cognitive impairment. *Journal of Clinical & Experimental Neuropsychology* 35:9, 946-959.

Feng C, Gu R, Wu T, **Broster LS**, Shen X, Tian T, Luo Y-J, Krueger F (2013). The Flexible Fairness: Equality, Earned Entitlement, and Self-Interest. *PLoS ONE* 8:9, e73106.

Zhang D, Gu R, Wu T, **Broster LS,** Luo Y, Jiang Y, Luo Y-J (2013). An electrophysiological index of changes in risk decision-making strategies. *Neuropsychologia* 51:8, 1397-1407

Wu T, Luo Y, **Broster LS**, Gu R, Jiang Y (2013). The impact of anxiety on social decision-making: behavioral and electrodermal findings. *Social Neuroscience*, 8:1. doi:10.1080/17470919.2012.694372

Broster LS, Blonder L, Jiang Y (2012). Does emotional memory enhancement assist the memory-impaired? *Frontiers in Aging Neuroscience*, 4:2. doi: 10.3389/fnagi.2012.00002.

Zhou, T, **Broster, LS**, Jiang, Y, Bao, F, Wang, H, Li, J (2012). Deficits in retrospective and prospective components underlying prospective memory tasks in amnestic mild cognitive impairment, *Brain Behavior and Functions*, 8-39; doi: 10.1186 /1744-9081-8-39.

Gu, R., Lei, Z, **Broster, LS**, Wu, T, Jiang, Y, Luo, Y (2011). Beyond valence and magnitude: a flexible evaluative coding system in the brain, *Neuropsychologia*, 49:14, 3891-97. doi:10.1016/j.neuropsychologia.2011.10.006.

Abstracts, International

Broster LS, Jenkins SL, Jicha GA, Jiang Y (2014) Altered Neural Responses to Affective Repetition in Persons with Mild Cognitive Impairment, *Organization for Human Brain Mapping*, Hamburg, Germany.

Broster LS, Khan A, Gu R, Jenkins SL, Kryscio RJ, Kelly T, Lynam D, Dewall CN, Milich R, Bardo M, Estus S, Jiang Y (2014). Neuropeptide Y Expression and Perseverance Trait Modulate Brain Responses to Decision-Making, *Organization for Human Brain Mapping*, Hamburg, Germany.

Yu J, Li R, Jiang Y, **Broster LS**, Li J (2014). Altered Network Associated with Repetition Effects in Mild Cognitive Impairment Patients, *Organization for Human Brain Mapping*, Hamburg, Germany.

Broster LS, Jenkins SL, Jicha GA, Jiang Y (2014) Altered Neural Responses to Affective Repetition in Persons with Mild Cognitive Impairment, *Association for Clinical & Translational Science*, Washington, DC.

Broster LS, Li J, Smith CD, Jicha GA, Heflin M, Munro NB, Hively LM, Jiang Y (2013). Unique electrophysiological signatures in mild cognitive impairment and Alzheimer disease, *Annual Meeting of Organization for Human Brain Mapping.* Seattle, WA, June 16-20, 2013.

Huan H, **Broster LS**, Jiang Y, Ding MZ (2012). Altered parietal functional connectivity in patients with mild cognitive impairment, *Annual Meeting of the Society for Neuroscience 2012,* 545.05/F7 (New Orleans, Tuesday, Oct 16, 2012, 8:00 AM - 9:00 AM).

Broster LS*,* Gu R, Wing S, Guo C, Clark J, Heflin M, Jicha G, Jiang Y. (2012). Functional Amygdala Changes Associated with a Working Memory Task in Mild Cognitive Impairment, *Organization for Human Brain Mapping*, 7, Beijing, China.

Jiang Y**, Broster LS**, Guo C, Clark J, Walsh E, Heflin M, Jicha, GA (2012). Frontal neuroimaging indicators for mild cognitive impairment during working memory, *Abstracts for Annual Meeting of Organization for Human Brain Mapping, 886. Beijing, China.*

Li J, **Broster LS**, Smith CD, Jicha GA, Jiang Y (2012). Differentiations between MCI and normal older adults: An ERP study on working memory decline, *Organization for Human Brain Mapping*, 30, Beijing, China.

Li, J, **Broster LS**, Smith CD, Jicha GA, Jiang Y (2012). Effective neural markers for working memory decline: differentiations between MCI and normal older adults, *Abstract for the Annual Meeting of Cognitive Neuroscience Society*, Chicago.

Broster LS, Guo C, Clark J, Jicha GA, Wing S, Heflin M, Jiang Y (2012). Functional changes in frontal, but not posterior, cortices for repetition effects in mild cognitive impairment, *Cognitive Aging Conference*, Atlanta, USA, April, 2012.

Broster LS*,* Li J, Smith CD, Jicha GA, Munro NB, Hively LM, Jiang Y (2011). Left frontal brain potentials differentiate mild cognitive impairment from normal aging during a working memory task, *Abstracts for Annual Meeting for Society for Neuroscience 2011*, Sat. Nov. 12 1pm, Washington, DC.

Munro NB, De Bock TJ, Das S, Mohsin M, Hively LM, Zhao X, McBride J, Li J, **Broster LS**, Smith CD, Jicha GA, Jiang Y (2011). Early Detection of Mild Cognitive Impairment Using Nonlinear Analysis of EEG via Tsallis Entropy-Based qEEG and Support Vector Machine Classification, *2011 Annual ORNL Biomedical Science & Engineering Conference* (March 16-17, 2011) Oak Ridge, TN.

Munro NB, De Bock TJ, Das S, Mohsin M, Hively LM, Zhao X, McBride J, Li J, **Broster LS**, Smith CD, Jicha GA, Jiang Y (2011). Nonlinear Analysis of EEG for Early Detection of Cognitive Decline, Abstract #45, *Annual Conference of Organization for Human Brain Mapping, Quebec City, Canada.*

Abstracts, Regional

Broster LS, Jenkins SL, Tarrant SD, Jicha GA, Jiang Y (2014) Altered Neural Responses to Affective Repetition in Persons with Mild Cognitive Impairment, *University of Kentucky College of Medicine Center for Clinical and Translational Science Spring Conference*, Lexington, KY

Broster LS, Jenkins SL, Tarrant SD, Jicha GA, Jiang Y (2014) Altered Neural Responses to Affective Repetition in Persons with Mild Cognitive Impairment, *University of Kentucky College of Medicine Alpha Omega Alpha (AOA) Groves Memorial and MD/PhD Student Research Day,* Lexington, KY

Broster LS, Li J, Smith CD, Jicha GA, Heflin M, Munro NB, Hively LM, Jiang Y (2013). Unique electrophysiological signatures in mild cognitive impairment and Alzheimer disease, *Markesbery Symposium on Aging and Dementia,* Lexington, KY

Broster LS, Li J, Smith CD, Jicha GA, Heflin M, Munro NB, Hively LM, Jiang Y (2013). Unique electrophysiological signatures in mild cognitive impairment and Alzheimer disease, *University of Kentucky Spring Neuroscience Day,* Lexington, KY

Broster LS, Li J, Smith CD, Jicha GA, Heflin M, Munro NB, Hively LM, Jiang Y (2013). Unique electrophysiological signatures in mild cognitive impairment and Alzheimer disease, *University of Kentucky College of Medicine Alpha Omega Alpha (AOA) Groves Memorial and MD/PhD Student Research Day,* Lexington, KY

Broster LS*,* Wing S, Gu R, Guo C, Clark J, Heflin M, Jicha G, Jiang Y. (2012). Increased amygdala functional connectivity during working memory among patients with mild cognitive impairment, *Markesbery Symposium on Aging and Dementia,* Lexington, KY

Broster LS*,* Wing S, Gu R, Guo C, Clark J, Heflin M, Jicha G, Jiang Y. (2012). Increased amygdala functional connectivity during working memory among patients with mild cognitive impairment, *South-Central Regional MD/PhD Conference,* Lexington, KY

Broster LS, Guo C, Clark J, Jicha GA, Wing S, Heflin M, Jiang Y (2012). Functional changes for anteriocortical, but not posteriocortical, repetition effects in mild cognitive impairment, *University of Kentucky College of Medicine Alpha Omega Alpha (AOA) Groves Memorial and MD/PhD Student Research Day,* Lexington, KY

Broster LS, Li J, Smith CD, Jicha GA, Jiang Y (2011). Event-related potentials as biomarkers for early mild cognitive impairment detection, *University of Kentucky College of Medicine Center for Clinical and Translational Science Spring Conference*, Lexington, KY

Broster LS, Li J, Smith CD, Jicha GA, Jiang Y (2011). Event-related potentials as biomarkers for early mild cognitive impairment detection*, University of Kentucky College of Medicine Neuroscience Day*, Lexington, KY.

Broster LS, Li J, Smith CD, Jicha GA, Jiang Y (2011). Early Alzheimer's patients benefit from repetition in a working memory paradigm*, University of Kentucky Cognitive Science Symposium*, Lexington, KY

Broster LS, Li J, Smith CD, Jicha GA, Jiang Y (2011). Early Alzheimer's patients benefit from repetition in a working memory paradigm, *University of Kentucky College of Medicine Alpha Omega Alpha (AOA) Groves Memorial and MD/PhD Student Research Day*, Lexington, KY