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The Behavior and Electrophysiology of Directed Forgetting in the Auditory Domain

by

Maya Elizabeth Cano

A dissertation submitted in partial satisfaction of the

requirements for the degree of

Doctor of Philosophy

in

Neuroscience

in the

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of the

University of California, Berkeley

Committee in charge:

Professor Robert T. Knight, M.D. (Chair)

Professor Silvia A. Bunge, Ph.D.

Professor Arthur P. Shimamura, Ph.D.

Professor Allison G. Harvey, Ph.D.

Professor Charan Ranganath, PhD.

Fall 2014

Abstract

The Behavior and Electrophysiology of Directed Forgetting in the Auditory Domain

by

Maya Elizabeth Cano

Doctor of Philosophy in Neuroscience

University of California, Berkeley

Professor Robert T. Knight, Chair

There are many instances in life when a person wants or needs to forget a memory. These unwanted memories can range from something that is simply now irrelevant such as an outdated fact, to something as serious as a traumatic experience. In extreme cases such as post-traumatic stress disorder, the benefit of forgetting becomes obvious. As such, it is important that we understand not only how our brain is able to remember, but also how it is able to forget. Unlike the traditional view of incidental forgetting, recent studies have shown that forgetting can be a strategic and active process. However, the mechanisms by which we can intentionally suppress our memories are not fully understood. Moreover, most of the directed forgetting research has focused on suppressing visual memories. A more complete understanding of the way we can exert inhibitory control over our memories should include all sensory modalities. To address this issue, we examined whether similar electrophysiological findings, as reported in visual electroencephalography (EEG) studies of directed forgetting, would be observed in the auditory domain. Additionally, the role of the prefrontal cortex in this higher-order process was investigated. Here, we utilized the Think/No-Think paradigm to examine the neural correlates of the cognitive control of memory in three studies. First, we compared findings from healthy young adults in two tasks that varied in the number of to-be-remembered and to-be-forgotten repetitions, and found that behavioral and electrophysiological evidence points to similar effects using auditory stimuli, but that it may be more difficult to achieve than the inhibition of visual memories. Second, we extended those findings to older adults, and found that they too showed behavioral and EEG evidence of successful suppression of unwanted auditory memories. Third, we determined that prefrontal cortex plays a causal role in the ability to actively inhibit auditory memories by examining the behavioral and EEG effects of unilateral frontal lesions in a patient cohort. The behavioral evidence for the inhibition of auditory memory and the corresponding electrophysiology is a step toward a more complete picture of how we intentionally suppress unwanted memories.

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Dedication

To my parents, Patricia Heusner and Raul Cano, who have always told me that I am a grape.

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I have received a tremendous amount of help and encouragement from so many people throughout my graduate career. First and foremost, I would like to thank my adviser and mentor, Prof. Robert Knight, who has provided me with guidance, reassurance, and unending support.

I owe a great debt of gratitude to several of my previous and current labmates. In particular, I would like to share my appreciation for Kristopher Anderson, Avgusta Shestyuk, Bradley Voytek, Adeen Flinker, Aurelie Bidet-Caulet, and Matar Haller, who have kindly offered their time, opinions, patience, and friendship to me. Without their help, I would have been lost.

I am extremely lucky to have met Kris, the love of my life, while in the Knight lab. Kris has helped me both with scientific pursuits and personal goals, and I continue to learn from him every day.

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CHAPTER 1

INTRODUCTION

Much progress has been made in our understanding of human memory. We now have realistic models of working memory (Baddeley & Hitch, 1974), long-term encoding and retrieval (Atkinson & Shiffrin, 1968), and this knowledge has contributed to practical applications in everyday life, including a better understanding of numerous neurological and psychiatric disorders (Luria, 1989; Fisher & Geiselman, 1992; Robinson, 1946; Kliegel, Altgassen, Hering, & Rose, 2011; Monchi, Taylor, & Dagher, 2000). However, there are still many aspects of memory processing that are poorly understood. One often overlooked topic in the memory literature is the concept of forgetting. Although remembering and forgetting are intricately intertwined, there are ways in which we can examine them independently. Forgetting has often been viewed as simply a failure of memory, and yet increasing evidence suggests that it may play an important and adaptive function (Bjork, 1989). If we take into account our brain's limited storage and processing capacity, then successful forgetting appears to be a crucial mechanism through which we can maintain efficient and speedy memory performance. Over the past century, the forgetting literature has formed several theories as to why and how we forget, but the field has not yet converged on a cohesive model of forgetting.

Early studies of forgetting date back to at least the late nineteenth century, when Ebbinghaus (1885) meticulously recorded his own rate of forgetting. This prompted one of the earliest theories of forgetting - that of *decay*, which posited that memories, if not reinforced, simply erode over time. Although there is some neural evidence in support of this theory regarding short-term memory (Fuster, 1995; Jha & McCarthy, 2000), it has been rejected as an explanation for forgetting in long-term memory because older memories can be stronger than some newer ones (e.g., Keppel & Underwood, 1962; McGeoch, 1942). However, this theory and subsequent research opened the field to new ways of approaching forgetting as a question independent of remembering, and led to several alternative theories.

Interference theory grew out of direct opposition to decay theory, and argues that it is not *time* that produces forgetting, but *interference* of new or competing information during that time (McGeoch, 1942). Two main forms of interference have been described: *proactive interference* and *retroactive interference*. Proactive interference occurs when old memories prevent the adequate learning of new information. This is exhibited in Bergstrom's (1893) card sorting task, during which learning the first sorting rule interferes with the successful implementation of a second rule. In another example, when research participants are asked to learn lists of words, as the number of lists learned increases, the retention of the last list decreases (Underwood, 1957). In contrast, with retroactive interference, new memories block the successful retrieval of old memories. This effect is classically demonstrated by the AB-AC paradigm (Briggs, 1954). In this task, participants learn a list of item pairs (A-B pairs), followed by learning of a new list (A-C pairs). Note that now A items are cues for two different items. When participants are then asked to recall B items following the A cue, they are more impaired

than if the second list had consisted of new cue items (i.e., D-C). While there is clear evidence that interference can contribute to forgetting, the theory addresses only certain cases where multiple separate items (i.e., B and C) are to be associated with a single item (A).

Retrieval based theories of forgetting have also been proposed such as *cue-dependent*, *context-dependent*, and *state-dependent* forgetting. Each of these theories operates under the same basic principles, suggesting that if circumstances during retrieval are not similar to those at the time of encoding, forgetting can occur (Tulving & Pearlstone, 1966; Tulving & Thomson, 1973). Such memories would still be stored but would not be accessible under certain circumstances (Tulving, 1974).

Interference based and retrieval based theories of memory are not necessarily incompatible with each other, and it is likely that there are multiple mechanisms of forgetting. For example, in a study by Tulving and Psotka (1971) utilizing remembered categorical word lists, retroactive interference was found to be caused by the loss of retrieval cues, as poorly recalled words in particular categories following interference were later recalled after being cued by the category. This result indicates that some types of interference are caused by a loss of the retrieval cue, not the actual memory trace.

However, loss of a retrieval cue may not always be a simple act of interference, but may also include inhibitory processes. In *retrieval-induced forgetting*, forgetting occurs when the act of retrieving one thing competes with the act of retrieving the desired memory (Anderson, Bjork, & Bjork, 1994). In this paradigm, as described by Kuhl and Wagner (2009), participants learn category-cue pairs (i.e., "Fruit-apple", "Fruit-banana", "Furniture-desk", "Furniture-chair"). Then, subjects practice retrieving some of the pairs from some of the categories (i.e., "Fruit-apple"). Finally, they are asked to recall all of the pairs. Retrieval-induced forgetting occurs when the probability of recalling "banana" is less than either "chair" or "table" because the practice of recalling "apple" inhibits the recollection of "banana" as an alternate fruit category response. That is, the initial act of recalling inhibits successful retrieval of the unpracticed items in the practiced category. Although this task looks much like the one employed by Tulving and Psotka described above, the same forgetting effect has been found using cue-independent subsequent memory tests (Johnson & Anderson, 2004). For instance, returning to the same example, if "banana" was later probed with a new category cue in a stem completion task (e.g., "Monkey-b"), "banana" would still be less likely to be recalled. Although passive interference may still play a role in preventing retrieval in the same-probe test (i.e., "Fruit-?"), inhibitory mechanisms appear to be involved, as demonstrated by the cue-independent test (i.e., "Monkey-b"). Participants are likely not consciously employing inhibitory control over their forgetting, but rather are using an implicit strategy to remember in the retrieval practice phase.

Other experimental tasks have been created to explore a more explicit strategy-based form of forgetting. In *directed forgetting*, participants are given instruction about what information they do not need to remember. Although many variations have been

developed over the years, there are two main task formats: list method and item method. In the list method, participants learn two lists of items, the first either denoted as a practice list or specifically as a list that does not need to be remembered (Block, 1971). Then, they are given a second list to remember. After learning the second list, participants are subjected to a surprise recall test of all items. Directed forgetting occurs when a smaller number of first-list items are remembered compared to a control, in which both lists are instructed to be remembered. The item method is similar, but forgetting operates on a trial-by-trial basis (Basden, Basden, & Gargano, 1993; Bjork, LaBerge, & Legrand, 1968; Johnson, 1994; Woodward & Bjork, 1971). Before any learning takes place, participants are instructed that there are some items that they will have to remember, and some that they will not. After all items are presented with forget/remember instruction, they are then tested on all items in a recall or recognition test. The directed forgetting effect is observed when to-be-remembered items are remembered at a higher rate than to-be-forgotten ones. It is thought that directed forgetting can be elicited in either of two ways: through passive decay of a working memory trace, or through active suppression (Zacks, Radvansky, & Hasher, 1996). Therefore, while the results from standard directed forgetting paradigms might indeed be an effect of active memory suppression, findings of successful forgetting in these studies could also be explained by processes that are unrelated to memory inhibition such as shallow encoding.

In 2001, Anderson and Green introduced a behavioral task that takes memory and forgetting, and manipulates them independently relative to a baseline condition. In this Think/No-Think (TNT) paradigm, they were able to show that intentional forgetting is an active process. Think/No-Think, which resembles a modified version of the Go/No-Go task, probes more specifically how already formed memories can be selectively enhanced or suppressed. In this task, subjects first learn word pairs and then are instructed to either retrieve or suppress the second item in a word pair when presented with the first item of the pair. Critically, a subset of the learned pairs is not seen again until a subsequent memory retrieval test, and serves as a baseline condition. The “Think” items (i.e., those that were retrieved during the task) were better recalled as a function of trial repetition, such that the more times a word was retrieved, the more likely it was remembered in a later memory test. Furthermore, the to-be-suppressed, or “No-Think” items, were recalled less often than baseline. This below-baseline memory result for No-Think trials provided evidence that forgetting can be an active, controllable process.

A follow-up study using the same task revealed further evidence for an active form of suppression (Anderson et al., 2004). In an fMRI experiment, Anderson and colleagues found that the anterior cingulate cortex and frontal brain regions were more active during No-Think compared to Think trials. This frontal increase in activation was also associated with a decrease in hippocampal BOLD signal, suggesting that the prefrontal cortex plays an active role in the inhibition of memory retrieval.

Another study that used non-verbal memory found similar effects, although fMRI activity was lateralized to the right hemisphere (Depue, Banich, & Curran, 2006). However, it is

unclear whether it is the nature of the stimuli or key elements of successful memory suppression that produced this lateralization. Taken together, these findings support an active inhibitory mechanism for the control of forgetting.

To date, several studies have replicated the original behavioral findings and have extended the mounting evidence for forgetting as an active process using additional measures such as electroencephalography (EEG). However, all of these studies have examined various forms of visual memories. As our memories are multisensory, it is necessary to determine if intentional forgetting can suppress memories across modalities. As auditory memory differs from that of visual memory, it is possible that behavioral and electrophysiological responses to repeated attempts to inhibit an already formed auditory memory might also vary from that of a visual one.

How auditory forgetting may interact with age is another unaddressed question. A paucity of research has examined age-related differences in intentional memory inhibition. Using directed-forgetting tasks, older adults have been reported to be less able to suppress to-be-forgotten items than younger ones (Sahakyan, Delaney, & Goodmon, 2008; Zacks et al., 1996; Zellner & Bäuml, 2006). Recently, Healey et al. (2014) showed that below-baseline suppression of response time for interference-caused inhibition was absent in older adults. In an experiment examining the direct intentional suppression of memory using the TNT paradigm, (Anderson, Reinholz, Kuhl, & Mayr, 2011) employed the Think/No-Think paradigm for younger and older adults in the visual modality. They found comparable suppression scores between young and older adults when they were tested with the same cues used for suppression practice, but found that only young adults were able to suppress below baseline in an independent probe test. If and how older adults can intentionally suppress *auditory* memories has not yet been explored.

Another important question centers on the anatomical structures important to the ability to actively suppress unwanted memories. The prefrontal cortex has been implicated in the strategic manipulation of forgetting through EEG and fMRI studies, but the extent to which that area is necessary for the preservation of this function is unclear. Patients with damage to prefrontal cortex have demonstrated deficits in some inhibitory cognitive abilities (Andres, Van der Linden, & Parmentier, 2007; Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003; Knight, Staines, Swick, & Chao, 1999; Krämer et al., 2013; Shimamura, 1995). However, few studies have examined directed forgetting in patients with restricted frontal damage. Surprisingly, intact directed forgetting has been found in patients with unilateral frontal lesions using variants of the list-method directed-forgetting paradigms (Andres et al., 2007; Andrés, 2002; Schmitter-Edgecombe, Marks, Wright, & Ventura, 2004). However, Anderson has argued that the Think/No-Think task may require a greater amount of cognitive control than that needed for standard directed forgetting tasks, and so may yield different results (Anderson et al., 2011).

In this thesis, I examine behavior and electrophysiology of auditory directed forgetting in an adapted version of the Think/No-Think paradigm. I aim to show that directed forgetting can successfully be produced when the to-be-inhibited information is

presented in the auditory modality, and that the corresponding electrophysiological effects are similar to what is seen in the visual domain. I further investigate how this ability and brain responses are affected in older adults, and then seek to show that the prefrontal cortex plays a causal role in the ability to intentionally inhibit unwanted memories.

CHAPTER 2

An EEG study investigating the cognitive control of memory using an auditory directed-forgetting task.

ABSTRACT:

The neural basis of directed forgetting is receiving increased attention, with a particular focus on the precise mechanisms by which memory suppression is enabled. To assess whether directed forgetting extends across sensory modalities, we examined whether similar electrophysiological findings, as reported in visual electroencephalography (EEG) studies of directed forgetting, would be observed in the auditory domain. Here, we utilized the Think/No-Think paradigm to examine the neural correlates of the control of memory inhibition in healthy young adults when to-be-forgotten and to-be-remembered items are presented auditorily.

In two different experiments, we adapted Anderson and Green's (2001) Think/No-Think paradigm to EEG and the auditory domain. Each experiment utilized a different number of Think/No-Think repetitions. Behaviorally, we found no accuracy-based suppression effects in either the 5-repetition or 18-repetition experiments, although we were able to observe a suppression effect by examining response times. This revealed a significant response latency effect supporting below-baseline memory suppression in the 18-repetition group. We also examined task-related EEG activity during attempted memory retrieval and inhibition to both a visual instruction cue and to the presentation of the auditory memory cue word stimulus. Event-related potentials (ERPs) revealed two main memory manipulation effects: 1) No-Think cues produced an enhanced visual N1 compared with Think, followed by a centralized P2 component that was larger for Think cues, 2) Words produced a sustained late (beginning 500 ms) main effect, such that Think was more positive than No-Think, reflecting the memory retrieval effect.

The observed event-related potential (ERP) pattern is similar to that reported in visual studies and supports a modality non-specific mechanism for directed forgetting. The EEG data also provides evidence supporting differing roles and time courses of prefrontal and parietal cortices in the flexible control of auditory memory.

INTRODUCTION

Memory is an essential part of our cognitive lives, but it is becoming increasingly evident that forgetting also plays an important role in successful functioning. Many memories seem to decay over time (Ebbinghaus, 1885), but what is not well understood is how this process occurs. Traditionally, the act of forgetting has been treated as a passive process, characterized simply as a failure to remember or refresh events (i.e., failure to encode or retain the information) but recent work suggests that prefrontal dependent processes are engaged in active forgetting. Although forgetting often has a bad connotation, the act of forgetting can have clear benefits. For instance, an inability to

forget would result in an overwhelming amount of stored unnecessary information, which could interfere with encoding and retrieval of relevant information. Furthermore, some memories may be harmful to an individual, and forgetting or even reducing the strength of memory of this information would be beneficial. Given the utility of this forgetting process, a thorough understanding of its mechanisms is warranted.

Historically, the process of forgetting has been addressed in various ways. For example, retrieval-induced forgetting, in which the retrieval of particular items inhibits the memory for or the ability to retrieve related items, has been proposed as a mechanism of forgetting (Anderson et al., 1994). Additionally, directed forgetting paradigms using both the list (MacLeod, 1975) and item methods (Elmes, Adams, & Roediger, 1970), have been utilized to investigate how the instruction to forget certain stimuli affects later memory recall. However, findings of successful forgetting in these studies could be explained by processes that are unrelated to memory inhibition. For instance, retrieval-induced forgetting can be explained by automatic interference at the time of recall, while failure in directed forgetting may be due to unsuccessful shallow encoding. Although these studies have shown that forgetting can be manipulated, they do not necessarily offer a good model for intentional inhibition of memory.

Anderson and Green introduced the concept of forgetting as an explicit, and controllable active process in 2001. To test this, they developed the Think/No-Think (TNT) paradigm, a modified Go/No-Go task that probes more specifically how already formed memories can be selectively enhanced or suppressed. In this task, subjects first learn word pairs and then are instructed to either retrieve or suppress the second item in a pair when presented with the first item of the pair. Critically, a subset of the learned pairs is not seen again until a subsequent memory retrieval test, and serves as a baseline condition. The “Think” items (i.e., those that are submitted to practiced retrieval during the task) were found to be better recalled as a function of trial repetition, such that the more times a word was retrieved, the more likely it was to be remembered in a later memory test. Furthermore, the suppressed or “No-Think” items were recalled at a level less than baseline. This below-baseline memory result for No-Think trials provided evidence that forgetting can be an active, controllable process.

A follow-up fMRI study using the same task revealed further evidence for an active form of suppression (Anderson et al., 2004). It was found that bilateral prefrontal brain regions were more active during No-Think compared to Think trials. This frontal control network increase in activation was also associated with a decrease in hippocampal BOLD signal, suggesting that prefrontal cortex plays an active role in inhibiting memory formation in medial temporal regions. Another study that used non-verbal memory found similar effects, although fMRI activity was lateralized to the right hemisphere (Depue et al., 2006). However, it is unclear whether it is the nature of the stimuli or key elements of successful memory suppression that produce this lateralization. Regardless, all these findings support an active suppression mechanism for the control of forgetting.

Many subsequent studies have replicated the initial behavioral findings of the Think/No-Think paradigm (Anderson et al., 2011; Anderson & Levy, 2009; Bergström, de Fockert,

& Richardson-Klavehn, 2009; Bergström, Velmans, de Fockert, & Richardson-Klavehn, 2007; Depue, Curran, & Banich, 2007; Depue et al., 2013; Joormann, Hertel, LeMoult, & Gotlib, 2009a; Paz-Alonso, 2009) although some have failed to find below-baseline forgetting in the No-Think condition (Bergström, de Fockert, & Richardson-Klavehn, 2009; Bulevich, Roediger, Balota, & Butler, 2006; Mecklinger, Parra, & Waldhauser, 2009).

Some electrophysiological studies employing the TNT paradigm have found early frontal components that may reflect the increased activation seen with fMRI. They have also consistently found a reduction in the late left parietal positivity, an event-related potential (ERP) component associated with successful memory retrieval (Allan & Rugg, 1997), for No-Think compared to Think trials (Bergström et al., 2007; Depue et al., 2013; Mecklinger et al., 2009). However in most TNT experimental designs, the instruction cue (i.e., Think or No-Think) and the cue word are presented simultaneously, making it difficult to disentangle instruction-based responses from memory inhibition of the particular item.

To date, all of these Think/No-Think studies have utilized a variety of visual stimuli, including faces and scenes (Depue et al., 2006; 2007), and neutral and emotional words (van Schie, Geraerts, & Anderson, 2013). However, memories that are rooted in other sensory domains have not yet been examined. In two related experiments, we examine intentional memory suppression using a modified version of the TNT task using EEG to relate both the behavioral and neural correlates of the cognitive control of auditory memory to its visual counterparts.

EXPERIMENT 1:

MATERIALS AND METHODS

PARTICIPANTS

A total of 16 English-speaking undergraduate students (10F, 18-25 years) participated for course credit or monetary compensation (\$10/hour). All participants reported an absence of neurological and psychiatric disorders, normal or corrected-to-normal vision, and provided written informed consent approved by the University of California, Berkeley Committee for Protection of Human Subjects.

STIMULI AND DESIGN

We developed a modified version of Anderson et al.'s (2004) visual Think/No-Think (TNT) paradigm. In this version all word stimuli were presented in the auditory domain. Only the instruction cues were presented visually (see Figure 2-1).

Stimuli consisted of 68 pairs of English words developed for this experiment, which paralleled the procedures used in previous TNT studies, and were presented auditorily. Of the 68 word pairs, 8 were used for practice, and the remaining 60 were split evenly into 3 groups for Think, No-Think, and Baseline conditions. Five repetitions of each

Think and No-Think cue word were used in the Think/No-Think phase of the experiment.

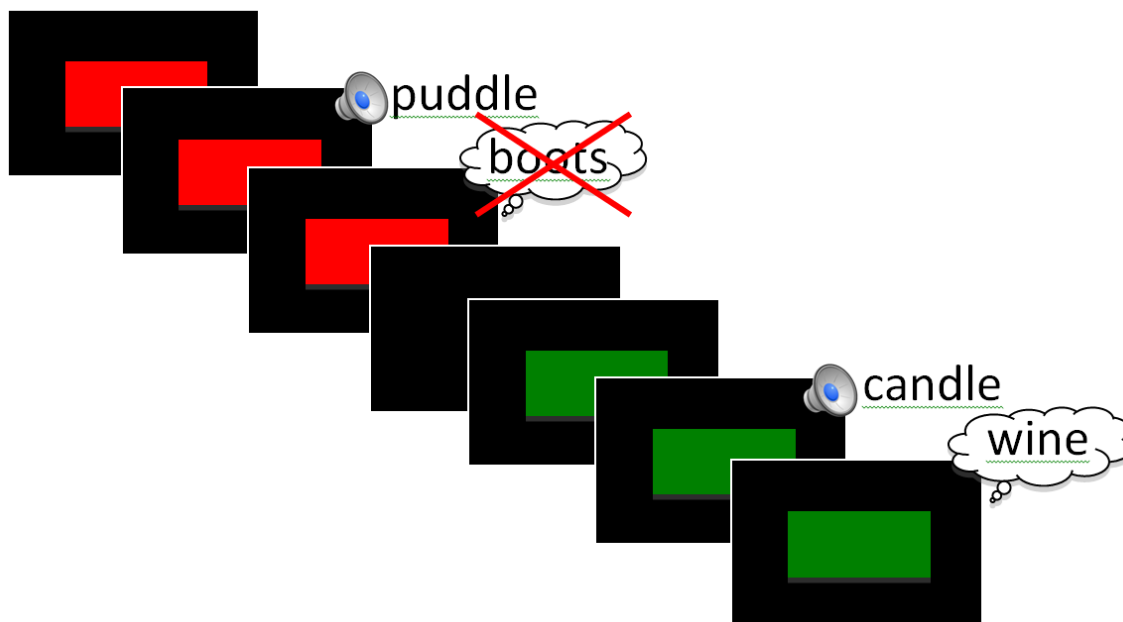
PROCEDURE

Learning: In the initial learning phase of the experiment, all 68 word pairs were presented with 1000 ms between the onset of the first and second word of each pair and a 6600 ms inter-trial interval. Participants were asked to try to learn the pairs such that if they are given the first word, or “cue word”, they will be able to respond with the second, or “target word”.

Recall: Recall memory was tested immediately following the initial study phase. Subjects were given the cue word of each pair and asked to respond with the target word, receiving feedback on each trial. They were asked to continue studying unlearned word pairs until each item was recalled correctly exactly once. Recall for this phase was self-paced.

TNT: With the exception of practice items, all Think and No-Think cue words were presented 5 times in a randomized fashion during this phase of the experiment. Cue words designated as Baseline items were not presented, but rather retained for use in the later subsequent memory tests to serve as a measure of passive forgetting. On each TNT trial, subjects viewed a visual instruction cue that appeared centered on the screen preceding the auditory presentation of the cue word. We separated the cue and word presentation because anticipation of to-be-inhibited item has been shown to have differential effects on ERPs (Hanslmayr, Leipold, Pastotter, & Bauml, 2009) and also increase later forgetting of items (Hanslmayr, Leipold, & Bäuml, 2010). Participants were instructed to either silently recall (green box; Think words) or inhibit (red box; No-Think words) the target word of each word pair after hearing the cue word. It was stressed to all participants that on No-Think trials, it was important to keep the target word out of mind and not to think about it even after the trial was over. This was instructed since intentional forgetting can be achieved with either thought substitution or by direct suppression of items (Bergström et al., 2009; Hertel & Calcaterra, 2005), which produce differing brain mechanisms (Benoit & Anderson, 2012). All participants were instructed to directly suppress, and not merely to substitute the to-be-suppressed word with an alternate item. In each trial, the instruction cue appeared for 900 ms with a 100 ms jitter before the first word of each Think or No-Think pair was presented (Figure 2-1). The instruction cue remained on the screen for the entirety of the word presentation. Inter-trial interval was 3600 ms with a 500 ms uniformly distributed jitter.

Figure 1-1. Schematic of the TNT phase of the experiment for an example No-Think (red) and Think (green) trial. See text for stimulus timing.



Subsequent Memory: Subsequent memory was tested using both the independent and the same probe method developed from Anderson and Green's (2001) TNT visual paradigm. In the independent-probe test, subjects were given a semantic category followed by a letter and were instructed to respond with a word that fit into that category and began with that letter. Participants were given 5000 ms to respond before the automatic advancement to the next trial. Each semantic category corresponded to a target word from the earlier learned list, and was primed with the letter the target word began with. In the same probe test, subjects were auditorily presented with the first word of each pair and asked to respond with the second word of the pair. They were given 5000 ms to respond before the automatic advancement to the next trial.

ELECTROPHYSIOLOGICAL RECORDINGS AND ANALYSIS

Scalp EEG was recorded at 1024 Hz from a 64 channel active electrode system (Biosemi; 10-20 system positions). Additional electrodes were used for reference (earlobes), and to record ocular (EOG) activity.

Offline, the data were preprocessed and analyzed using MATLAB 2011b, custom scripts and the EEGLAB toolbox (Delorme & Makeig, 2004). Independent-component analysis (ICA) was used to remove vertical and horizontal EOG activity. Excessively noisy electrode channels were determined by visual inspection and replaced using spherical spline interpolation of the voltage from surrounding electrodes. The data were re-referenced using current source density (CSD). We used a CSD reference using the Matlab implementation of a spherical spline algorithm (Kayser & Tenke, 2006; Perrin, Pernier, Bertrand, & Echallier, 1989) to obtain the second spatial derivative of the scalp voltage ($\mu\text{V}/\text{m}^2$ units; flexibility parameter $m = 4$; smoothing parameter $\lambda = 5 \times 10^{-5}$).

Positive values of the CSD indicate local current flow out of the skull and negative values indicate current flow into the skull. The CSD transformation allows for a greater degree of independence from the location of reference electrode(s) (Luck, 2014; Tenke & Kayser, 2012) and provides a more focal spatial estimation of the underlying cortical activity (Gevins, 1989; Nunez & Pilgreen, 1991). The data were then bandpass filtered between 0.1 and 35 Hz and downsampled to 120 Hz.

Epochs were created for both cue-locked and word-locked activity for Think and No-Think conditions. All trials containing activity greater than 100uV were removed and the remaining trials were subjected to an iterative artifact rejection process that removed any trials containing data that exceeded 5 standard deviations from the mean of all data at each time point. This was done iteratively until no trials remained that fit that criterion.

Think and No-Think ERPs were created from the artifact-rejected data. Both Word and Cue locked trials were baseline corrected from -100 to 0 ms prior to stimulus onset and then averaged within each subject.

ERP STATISTICAL ANALYSIS

A multi-step permutation method was used to determine differences in ERPs between the Think and No-Think conditions. The null hypothesis that we are testing against is that there is no difference in scalp-evoked activity due to condition.

For each subject, we first computed 2000 null ERPs for each condition at each channel. These null ERPs were obtained from subsets of trials independently drawn from the larger set of the combined trials from both conditions. The number of trials drawn from the combined set for each condition was the same as the number of trials in that condition. Each of the 2000 subsets of trials in each condition was baseline corrected and averaged to obtain a null ERP.

Following this, a set of 50,000 null difference waves (No Think-Think) was computed for each subject at each channel. These difference waves were obtained by subtracting one randomly selected null Think ERP from another randomly selected null No Think ERP. True difference waves were also obtained for each subject using unshuffled trials.

The true and null data were then submitted to a two-tailed test based on the cluster mass statistic (Bullmore et al., 1999). All time points between 0 and 750 ms following Cue stimuli and 0 and 1500 ms following Word stimuli at all 64 scalp electrodes were included in the test (5760 and 11520 total comparisons for Cue and Word, respectively). First, 50,000 across subject averages were computed using the 50,000 null difference waves in each subject. T-scores were then computed for each null grand average difference wave by comparing it to the entire distribution of null grand average difference waves at every time point. This results in 50,000 sets of 5760 (64 channels x 90 time points) and 11520 (64 channels x 180 time points) t-scores for Cue and Word stimuli, respectively.

For each set, all t-scores corresponding to uncorrected p-values of 0.01 or less were formed into clusters with any neighboring such t-scores. Electrodes within approximately 5 cm of one another were considered spatial neighbors and adjacent time points were considered temporal neighbors. The sum of the t-scores in each cluster is the "mass" of that cluster and the most extreme cluster mass in each of the 50,000 sets of tests was recorded and used to estimate the distribution of the null hypothesis.

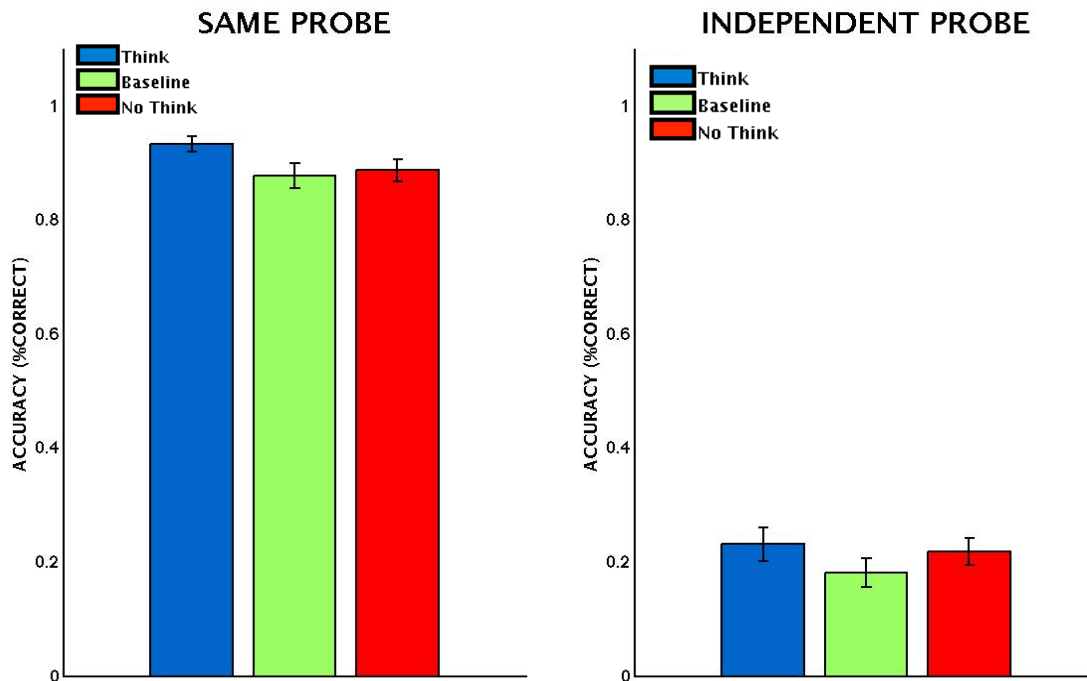
Clusters were then obtained from the true data and the percentile ranking of the mass of each cluster from the true data was used to derive its corrected p-value. The p-value of the cluster was assigned to each member (time-channel point) of the cluster and points that were not included in a cluster (due to small t-score) were given a p-value of 1. Differences between conditions with a corrected p-value less than 0.05 were considered significant.

This permutation test was used instead of mean amplitude analyses of variance (ANOVAs) because it provides much better spatial and temporal resolution than conventional ANOVAs while at the same time maintaining weak control of the family-wise alpha level at 0.05. The cluster mass statistic was chosen for this permutation test because it has been shown to have relatively good power for ERP effects (Groppe, Urbach, & Kutas, 2011). See Luck (2014) as well as Maris and Oostenveld (2007) for further review of this method.

RESULTS

BEHAVIORAL RESULTS

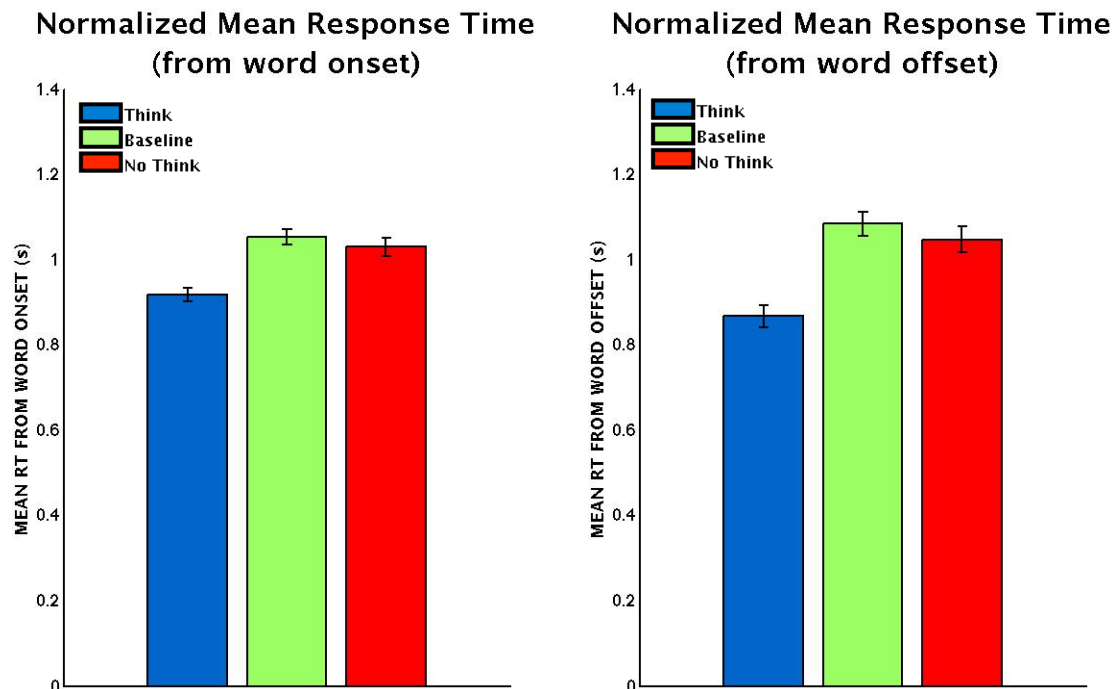
Figure 1-2. Accuracy (% correct) for Think, Baseline, and No-Think conditions in the Same and Independent Probe tests from Experiment 1. Overall ANOVAs were not significant for either test.



Accuracy: We conducted one-way repeated-measures analyses of variance (rmANOVAs) on accuracy for Same-Probe and Independent-Probe tests. Accuracy was defined as the proportion of items that received correct responses with the appropriate target word. We found a trend toward significance for the main effect of memory condition for Same Probe accuracy, such that Think items were recalled more often than No-Think and marginally more often than Baseline ($F(1,15)=3.84, p<0.10$). There was no difference in accuracy for Independent Probe memory conditions (Figure 2-2).

Response Time: Previous research has shown that examining response times can more readily index memory performance (Waldhauser, 2012). Accordingly, we further examined whether any trace of direct suppression was evident by analyzing response times for the Same Probe test, from both the onset and offset of the cue word to the onset of the correct response. In one-way rmANOVAs, we found significance between the conditions (mean from onset: $F(1,15)=10.18, p<0.0005$; mean from offset: $F(1,15)=11.01, p<0.0005$). In both cases, we found memory facilitation of Think items compared to both Baseline and No-Think, but found no differences between Baseline and No-Think response times (Figure 2-3).

Figure 1-3. Experiment 1 response times for normalized mean and median responses from word onset and word offset. Onset: $F(1,15)=10.18, p<0.0005$; Think vs. Baseline ($p<0.05$); Think vs. No-Think, $p<0.05$. Offset: $F(1,15)=11.01, p<0.0005$; Think vs. Baseline ($p<0.05$); Think vs. No-Think ($p<0.05$).



ERP RESULTS

Cues: Figure 2-4 shows ERP (A) cue waveforms at 3 frontal (AF3, AFz, AF4) and 3 central (C3, Cz, C4) electrode sites, (B) the results of our combined permutation and cluster analysis, and (C) topographic head plots at 4 time points where the strongest effects are observed. Electrodes with a corrected $p<0.05$ significant difference between conditions at that time point are starred on the topographic plots. Any non-significant differences are masked in the permutation cluster plot. The results of the permutation and cluster analysis reveal a series of effects. An early negative deflection of the ERP from about 100 to 130 ms at central electrode sites was larger for Think compared to No-Think cues. This was followed by a P2 component effect that was more positive for Think compared to No-Think at frontal sites, but reversed polarity at posterior electrode locations. The last cluster, a sustained Think negativity occurred during the late stage of the cue period, beginning at about 700 ms, and remaining until the end of the trial. Because this difference appeared at the end of the trial and preceded word onset, it may reflect a form of preparatory processing.

Words: Figure 2-5 shows (A) Word ERPs at 3 frontal (F3, Fz, F4) and 3 parietal (P3, Pz, P4) electrode sites to highlight the lateralized memory retrieval effect and concurrent frontal activity, (B) significant results from the permutation and cluster analysis, and (C) topographic plots of the effects at five time points during the Word epoch. Electrodes with a corrected $p<0.05$ condition effect are marked with an asterisk on each

topographic plot. The cluster analysis revealed 3 effects. First, a centralized Think > No-Think effect was seen beginning at around 400ms. This effect begins and peaks during word presentation, which may reflect additional attention allocated to Think words while they are being heard. Second, we observed an increase in Think compared to No-Think trials starting around 900 ms at left lateralized posterior electrode sites, reliably demonstrating the parietal memory retrieval effect observed in previous TNT studies employing EEG (e.g., Bergström et al., 2007; Mecklinger et al., 2009). This parietal activity was followed by an anterior (see Figure 2-5C, 1300 ms) increase in No-Think activity beginning at about 1.1s which may be related to frontal No-Think increases in BOLD activity seen in fMRI studies (e.g. Anderson et al., 2004).

Importantly, although we did see a significant reduction of the parietal positivity for No-Think trials compared to Think trials, a positivity in No-Think words was still present. This is in agreement with the behavioral findings, as although the frontal activity and significant reduction in No-Think words suggests that participants were attempting inhibition, they did not succeed at fully suppressing No-Think words, and behavioral results showed no evidence of successful memory inhibition.

Figure 1-4. Experiment 1 Cue- locked ERP data. (A) ERP waveforms from three frontal and three central electrode channels. (B) No-Think – Think significant t-scores at all electrodes and time points. (C) Topographies at four time points showing significant condition differences. Electrodes that show a significant difference at corrected $p < 0.05$ are marked with an asterisk.

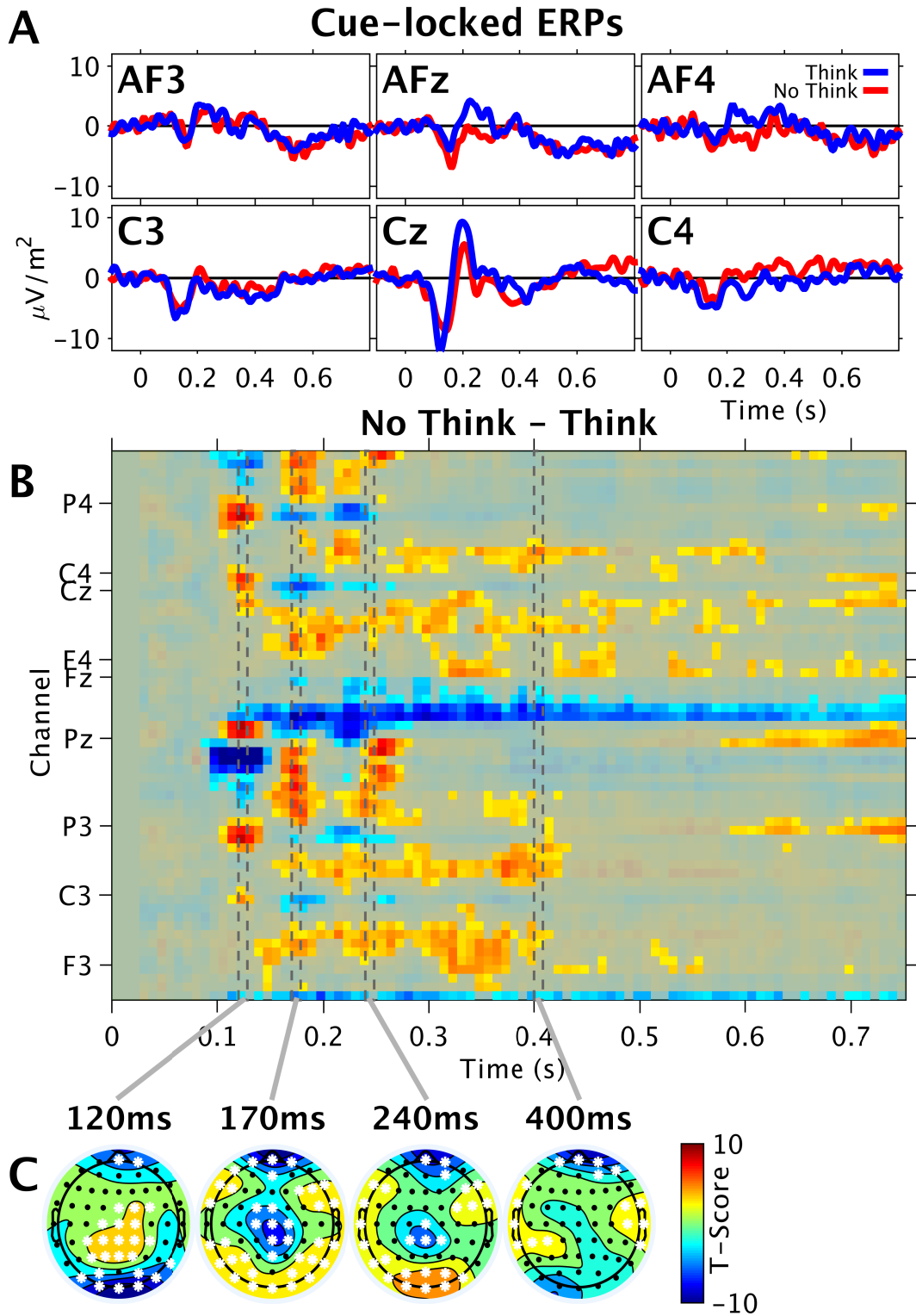
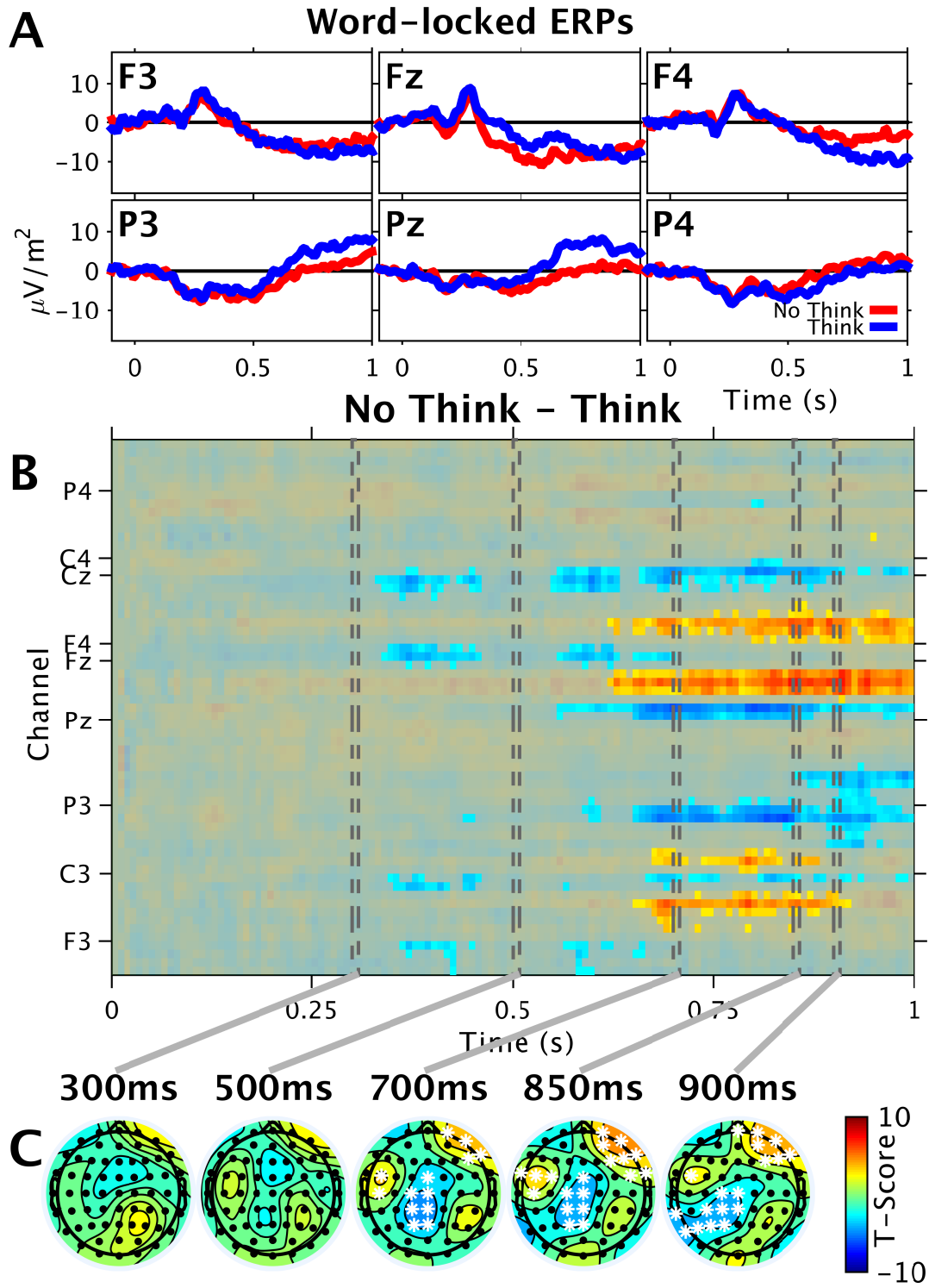
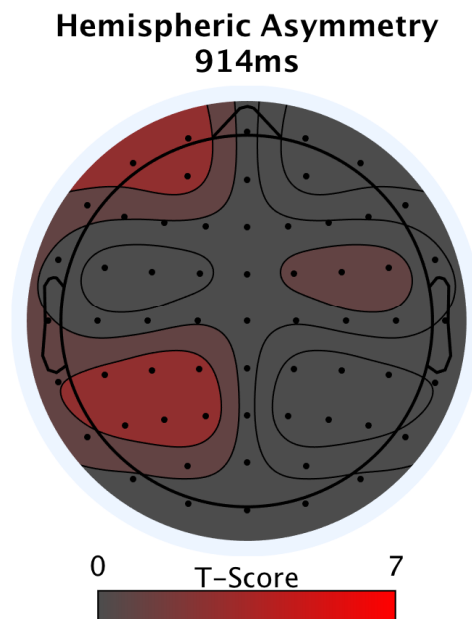


Figure 1-5. Experiment 1 Word- locked ERP data. (A) ERP waveforms from three frontal and three parietal electrode channels. (B) No-Think – Think significant t-scores at all electrodes and time points. (C) Topographies at five time points showing significant condition differences. Electrodes that show a significant difference at corrected $p < 0.05$ are marked with an asterisk.



We further investigated Word ERPs to determine if the retrieval response was indeed lateralized. We did a second permutation analysis to address this issue. The methodology was exactly the same as for the previous analysis, except the two conditions compared were 1) difference waves between Think and No Think words and 2) these same difference waves mirrored across the midline electrodes. Figure 2-6 shows a topographic plot of any hemispheric asymmetries at the time point of maximal difference between conditions. We determined this time point by summing the absolute value of the t-scores across channels for every time point during the Word epoch and selecting the time point with the greatest value after smoothing using a 100ms moving average. Areas on the plot colored red have a numerically bigger condition difference in that hemisphere compared to the other. All electrodes with a significant laterality difference are marked with a white asterisk. We found no significant electrodes, indicating that although we observed significant condition differences in left parietal areas in the initial analysis, these effects were not strong enough to survive lateralization analysis significance thresholding.

Figure1- 6 Experiment 1 lateralization effect during Word trials at the maximal condition difference time point. Locations with difference scores larger than their opposite hemisphere counterpart appear in red. Electrodes with significant differences <0.05 are indicated with an asterisk. There were no significant hemispheric differences at any electrode sites.



DISCUSSION

Behaviorally, we found memory facilitation in the Same Probe test, but found no sign of direct inhibition, which would be indexed by below-baseline accuracy in No-Think responses. We also found no differences among conditions in the Independent-Probe test. Further analysis of response times for correct responses in the Same-Probe test

yielded a significant facilitation effect, but again found no suggestion of direct inhibition. We hypothesize that the lack of a behavioral inhibition effect might be due to too few repetitions, and not necessarily a result of presenting items in the auditory modality.

Although no behavioral suppression effects were found, we observed differences in the ERPs between Think and No-Think trials in both the Cue and Word periods of the Think/No-Think phase of the experiment. These effects were similar to that reported in other studies that employed EEG and the visual TNT paradigm. For instance, in the Cue period, we observed a P2-like component that produced an increased positivity for Think compared to No-Think cues that switched polarity at more posterior electrodes (e.g., Bergstrom et al., 2007, Mecklinger et al., 2009). In Bergstrom et al.'s (2007) discussion of this effect in the TNT phase, the authors suggest that this response may be due to two ERP correlates of visual selective attention, the *frontal selection positivity* and the *posterior selection negativity*. Given our behavioral results, we believe that these ERP findings are specific to facilitation in the Think condition and are not markers of inhibitory control. We also found two other condition differences that are not consistently cited in the TNT literature. We observed an early visual N1 effect that was larger for No-Think compared Think trials. This effect, unlike the P2, is likely to reflect early selective attentional processing of the No-Think cue, potentially aiding in the attempted inhibition of No-Think words (Hillyard, Hink, Schwent, & Picton, 1973; Knight, Hillyard, Woods, & Neville, 1981). A final cue-locked condition effect, whereby No-Think cues were more negative-going than Think cues, emerged in the late cue period and remained through the end of the cue epoch. This effect was significant at frontal midline electrode sites and may reflect an anticipatory shift that readies the participant for the upcoming word.

In the word period, we expected to find the lateralized memory retrieval effect reported in other TNT visual studies (Bergström et al., 2007; 2009; Depue et al., 2013). We found significant condition differences at left parietal electrode sites, but did not find significant lateralization, which might be due to the weak condition effect. We observed positivities for both Think and No-Think words, indicating that items from both conditions were retrieved, although No-Think was significantly reduced compared to Think. This effect aligns with the behavioral evidence of enhanced accuracy for Think and no effect for No-Think. It is likely that attempts at memory inhibition were made during the Word period, but that there were not a sufficient number of repetitions to produce actual forgetting.

EXPERIMENT 2:

MATERIALS AND METHODS

PARTICIPANTS:

A second group of 16 undergraduate students (11F, 18-25 years) participated for course credit or monetary compensation (\$12/hour), and met all criteria specified in Experiment 1.

STIMULI AND DESIGN:

Experiment 2 used an auditory version of the TNT task and varied from Experiment 1 only in stimulus set and number of TNT repetitions as outlined below.

Experiment 2 used a subset of the stimuli used in Experiment 1. Stimuli consisted of 48 pairs. Of the 48 word pairs, 6 were used for practice and the remaining 42 were split into three groups of 14 for Think, No-Think and Baseline conditions.

PROCEDURE

Learning and *Recall* phases of Experiment 2 follow the same procedures as those in Experiment 1.

TNT: The TNT portion of the experiment was identical to that in Experiment 1, except there were 18 repetitions per word as opposed to 5 repetitions.

Subsequent Memory was identical to that in Experiment 1, but using the shorter wordlist for Experiment 2.

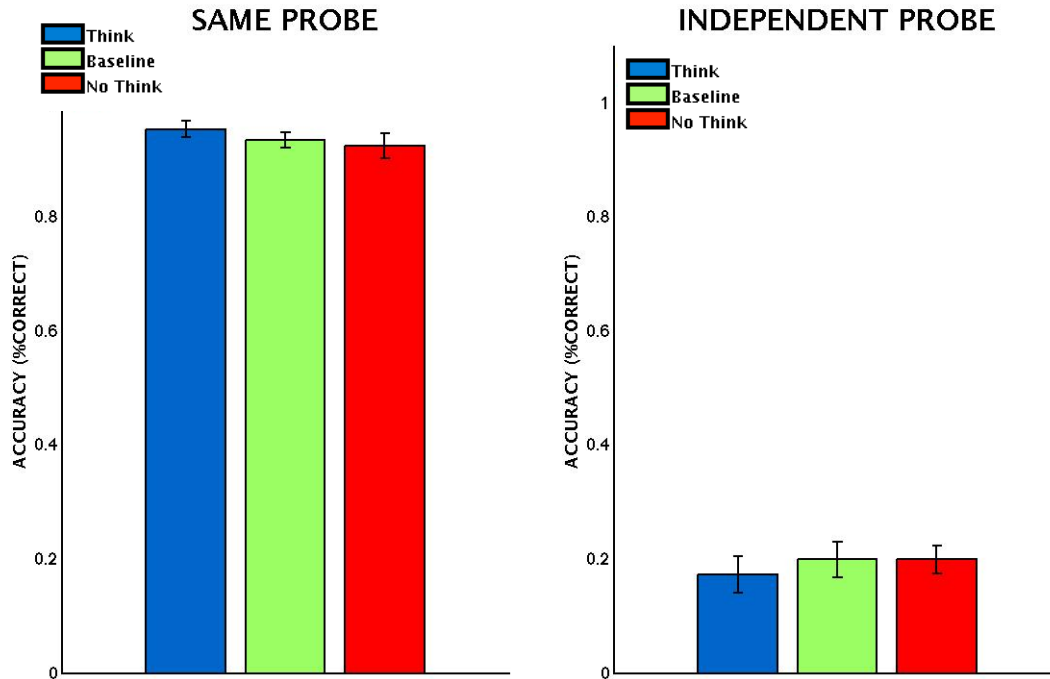
EEG RECORDINGS AND ANALYSIS

All data acquisition parameters and methods used for analysis were the same as in Experiment 1.

RESULTS

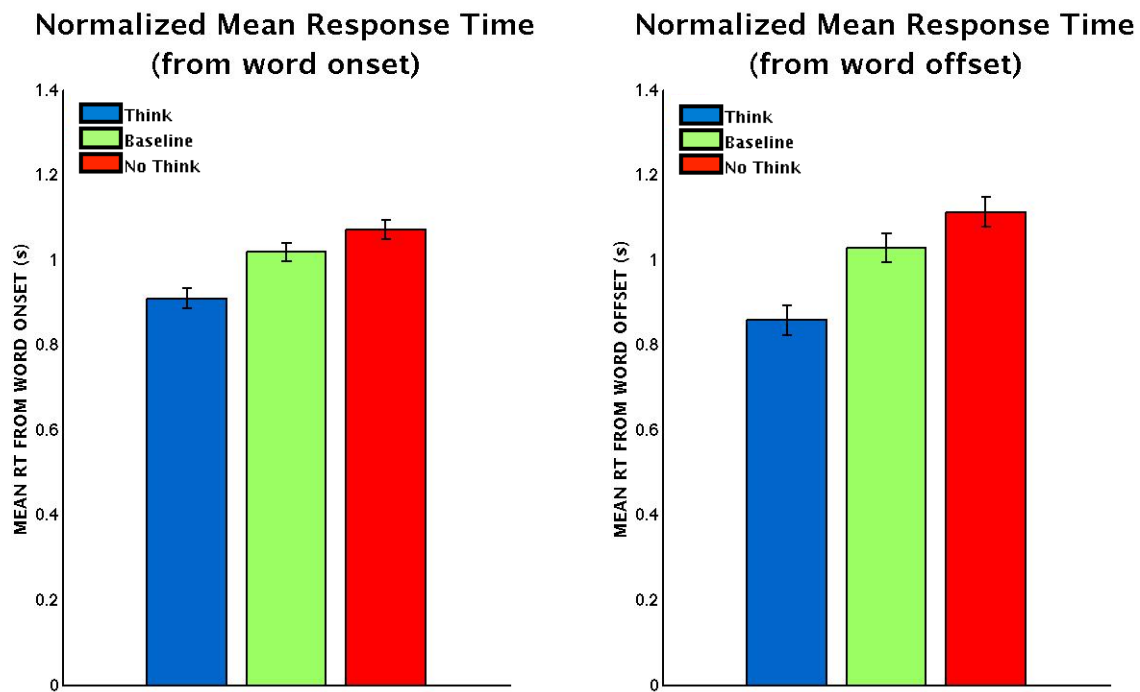
BEHAVIORAL RESULTS

Figure 1-7. Accuracy (% correct) for Think, Baseline, and No-Think conditions in the Same and Independent Probe tests from Experiment 2. No significant results were found.



Accuracy: We conducted one-way repeated-measures analyses of variance (rmANOVAs) on accuracy for Same-Probe and Independent-Probe tests. Accuracy was defined as the proportion of items that were responded to with the appropriate target word. In the Same Probe test, although numeric values of the memory conditions were in the predicted direction, no significant differences were found for either test (SP test: *Response Time:* As in Experiment 2, we further examined whether any trace of direct facilitation or suppression was evident using response time metrics. We analyzed RTs for the Same Probe test, both from the onset and offset of the cue word to the onset of the correct response. In one-way rmANOVAs, we found a significant effect of memory condition when measuring mean latency from cue-word onset ($F(1,15)=5.8399, p<0.01$) and cue-word offset ($F(1,15)=6.59, p<0.005$), such that all memory conditions were different from each other, supporting both facilitatory and inhibitory effects (Figure 2-8).

Figure 1-8. Experiment 2 response times for normalized mean and median responses from word onset and word offset. Same-probe: Onset: $F(1,15)=6.59$, $p<0.005$; Offset: $F(1,15)=5.84$, $p<0.01$. All conditions different at $p<0.05$.



ERPS

Cues: Figure 2-9 shows (A) ERP waveforms for three frontal (AF3, AFz, AF4) and three central (C3, Cz, C4) electrode sites, (B) results from the permutation and cluster analysis for Cue, and (C) topographic plots at four different time points during the Cue period. Any difference that was significant at corrected $p<0.05$ at the depicted time point is starred on the head plot. The permutation and cluster analysis yielded an early visual N1 that was more enhanced for No-Think cues, a central P2 effect, consisting of increased response for Think compared to No-Think trials, with a polarity reversal in posterior sites. There was also an additional slow wave with increased Think compared to No-Think amplitude in the period just following the P2. The findings were very similar to what was reported in Experiment 1. However, in this case, the slow wave activity was intermittently significant, and was not continuously sustained to the end of the cue period.

Words: Figure 2-10 shows (A) ERP waveforms for three anterior (AF3, AFz, AF4) and three parietal electrodes (P3, Pz, P4), (B) results from the permutation and cluster analysis for Word, and (C) topographic plots at five different time points during the Word period. Any difference between conditions that was significant at corrected $p<0.05$ at the depicted time point is starred on the head plot. Permutation and cluster analysis highlighted 3 main effects. First, between approximately 200 and 500 ms, we found a

centralized Think > No-Think effect during the time that the word was being presented. Second, we observed an increase in Think compared to No-Think trials starting around 500 ms at left lateralized posterior electrode sites, again reliably demonstrating the parietal memory retrieval effect observed in previous TNT studies. The third effect seen was an anterior increase in No-Think compared to Think. Again these findings were similar to what was found in Experiment 1. A crucial difference, however, is that the memory retrieval component is almost completely abolished for No-Think trials, indicating successful memory suppression.

Figure 1-9. Experiment 2 Cue- locked ERP data. (A) ERP waveforms for three anterior (AF3, AFz, AF4) and three central (C3, Cz, C4) electrode channels. (B) No-Think – Think significant t-scores at all electrodes and time points. (C) Topographies at four time points showing significant condition differences. Electrodes that show a significant difference at $p < 0.05$ are marked with an asterisk

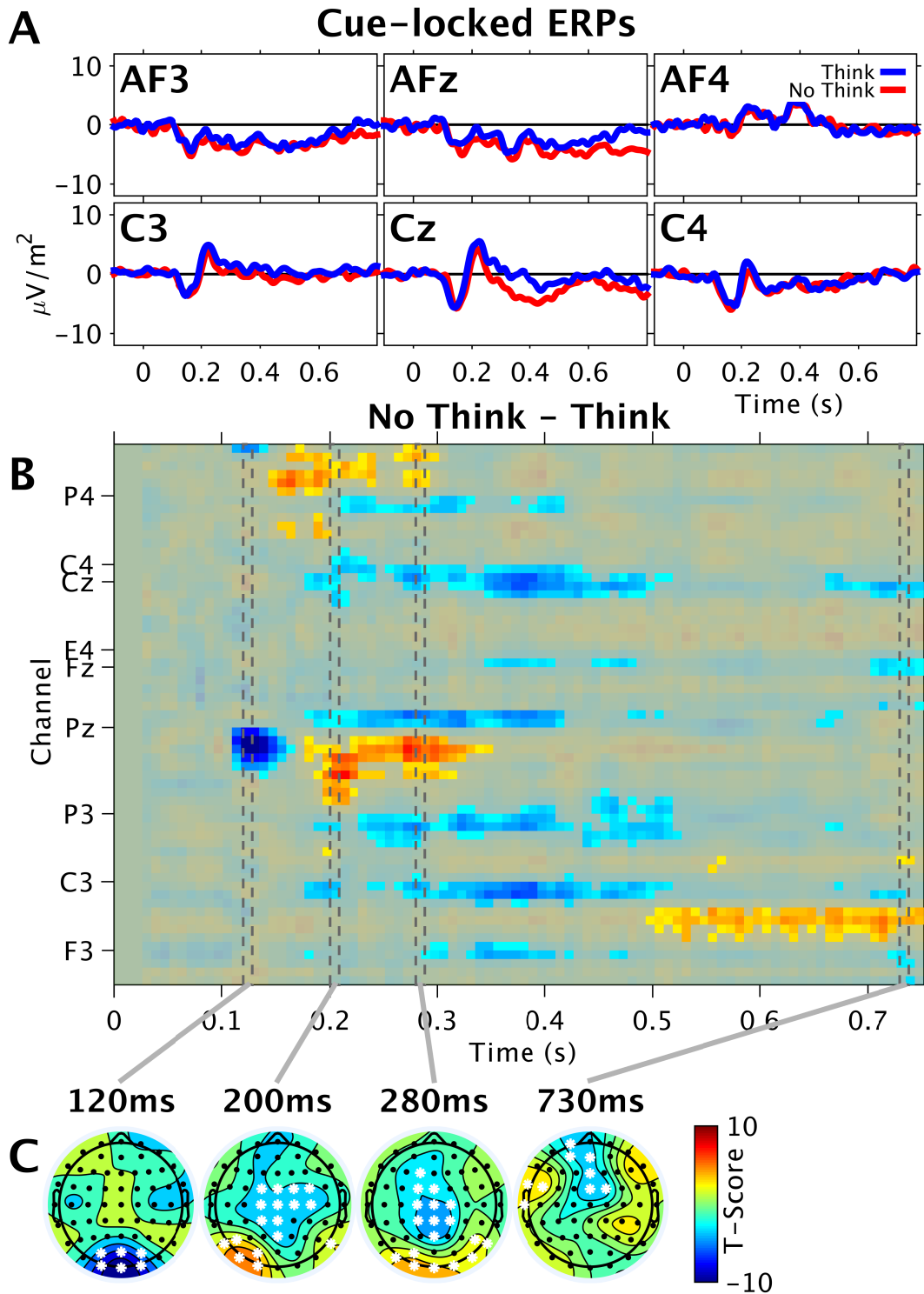
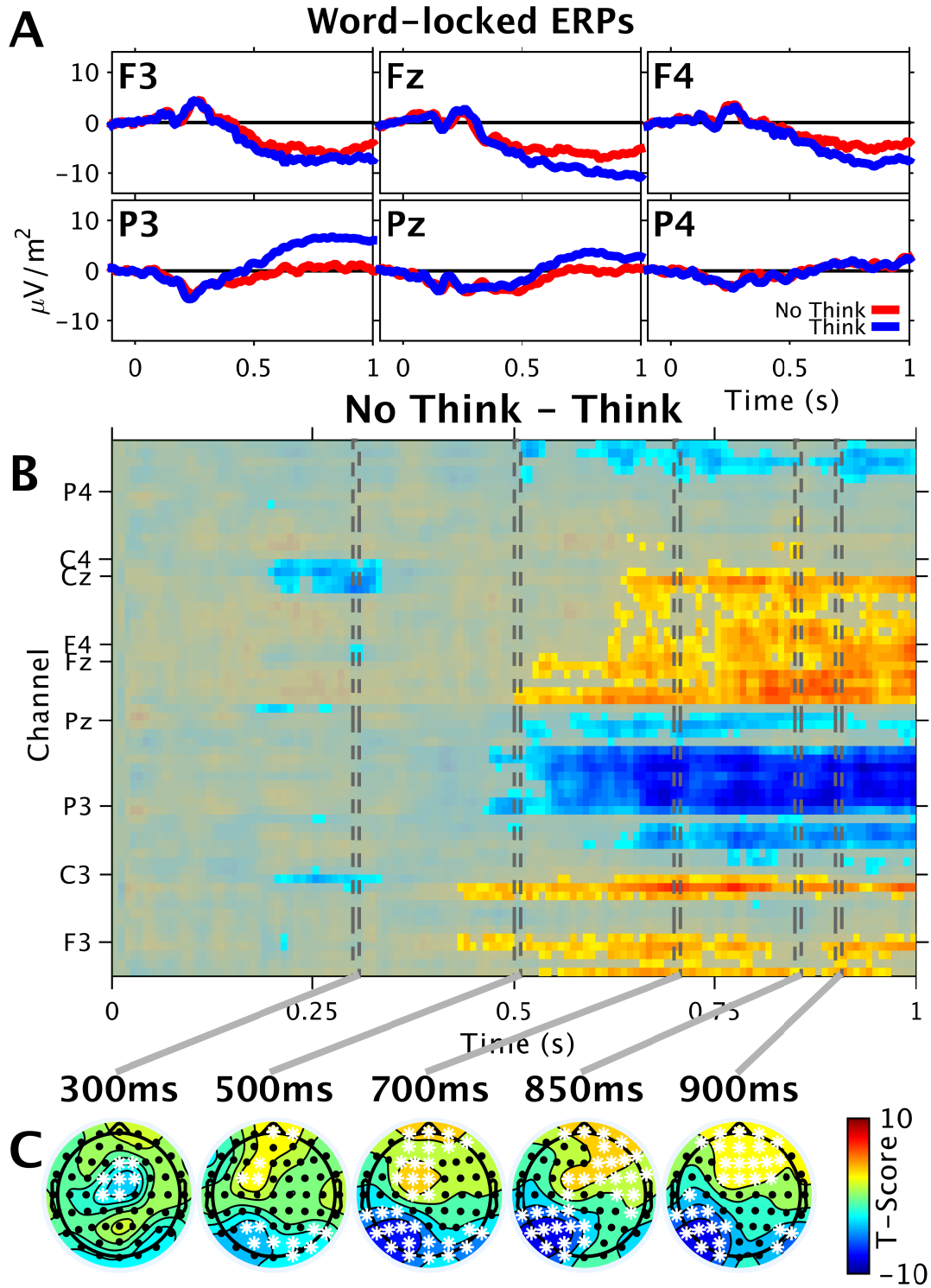
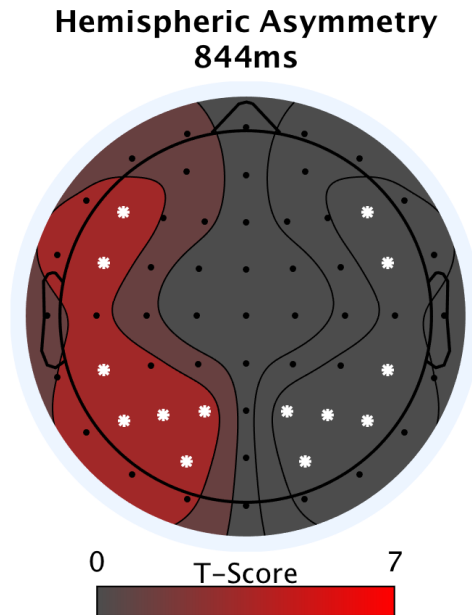


Figure 1-10. Experiment 2 Word- locked ERP data. (A) ERP waveforms from three frontal (F3, Fz, F4) and three parietal (P3, Pz, P4) electrode channels. (B) No-Think – Think significant t-scores at all electrodes and time points. (C) Topographies at five time points showing significant condition differences. Electrodes that show a significant difference at $p < 0.05$ are marked with an asterisk.



To quantify the lateralization difference, we followed the permutation and clustering lateralization procedure detailed in Experiment 1 and this time, found a significant lateralization effect, such that condition differences (Think > No-Think in the observed data), were larger over the left posterior region compared to right ($p < 0.05$) at the point of maximal condition difference (Figure 2-11).

Figure 1-11. Experiment 2 lateralization effect during Word trials at the maximal condition difference. Difference scores larger than the opposite side of the head are depicted in red. Electrodes with significant differences < 0.05 are indicated with an asterisk.



DISCUSSION

As in Experiment 1, we failed to find significant differences in accuracy for both Same- and Independent-Probe tests using auditory stimuli. We did produce the predicted behavioral memory pattern in the Same-Probe test, albeit non-significant. However, upon further examination of the responses made in the Same-Probe test, we confirmed a measure of direct facilitation and inhibition. Although accuracy for Think and No-Think items were not manipulated in relation to Baseline, we found that responses were indeed faster for Think and slower for No-Think items compared to Baseline, confirming auditory memory manipulability using the TNT paradigm.

Turning to the ERP effects, we found a similar N1 effect as in Experiment 1, comprised of a more negative response to No-Think trials in occipital locations. We also reproduce both a P2 Cue effect similar to that in Experiment 1 and to previous TNT studies (e.g.,

Bergstrom et al., 2007, Mecklinger et al., 2009). Additionally, we found evidence for suppression of the memory retrieval effect in No-Think trials, which was left lateralized.

The behavioral and ERP results from Experiment 2 demonstrate that with more practiced retrieval and inhibition, auditory memory can be manipulated in distinct ways, and that those effects are well reflected in the neuroelectric responses.

GENERAL DISCUSSION

Two experiments were conducted to determine whether auditory directed forgetting produced similar behavioral and EEG effects to that observed in the visual domain. To address this issue, we developed an auditory analogue of the classic visual Think/No-Think paradigm. In experiment 1, 20 word pairs and a relatively small number of repetitions ($n=5$) were used in the TNT phase of the experiment and we were unable to produce a robust classic TNT effect. While we found evidence for intentional memory enhancement, as reflected by the Think condition in both accuracy and response time, we found no significant difference between No-Think and Baseline subsequent memory, indicating that direct suppression of those items was not achieved.

In Experiment 2, we increased the number of repetitions to 18 in an effort to maximize the chances of producing the classic TNT effect. Although we decreased the number of word pairs, we greatly increased the number of trials as a result of the increase in the number of repetitions. In an experiment in which instruction cues switched half way through the TNT phase, yet still produced below baseline suppression of No-Think trials, Bergstrom et al. (2009) suggests that it is the amount of inhibitory practice and not simply practicing inhibiting specific items that produces a lasting forgetting effect. This idea is corroborated by evidence from individual differences, based on findings that participants who reported prior experience inhibiting unwanted memories were also more successful at forgetting in an experimental setting (Anderson & Levy, 2009). When we increased the amount of overall practice (300 No-Think trials in Experiment 2 compared to 100 in Experiment 1) we observed the predicted behavioral pattern (but n.s.) that has been seen in classic TNT studies along with similar ERP patterns in Experiment 1 and in previous TNT experiments using EEG. Importantly, our analysis of response time revealed that we produced a clear suppression effect, as we found significantly longer response times for No-Think items compared to Think and Baseline.

These results suggest that auditory memory may be more difficult to manipulate than visual memory, and that it may take more sensitive measures to examine memory inhibition in audition. Moderate activation of memories has been shown to render those memories more easily inhibited, as compared with weaker or stronger memories (Detre, Natarajan, Gershman, & Norman, 2013). If learning auditory words produces a stronger memory, it may take much more effort to inhibit it. Our research participants, university students, are particularly practiced in auditory learning (i.e., from lectures) and may find that they are so tuned to auditory learning that more than one experimental session is needed to fully develop the ability to suppress auditory memories.

Event-related ERPs locked to cue-onset were similar across experiments. In both Experiment 1 and 2, we observed an early visual N1 effect that was more negative to No-Think cues, which may represent enhanced attention to No-Think stimuli (Luck, Woodman, & Vogel, 2000). We also found similar P2 component effects across experiments, with Think > No-Think at central sites. The P2 has been shown to be modulated on the basis of attentional selection of visual stimulus features (e.g., Smid, Jakob, & Heinze, 1999). The Think cue may produce this P2 enhancement effect because it is a more relevant indicator of the upcoming memory task. In Experiment 2 we observed sustained Think and No-Think differences during the 300-500 ms time frame, but these differences were not continuous through the end of the cue phase as in Experiment 1. Perhaps this is because the shorter list of learned word pairs in Experiment 2 meant that the stimuli were over-learned or that participants found the task easier as experimental time passed, not necessitating a sustained shift of focus.

Word-locked activity produced effects similar to that observed in the visual domain, although those found in Experiment 2 were stronger and more consistent with what has been documented previously. Adding more repetitions in Experiment 2 helped to localize the memory retrieval effect, and to completely suppress the ERP correlate of memory retrieval for No-Think items as opposed to the partial diminishment of the effect seen in Experiment 1. This effect, consisting of a positivity reduction in the No-Think condition compared to Think, likely represents an increase in the suppression ability gained by additional repetitions.

This present study offers encouraging evidence for the ability to inhibit auditory memories using the TNT paradigm. The ERP effects shown here are in line with those presented in the visual domain. Visual studies report an early N1, P2 and left lateralized parietal effect. Although we did not find below-baseline forgetting according to an accuracy measure, the combination of response time and ERP effects suggests that auditory directed forgetting mechanisms are similar to that of the visual domain, although likely more difficult to achieve. One of the most attractive aspects of the TNT model is that items that are to-be-forgotten are ideally forgotten below baseline levels of forgetting. In this way, we see clear benefits to this method in terms of adapting it for clinical purposes. However, to date all TNT experiments have used visual stimuli. For instance, traumatic memory recall in PTSD patients are not only visual, but are often additionally full of auditory, olfactory, tactile, and even taste information. This study extends the current literature by suggesting that all modalities of memory may be able to be suppressed, but that they may not be equivalent in the degree of suppressability. Further research combining or directly contrasting different memory modalities may provide insight into how real-life memories might be successfully suppressed.

CHAPTER 3

EEG and behavioral evidence for auditory directed forgetting in older adults

ABSTRACT

The purposes of this study are twofold: 1) While the majority of directed forgetting studies have used visual stimuli, we sought to determine whether intentional forgetting extends to other sensory modalities 2) We aimed to examine the behavioral and neuroelectric effects of auditory directed forgetting in older adults.

To address these issues, we recorded electroencephalography (EEG) during a modified auditory version of the Think/No-Think (TNT) paradigm with healthy older adults. Participants underwent a modified variation of the TNT task in which all learned word pairs were presented in the auditory domain. In the main phase of the experiment, participants were presented with the first word of each pair, preceded by a visual instruction cue, which indicated either to silently retrieve the second word of the pair or to inhibit recollection of the second word of the pair. Subsequent memory was assessed by two methods: 1) a same-probe test in which target words are probed by the original paired memory cue word, and 2) an independent-probe test in which a semantic category and single-letter stem (first letter of the target word) probe for the target word. Both tests are intended to determine the effect of instruction on later memory.

Here, we examined task-related EEG activity during intentional memory retrieval and inhibition. Behaviorally, older adults showed a directed forgetting effect similar to that seen in previous studies using young adults, such that No-Think words were forgotten at a higher rate than Baseline and Think words. This behavioral effect demonstrates successful active memory suppression for No-Think items. ERPs were examined during two periods of the Think/No-Think phase of the experiment and were time-locked to both instruction cue onset and word onset. Cue-related activity produced an early N1 effect (100-175 ms) in which No-Think cues were more negative than Think cues in both visual and anterior areas, supporting evidence for an increased early attention effort for No-Think instruction cues. This effect was reversed in polarity at central sites. A fronto-central P2 (200-300 ms) component was enhanced for Think compared to No-Think trials (200-300 ms) and produced a sustained difference at fronto-central electrode sites through the end of the cue period, which may reflect the process of frontal cortex preparing to selectively attend to the upcoming Think cue word. Word-related activity produced early condition differences at central and lateral fronto-central electrode sites, but converged to a left-lateralized parietal Think > No-Think response starting around 500 ms, and remaining through the end of the word period, reflecting the active inhibition of the particular item in memory.

These behavioral and ERP data provide evidence that auditory directed forgetting in older adults elicits similar effects to those seen in the visual directed-forgetting domain in young adults, and that these effects can also be reliably elicited.

INTRODUCTION

As we age, it is generally accepted that we become more forgetful. Indeed, many studies have shown that older adults have poorer memory than their younger counterparts (Craik, Birren, & Schaie, 1977). The memory 'forgetting literature' demonstrates that as we get older, our ability to remember things that we want to remember becomes worse, making older adults more prone to incidental forgetting (Light, 1991). However, there is relatively little research that examines to what extent we are able to forget the things we actively want to forget as we age (Titz & Verhaeghen, 2010). Given the increased interest in the cognitive control of memory in recent years, how active memory inhibition might be affected by age is an important and unresolved question.

It has been proposed that forgetting can be manipulated by inhibitory mechanisms and that the stopping of the retrieval of a memory is much the same as the stopping of other forms of pre-potent responses (Anderson & Weaver, 2009; MacDonald & Joordens, 2000). Studies investigating inhibition in other cognitive domains such as attention (Bidet-Caulet, Mikyska, & Knight, 2010; Kastner & Ungerleider, 2000; Knight et al., 1999), working memory (Gazzaley et al., 2008; Gazzaley, Cooney, Rissman, & D'Esposito, 2005), and behavioral responses (Aron et al., 2003; Kramer et al., 2013), have attributed control over these processing to the prefrontal cortex. Aging research has demonstrated a decline in prefrontal function (Raz & Rodrigue, 2006) and inhibitory control in older adults (Coxon, Van Impe, Wenderoth, & Swinnen, 2012; Gazzaley et al., 2008; Hasher & Zacks, 1988). If intentional forgetting of learned memories relies on the same control mechanisms used for other means of inhibitory control, then below baseline memory suppression in older adults may be impaired.

A few studies have sought to find behavioral differences in the ability of older adults to actively inhibit memory. Older adults have been reported to be less able to suppress to-be-forgotten items than younger ones (Zacks et al., 1996; Sahakyan et al., 2008; Zellner & Bauml, 2006). Recently, Healey and colleagues (2014) showed below-baseline suppression of response time for interference-caused inhibition was absent in older adults. In an experiment examining the direct intentional suppression of memory, Anderson et al. (2011) employed the Think/No-Think paradigm for younger and older adults in the visual modality. They found comparable suppression scores between young and older adults when they were tested with the same cues used for suppression practice, but found that only young adults were able to suppress below baseline in an independent probe test.

What is still unknown is how sensory modality may affect memory suppression ability. Some evidence suggests that auditory memory may be less robust compared to visual memory (e.g., Cohen, Horowitz, Wolfe, & Treisman, 2009). It is reasonable to suspect that if memory from different modalities cannot be intentionally remembered equally, there may also be modality differences for intentional forgetting.

The limited number of studies looking at the cognitive control of intentional forgetting in aging led us to examine more closely the details by which older adults can flexibly enhance and inhibit their own memory. Here we adapt the Think/No-Think paradigm to the auditory domain, presenting all learned and probed material auditorily to examine to what extent older adults can both inhibit and strengthen memory of a paired associate, measured directly with a same-probe memory test and indirectly with an independent probe test. We investigate the neuroelectric activity associated with retrieval and inhibition attempts and relate these ERP effects to those found in visual memory suppression.

MATERIALS AND METHODS

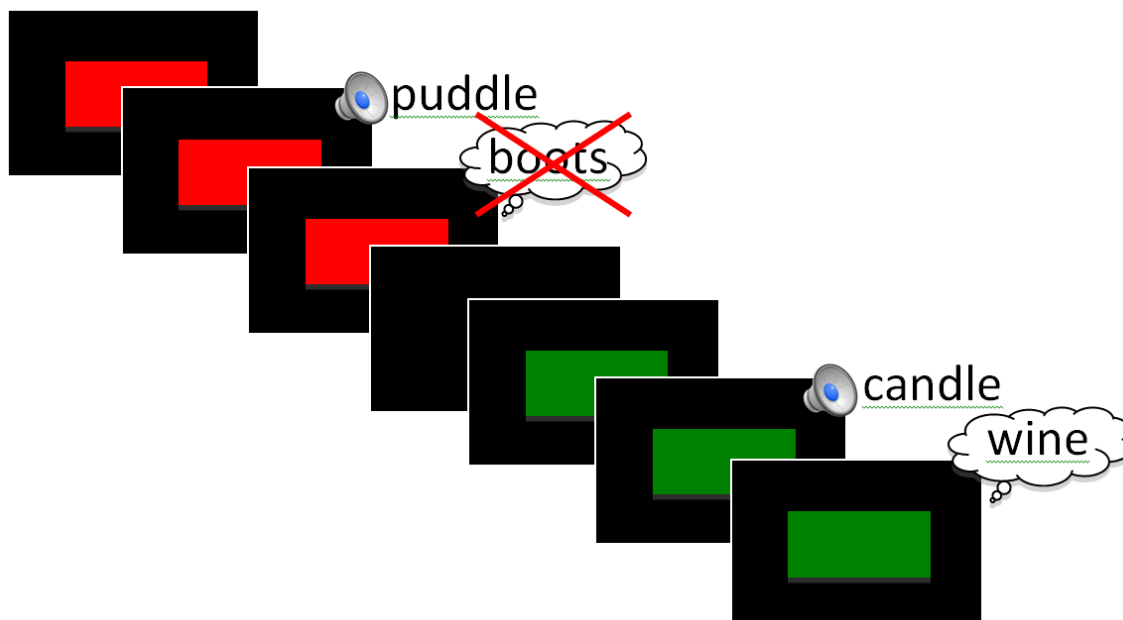
PARTICIPANTS

EEG was recorded from 17 older adults (11F, mean age: 59.2). All participants were native English speakers, reported to be free of any neurological disorders, and provided written informed consent approved by the University of California, Berkeley Committee for Protection of Human Subjects. Participants received monetary compensation of \$20/hour.

STIMULI AND DESIGN

We developed a modified version of Anderson and Green's (2001) visual Think/No-Think (TNT) paradigm. In this version all word stimuli were presented in the auditory domain. Only the instruction cue items were presented visually (see Figure 3-1).

Figure 2-1. Schematic of the TNT phase of the experiment for an example No-Think (red) and Think (green) trial. See text for stimulus timing.



Stimuli consisted of 48 pairs of English words developed for this experiment, which paralleled the procedures used in previous TNT studies, and were presented auditorily. Of the 48 word pairs, 6 were used for practice, and the remaining 42 were split evenly into 3 groups for Think, No-Think, and Baseline conditions. Each of the Think and No-Think items were presented 18 times during the Think/No-Think phase of the experiment.

PROCEDURE

Learning: In the initial learning phase of the experiment, all 48 word pairs were presented with 1000 ms between the onset of the first and second word of each pair and a 6600 ms inter-trial interval. Participants were asked to try to learn the pairs such that if they are given the first word, or “cue word”, they will be able to respond with the second, or “target word”. They listened to each pair once before moving on to the recall phase of the experiment.

Recall: Recall memory was tested immediately following the initial study phase. Subjects were given the cue word of each pair and asked to respond with the target word, receiving feedback on each trial. They were asked to continue studying unlearned word pairs until they reached 100% accuracy, such that each target word was recalled correctly exactly once. Recall for this phase was self-paced.

TNT: On each trial, subjects viewed a visual instruction cue that appeared centered on the screen preceding the auditory presentation of the cue word. We separated the cue and word presentation because anticipation of to-be-inhibited item has been shown to have differential effects on ERPs (Hanslmayr et al., 2009) and to also increase later forgetting of items (Hanslmayr et al., 2010). Participants were instructed to either silently

recall (green box; Think words) or inhibit (red box; No-Think words) the target word of each word pair after hearing the cue word. It was stressed to all participants that on No-Think trials, it was important to keep the target word out of mind and not to think about it even after the trial was over. This was instructed since intentional forgetting can be achieved with either thought substitution (by which a new word is mentally used to replace the target word in the original pairing), or by direct suppression of items (Hertel and Calcaterra, 2005; Bergstrom et al, 2009), which produce differing brain mechanisms (Benoit and Anderson, 2012). Given we were interested in direct suppression all participants were instructed to directly suppress, and not merely to substitute the to-be-suppressed word with an alternate item. In each trial, the instruction cue appeared for 900 ms with a 100 ms jitter before the first word of each Think of No-Think pair was presented (Figure 3-1). The instruction cue remained on the screen for the entirety of the word presentation. Inter-trial interval was 3600 ms with a 500 ms uniformly distributed jitter. Think and No-Think trials were randomly presented 18 times throughout this phase of the experiment.

Subsequent Memory: Subsequent memory was tested using both the independent and the same probe method developed from Anderson and Green's (2001) TNT visual paradigm. In the independent-probe test, subjects were given a semantic category followed by a letter and were instructed to respond with a word that fit into that category and began with that letter. Participants were given 5000 ms to respond before the automatic advancement to the next trial. Each semantic category corresponded to a target word from the earlier learned list, and was also primed with the letter the target word began with. In the same probe test, subjects were auditorily presented with the first word of each pair and asked to respond with the second word of the pair. They were given 5000 ms to respond before the automatic advancement to the next trial.

EEG RECORDING AND ANALYSIS

Scalp EEG was recorded at 1024 Hz from a 64 channel active electrode system (Biosemi; 10-20 system positions). Additional electrodes were used for reference (earlobes), and to record ocular (EOG) activity.

Offline, the data were preprocessed and analyzed using MATLAB 2011b, custom scripts and the EEGLAB toolbox (Delorme & Makeig, 2004). Independent-component analysis (ICA) was used to remove vertical and horizontal EOG activity. Excessively noisy electrode channels were determined by visual inspection and replaced using spherical spline interpolation of the voltage from surrounding electrodes.

The data were re-referenced using current source density (CSD). We used a CSD reference using the Matlab implementation of a spherical spline algorithm (Perrin et al, 1989, Kayser and Tenke, 2006) to obtain the second spatial derivative of the scalp voltage ($\mu\text{V}/\text{m}^2$ units; flexibility parameter $m = 4$; smoothing parameter $\lambda = 5 \times 10^{-5}$). Positive values of the CSD indicate local current flow out of the skull and negative values indicate current flow into the skull. The CSD transformation allows for a greater degree of independence from the location of reference electrode(s) (Luck, 2014, Kayser & Tenke, 2012) and provides a more focal spatial estimation of the underlying cortical

activity (Gevins, 1989, Nunez & Pilgreen, 1991). The data were then bandpass filtered between 0.1 and 35 Hz and downsampled to 120 Hz.

Epochs were created for both cue-locked and word-locked activity for Think and No-Think conditions. All trials containing activity greater than 100uV were removed and the remaining trials were subjected to an iterative artifact rejection process that removed any trials containing data that exceeded 5 standard deviations from the mean of all data at each time point. This was done iteratively until no trials remained that fit that criterion.

Think and No-Think ERPs were created from the artifact-rejected data. Both Word and Cue locked trials were baseline corrected from -100 to 0 ms prior to stimulus onset and then averaged within each subject.

ERP STATISTICAL ANALYSIS

A multi-step permutation method was used to determine differences in ERPs between the Think and No-Think conditions. The null hypothesis that we are testing against is that there is no difference in scalp-evoked activity due to condition.

For each subject, we first computed 2000 null ERPs for each condition at each channel. These null ERPs were obtained from subsets of trials independently drawn from the larger set of the combined trials from both conditions. The number of trials drawn from the combined set for each condition was the same as the number of trials in that condition. Each of the 2000 subsets of trials in each condition was baseline corrected and averaged to obtain a null ERP.

Following this, a set of 50,000 null difference waves (No Think-Think) was computed for each subject at each channel. These difference waves were obtained by subtracting one randomly selected null Think ERP from another randomly selected null No Think ERP. True difference waves were also obtained for each subject using unshuffled trials.

The true and null data were then submitted to a two-tailed test based on the cluster mass statistic (Bullmore et al., 1999). All time points between 0 and 750 ms following Cue stimuli and 0 and 1500 ms following Word stimuli at all 64 scalp electrodes were included in the test (5760 and 11520 total comparisons for Cue and Word, respectively). First, 50,000 across subject averages were computed using the 50,000 null difference waves in each subject. T-scores were then computed for each null grand average difference wave by comparing it to the entire distribution of null grand average difference waves at every time point. This results in 50,000 sets of 5760 (64 channels x 90 time points) and 11520 (64 channels x 180 time points) t-scores for Cue and Word stimuli, respectively.

For each set, all t-scores corresponding to uncorrected p-values of 0.01 or less were formed into clusters with any neighboring such t-scores. Electrodes within approximately 5 cm of one another were considered spatial neighbors and adjacent time points were considered temporal neighbors. The sum of the t-scores in each

cluster is the "mass" of that cluster and the most extreme cluster mass in each of the 50,000 sets of tests was recorded and used to estimate the distribution of the null hypothesis.

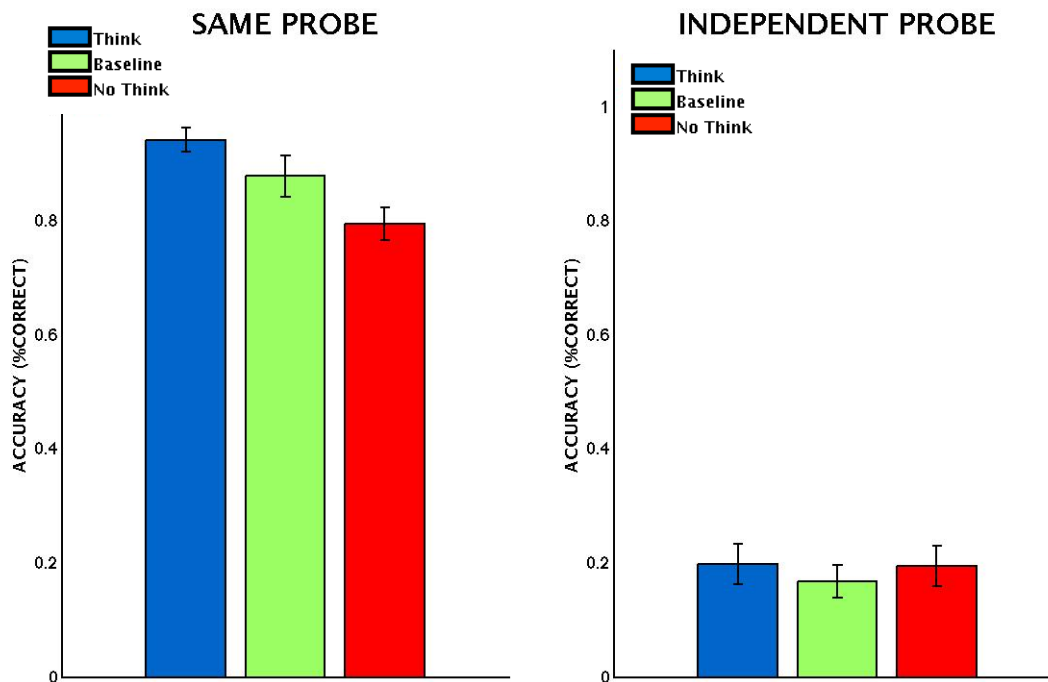
Clusters were then obtained from the true data and the percentile ranking of the mass of each cluster from the true data was used to derive its corrected p-value. The p-value of the cluster was assigned to each member (time-channel point) of the cluster and points that were not included in a cluster (due to small t-score) were given a p-value of 1. Differences between conditions with a corrected p-value less than 0.05 were considered significant.

This permutation test was used instead of mean amplitude ANOVAs because it provides much better spatial and temporal resolution than conventional ANOVAs while at the same time maintaining weak control of the family-wise alpha level at 0.05. The cluster mass statistic was chosen for this permutation test because it has been shown to have relatively good power for ERP effects (Groppe et al., 2011). See Luck (2014) as well as Maris and Oostenveld (2007) for further review of this method.

RESULTS

BEHAVIORAL RESULTS

Figure 2-2. Accuracy (% correct) for Think (blue), Baseline (green), and No-Think (red) items for Same and Independent Probe tests. Same-probe: Overall ANOVA, $F(1,16)=17.283$, $p<0.002$; Think vs. Baseline ($p<0.10$); Think vs. No-Think, $p<0.001$; Baseline vs. No-Think, $p<.05$. Independent-probe: n.s. for all comparisons.

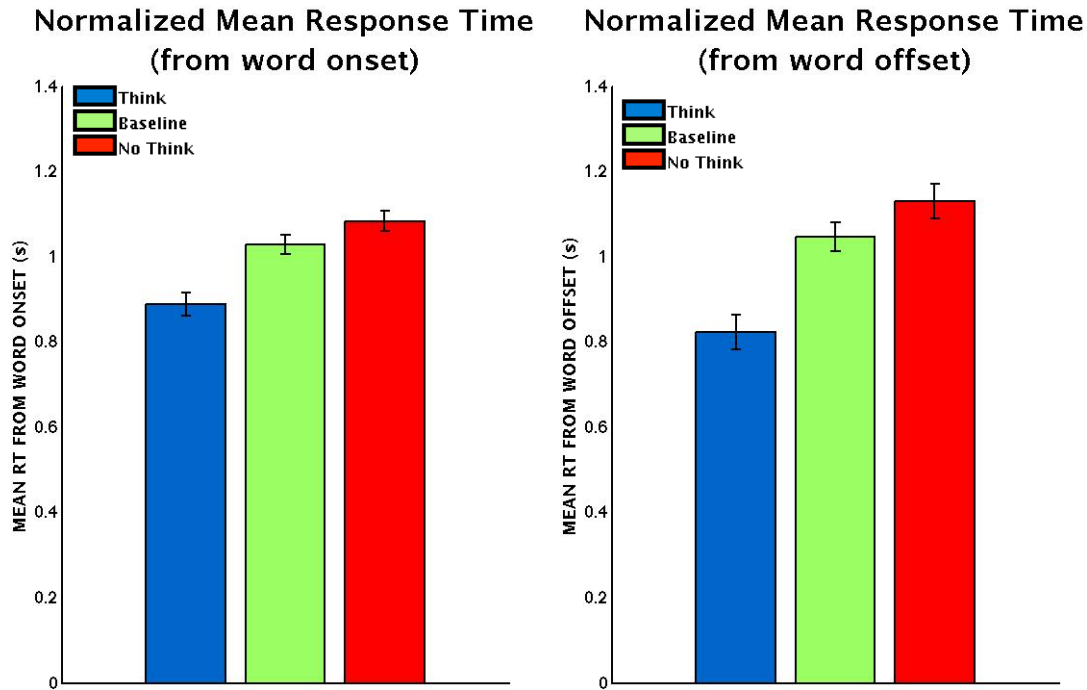


Accuracy: We conducted one-way repeated-measures analyses of variance (rmANOVAs) on accuracy for both same-probe and independent-probe subsequent memory tests across conditions (Think, Baseline, No-Think), see Figure 3-2. Accuracy was defined as the proportion of items responded to with the appropriate target word. For the same-probe test, we found a significance in the overall ANOVA ($F(1,16)=17.283$, $p<0.002$), with marginal differences between Think and Baseline ($p<0.10$, one-tailed), a significant difference between Think and No-Think ($p<0.001$, one-tailed), and critically, Baseline and No-Think ($p<.05$, one-tailed), all in the predicted direction. The independent-probe semantic priming test yielded no differences between memory conditions ($F(1,16)=0.010$, $p=0.76$).

Response time: We examined response time for correctly recalled items in the same probe test to determine if there was further evidence of inhibition for correct trials. The overall ANOVA was significant for mean onset ($F(1,16)=24.81$, $p<0.001$) and mean offset ($F(1,16)=23.16$, $p<0.001$), see Figure 3-3. We found the predicted pattern, such that Think items were faster to recall than Baseline ($p<0.005$) and No-Think ($p<0.001$)

items, and Baseline items were marginally faster than No-Think items ($p < 0.10$) for both onset and offset measures.

Figure 2-3. Mean normalized response time for correct Think (blue), Baseline (green), and No-Think (blue) items from word onset and offset in the Same Probe test. Normalized mean onset RT: Overall ANOVA, $F(1,16)=24.81$, $p < 0.001$; Think vs. Baseline, $p < 0.005$; Think vs. No-Think, $p < 0.001$ Baseline vs. No-Think, $p < 0.10$. Normalized mean offset RT: Overall ANOVA, $F(1,16)=23.16$, $p < 0.001$; Think vs. Baseline, $p < 0.005$; Think vs. No-Think, $p < 0.001$ Baseline vs. No-Think, $p < 0.10$ ($p < 0.10$). Independent-probe: n.s. for all comparisons.



ERP RESULTS

Cues: Figure 3-4 shows (A) cue ERP waveforms at 3 frontal (AF3, AFz, AF4) and 3 central (C3, Cz, C4) electrode sites, (B) the results of our combined permutation and cluster analysis, and (C) topographic head plots at 4 time points where the strongest effects are observed. Electrodes with a corrected $p < 0.05$ significant difference between conditions at that time point are starred on the topographic plots. Any non-significant differences are masked in the permutation cluster plot. The results of the permutation and cluster analysis reveal a series of electrophysiological effects. An early negative deflection of the ERP resembling an N1 component peaked at about 150 ms was larger for No-Think compared to Think at posterior and anterior electrode sites ($p < 0.05$), but was enhanced for Think compared to No-Think cues at central locations ($p < 0.05$). This was followed by a broadly distributed P2 component effect that was more positive for Think compared to No-Think at frontal and centro-parietal sites ($p < 0.05$), replicating the EEG effects demonstrated in previous TNT studies which used visual stimuli (Bergstrom et al., 2007; Mecklinger et al., 2009). The P2 amplitude condition difference produced a

sustained effect that persisted in fronto-central electrodes until through the end of the cue period ($p < 0.05$), similar to what has been shown by Hanslmayr et al. (2009) in young adults in the visual domain.

Words: Figure 3-5 shows (A) Word ERPs at 3 frontal (F3, Fz, F4) and 3 parietal (P3, PZ, P4) electrode sites to highlight the posterior lateralized memory retrieval effect and related frontal activity, (B) significant results from the permutation and cluster analysis, and (C) topographic plots of the effects at five time points during the Word epoch. Electrodes with a corrected $p < 0.05$ condition effect are starred on each topographic plot. The cluster analysis revealed differential processing of Think and No-Think words during the presentation of the word from 300-500 ms, such that central electrodes produced a more positive ERP for Think words ($p < 0.05$). A robust condition difference emerged at approximately 500 ms, such that No-Think words had a reduced positivity compared to Think words, and this effect was lateralized to left parietal electrodes ($p < 0.05$).

Figure 2-4. Cue-locked grand average ERP data. (A) ERP waveforms from three anterior (AF3, AFz, AF4) and three central (C3, Cz, C4) electrode channels. (B) No-Think – Think significant t-scores at all electrodes and time points. (C) Topographies at four time points showing significant condition differences. Electrodes that show a significant difference at $p < 0.05$ are marked with an asterisk.

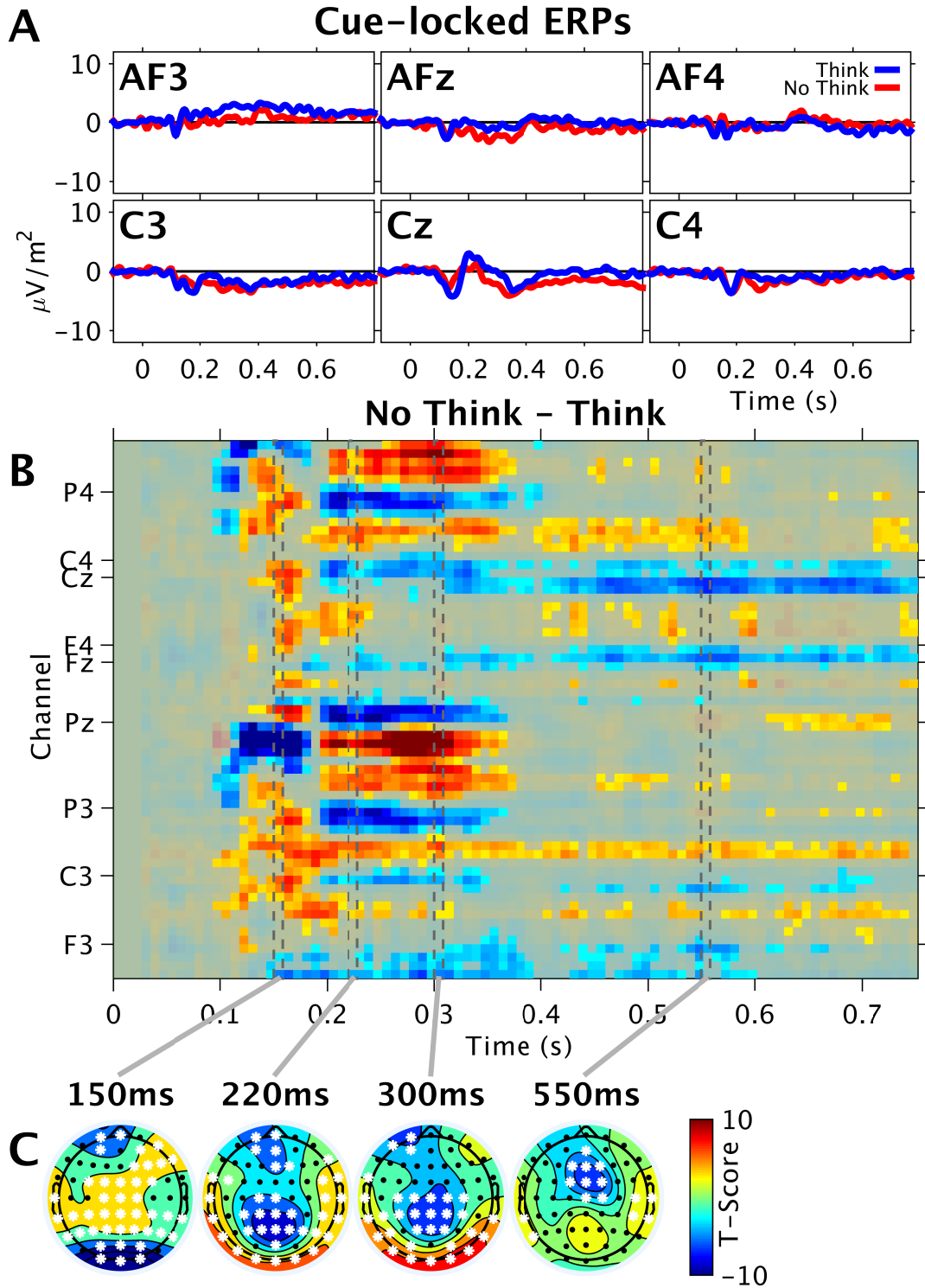
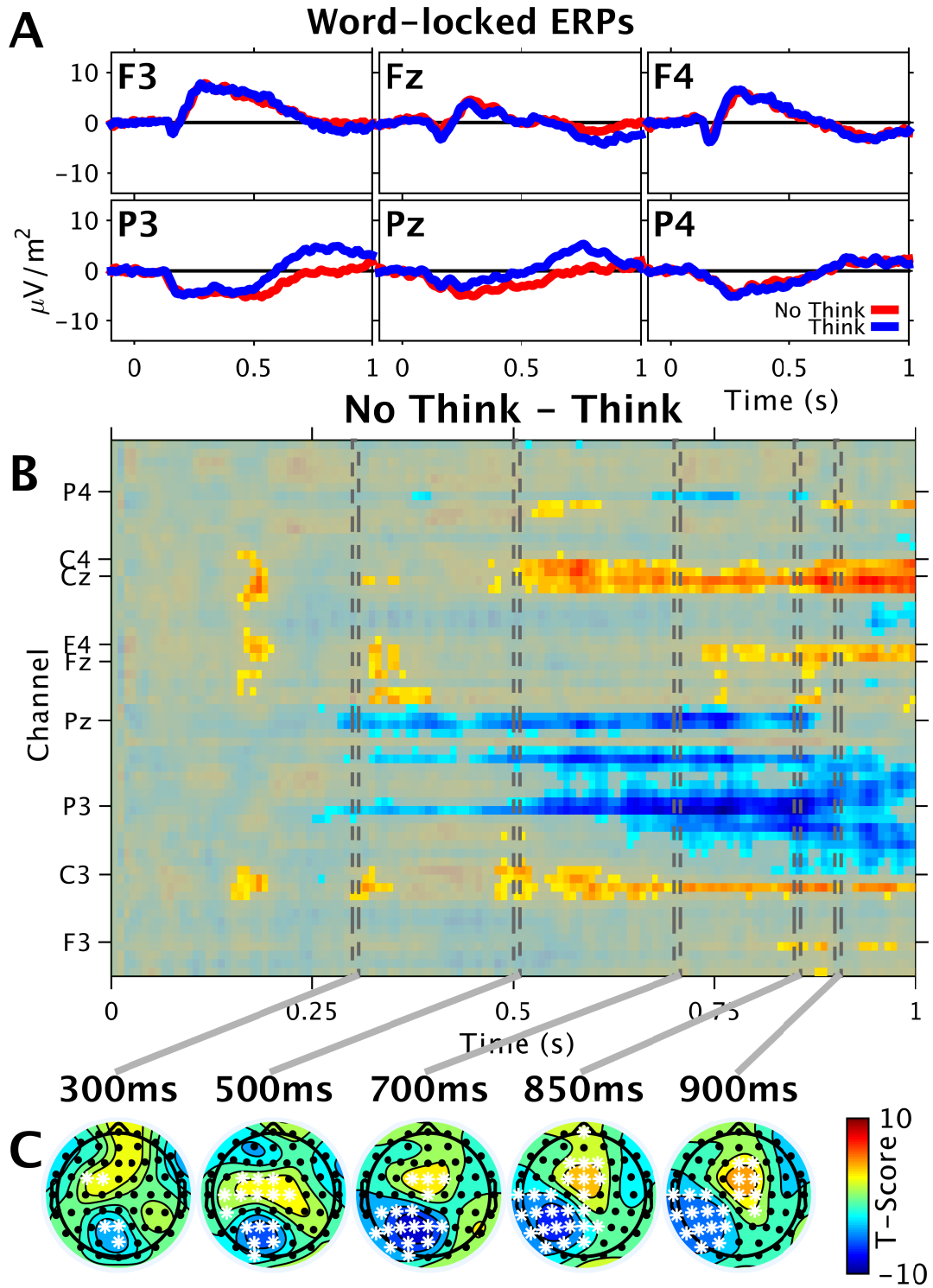
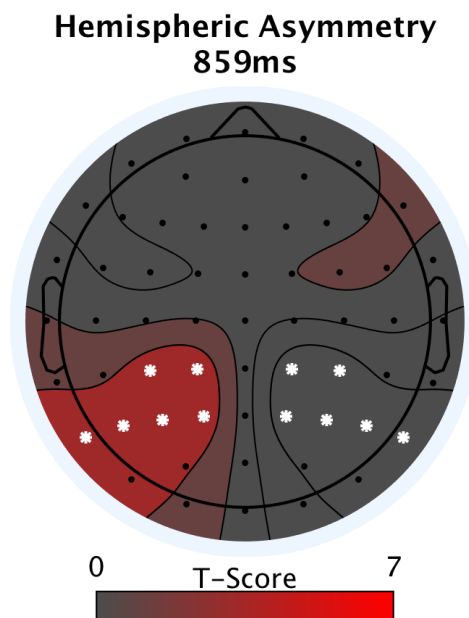


Figure 2-5. Word-locked grand average ERP data. (A: ERP waveforms from three frontal (F3,Fz,F4) and three parietal (P3,Pz,P4) electrode channels. (B) No-Think – Think significant t-scores at all electrodes and time points. (C) Topographies at five time points showing significant condition differences. Electrodes that show a significant difference at $p < 0.05$ are marked with an asterisk



We then inspected Word ERPs to determine if the retrieval response was lateralized as reported in the visual literature. We did a second permutation analysis to address this issue. The methodology was exactly the same as for the previous analysis, except the two conditions compared were 1) difference waves between Think and No Think words and 2) these same difference waves mirrored across the midline electrodes. Figure 3-6 shows a topographic plot of the posterior left-lateralized memory retrieval effect at the time point of maximal difference between conditions. We determined this time point by summing the absolute value of the t-scores across channels for every time point during the Word epoch and selecting the time point with the greatest value after smoothing using a 100ms moving average. Areas on the plot colored red have a bigger condition difference in that hemisphere compared to the other. All electrodes with a significant laterality difference are marked with a white asterisk. We found that posterior electrodes exhibited a significant hemispheric difference, such that conditions had a significantly larger difference on the left ($p < 0.05$), reflecting the memory retrieval effect seen in previous visual TNT studies and in our young adult auditory TNT studies.

Figure 2-6. Posterior laterality effect during Word trials at the point of maximal condition difference. Areas where the difference between conditions is larger on that hemisphere compared to the other are depicted in red. Electrodes with significant differences < 0.05 are indicated with an asterisk.



DISCUSSION

The results of our experiment show that older adults are capable of intentionally manipulating their auditory memory. Despite evidence for the decline of cognitive control, inhibitory processing, and memory with age (Coxon et al., 2012; Light, 1991), we found that older adults have the classic TNT forgetting effect when items are learned

and cued in the auditory domain. Critically, we found that memory is stronger for auditory words that underwent retrieval practice and weaker for words that underwent inhibition practice when compared to an unpracticed word baseline. These results are in line with that reported in the visual domain in young (Anderson & Levy, 2009, Bergstrom et al. 2007, Bergstrom et al. 2009, Depue et al. 2006, Joormann, Hertel, LeMoult, & Gotlib, 2009b; Depue et al., 2013; Paz-Alonso, 2010) and older adults (Anderson et al., 2011). Further, we found that memory inhibition as tested by an independent probe utilizing a semantic prime, was not elicited in older adults, mirroring the results found by Anderson and colleagues (2011).

While Anderson and colleagues concluded that their findings demonstrate that intentional forgetting becomes more difficult with age given the absence of suppression found in their independent probe test, we hesitate to conclude that our effect is due to the age of our research participants and not to the modality of our learning and test materials. Previous findings from young adults studied in our laboratory using auditory stimuli have also failed to produce any inhibitory modulation using the independent probe. Recent work done by Detre et al. (2013) demonstrated that intentional forgetting depends on an inverted U-shaped curve, such that moderate memories are more easily inhibited and subsequently forgotten. An alternative explanation for the null result in the independent probe test is that auditory memories, once learned, may lie on a different part of that curve, making them more difficult to inhibit.

The ERP effects we observed are also similar to those found in visual TNT studies and in our research in the auditory domain in younger subjects. In our experiment, we separated the instruction cue and cue word in order to examine each task segment separately. The increased amplitude for Think compared to No-Think in the P2 time frame has been reported using the TNT paradigm and EEG recordings (Bergstrom et al., 2007). Given our instruction cue was visual, we were not surprised to find a replication of this early ERP component. Additionally, we found an earlier N1 effect that had a larger response for Think trials at central electrode sites, possibly reflecting increased attention to the Think cue in preparation to retrieve the target word (Knight, 1981; Hillyard, 1973). We have observed a similar N1 effect in young adults in an auditory TNT experiment that used 20 word pairs instead of 14 as in this one. We interpret this to reflect a heightened amount of attention paid to the cue as a result of increased difficulty. The difficulty level in the young adult case was the increased number of word pairs to prepare for, while in the case of this experiment, we hypothesize that the task is simply more difficult for older adults. The N1 was larger for No-Think trials at both visual and anterior sites, which we have observed in both previous young adults experiments. Of most interest were the ERP effects elicited by the auditory word presentation. We found a condition effect that consisted of a Think positivity that was largest at parietal electrode sites and left lateralized, an effect that has been associated with successful memory retrieval (Allan & Rugg, 1997). In our case we observed a robust negative shift for the No-Think items that abolished the memory retrieval effect, supporting a suppression effect of No-Think word retrieval.

Behaviorally, we mirror the effects that Anderson et al. (2011) found for older adults in the visual domain. We have for the first time shown that auditory directed forgetting with the TNT paradigm can produce suppression effects in older adults. Additionally, our ERP findings demonstrate similar effects to those found in younger adults in the auditory domain in our studies and the visual domain by others (Anderson & Levy, 2009; Anderson et al, 2011; Bergstrom et al. 2007; Bergstrom et al. 2009; Depue et al., 2006; Joormann et al., 2009; Depue et al., 2013; Lambert et al., 2010; Paz-Alonso, 2010). Taken together the results provide evidence that memory inhibition is modality independent and utilizes similar means in young and older adults.

CHAPTER 4

Deficits in intentional memory inhibition after lateral prefrontal damage

ABSTRACT

Forgetting is commonly thought of as a simple failure of either memory encoding or retrieval. However, there is increasing evidence that forgetting can be an active process that benefits us in our everyday lives. Intentional memory inhibition has been implicated as a prefrontal-mediated process. To investigate to what extent intact lateral prefrontal cortex (PFC) is necessary for memory inhibition, we studied six unilateral prefrontal lesion patients in the Think/No-Think (TNT) paradigm. We found no behavioral evidence of active inhibition either from the same probe or the independent probe test. Response times suggested that memory was enhanced, indicated by a faster response, for the same probe test, but response times did not provide any evidence of active inhibition.

Event-related potentials also failed to show the intentional memory inhibition pattern in the word-locked EEG activity. We observed condition differences for the Word-locked stimuli. We observed a parietal memory retrieval component, commonly seen in visual and auditory TNT studies in young and older adults that were present for both Think and No-Think words in the PFC lesion patients, suggesting that No-Think words were retrieved instead of inhibited. Although we did find significant differences between the two conditions in the late word-locked time frame, behavioral results indicate that it likely represents an enhancement for Think trials rather than a suppression of No-Think trials. In addition, we did not find a left lateralization of the memory retrieval effect, but instead observed increased activity in the intact frontal cortex. These findings provide causal support for the role of lateral PFC in the successful inhibition of unwanted memories.

INTRODUCTION

The prefrontal cortex (PFC) has been implicated in numerous behaviors, specifically those that are guided by executive control. The lateral PFC has been highlighted as a critical cortical hub of top-down control (e.g., Gazzaley & D'Esposito, 2007) essential to normal everyday functioning. Many studies have investigated the PFC's involvement in top-down modulation of various cognitive abilities. For instance, PFC is able to exert control over attention (audition: Knight et al., 1981; Woods & Knight, 1986; Hillyard, Hink, Schwent & Picton, 1973; Bidet-Caulet et al., 2014; vision: Barceló, Suwazono, & Knight, 2000); Gehring & Knight, 2002; Yago, Duarte, Wong, Barceló, & Knight, 2004; Sinnett, Snyder, & Kingstone, 2009; Miller, Vytlačil, Fegen, Pradhan, & D'Esposito, 2011; Knight, 1997; olfaction: Zelano et al., 2005; and somatosensory: Seminowicz, Mikulis, & Davis, 2004), behavioral responses (Fletcher & Henson, 2001; Miller & Cohen, 2001; Jonides, Smith, Marshuetz, Koeppe, & Reuter-Lorenz, 1998; Konishi et al., 1999; Aron et al. 2003), and numerous memory processes such as encoding (see Blumenfeld & Ranganath, 2007 for a review) retrieval (Fletcher, Frith, & Rugg, 1997; Duarte, Ranganath, & Knight, 2005; Mangels, Gershberg, Shimamura, & Knight, 1996),

and working memory (Chao & Knight, 1997; Voytek & Knight, 2010; Müller, Machado, & Knight, 2002). See Szczepanski & Knight, (2014) for a recent review of PFC contributions to higher order functions.

Importantly, the prefrontal cortex has been shown to exert both excitatory and inhibitory control over stimulus processing (Knight, Staines, Swick & Chao 1999; Shimamura, 2000). Notably, excitation and inhibition can be manipulated independently (Gazzaley et al 2005, 2008; Kastner & Ungerleider, 2000; Bidet-Caulet et al, 2014). Many studies have investigated the PFC's importance in memory enhancement (Gershberg, 1995; Kapur et al., 1995; Rugg, Fletcher, Frith, Frackowiak, & Dolan, 1996). However, an emerging area of study has begun to focus on the role of the PFC in memory inhibition (Anderson et al, 2004; Anderson & Weaver, 2009). In this study, we focus on this latter process. That is, to what extent the PFC is necessary for the inhibition of memory retrieval.

In 2001, Anderson and Green developed a directed-forgetting paradigm that was designed to be able to examine direct inhibition of memory. This Think/No-Think task is a variation on the Go/No-Go paradigm, in which a pre-potent response is flexibly practiced or inhibited. In the Think/No-Think task, memories are the things that get a "Go" or "No-Go" manipulation. In their initial experiment, Anderson and Green trained participants on weakly associated word pairs. They then asked participants to selectively attempt to retrieve (Think) or inhibit (No-Think) the learned paired associate ("target word") when confronted with the first item of the pair ("cue word") on a trial-by-trial basis. Importantly, a third of the initially learned word pairs were excluded from this Think/No-Think phase of the experiment, in order to serve as a baseline measure of passive forgetting. Anderson and Green found that they were able to induce below-baseline suppression of No-Think words, demonstrating for the first time that intentional forgetting is an active process.

Follow-up studies by them and others have lent credence to the idea that this below-baseline forgetting is an active process (Anderson & Levy, 2009; Anderson et al., 2004; Bergstrom, de Fockert, & Richardson-Klavehn, 2010; Depue, Banich, & Curran, 2006; Depue, Curran, & Banich, 2007; Hanslmayr, Leipold, & Bauml, 2010; Hanslmayr, Leipold, Pastotter, & Bauml, 2010; Joorman, Hertel, Brozovich, & Gotleib, 2005; Lambert, Good, & Kirk, 2010; Paz-Alonso, Ghetti, Matlen, Anderson, & Bunge, 2009) although some have failed to find below-baseline forgetting in the No-Think condition (Bulevich et al., 2006; Mecklinger et al., 2009; Bergstrom et al., 2009). fMRI variants of the original task have found that No-Think inhibition was associated with control areas, including the lateral PFC (Anderson et al., 2004). These authors found that increased lateral PFC activity, as well as decreased hippocampal activity, were associated with to-be-suppressed trials. Since the hippocampus is an area known to be involved in memory retrieval, this provided strong evidence that the PFC works to down-regulate memory when suppression is attempted (Anderson et al., 2004; Depue et al., 2007).

Electrophysiological versions of the paradigm have further examined the neural responses elicited by attempted memory inhibition. The reported ERP effects have varied to some degree across experiments. The most robust and consistent finding

across studies is a reduction in the late left parietal positivity, an ERP component often associated with memory retrieval (Allan & Rugg, 1997), for No-Think compared to Think trials (Mecklinger et al., 2009; Bergstrom et al., 2007; Depue et al., 2013). This effect is manifested mainly as a prolonged ERP reduction for No-Think trials in left parietal areas, thought to index active memory inhibition of unwanted stimuli. The effect is also reduced in No-Think trials with increased inhibition practice (Hanslmayr et al., 2009).

Multiple studies have also found an enhanced cue-related P2 component, larger for Think compared to No-Think trials (Mecklinger, 2009; Bergstrom et al., 2007, 2009). Other ERP effects have been more variable and less consistent across experiments. For instance, Mecklinger and colleagues (2009), found a negativity around 400ms that was more pronounced for No-Think trials, which they liken to an N2 component thought to be involved in motor stopping. Bergstrom and colleagues noted an early negative deflection of the ERP at fronto-central sites at approximately 200ms, which was more negative for No-Think compared to Think trials. In these cases, however, instruction and cue words were not dissociable, since they were presented simultaneously. This makes it difficult to assign ERP responses to either strategic responses or to differential processing of the to-be-remembered or to-be-forgotten word. As employed in the present study, Hanslmayr et al. (2009) separated instruction and memory cues, but focused on sustained changes between the beginning and end of the Think/No-Think phase within each condition, rather than examining specific ERP components. Taken together, it is unclear what specific temporal electrophysiological effects are associated with memory suppression.

Based on the current fMRI and ERP evidence, intentional forgetting appears to be a frontally mediated process. However, few studies have examined directed forgetting in patients with restricted frontal damage. Because frontal patients have been shown to have deficits in inhibiting irrelevant stimuli (Andres & Van der Linden, 2002; Schmitter-Edgecombe et al., 2004; Bjork, 1970; Shimamura, 1995), it is logical that they may have similar difficulties in inhibiting unwanted memories. Surprisingly, intact directed forgetting has been found in patients with unilateral frontal lesions using variants of the list-method directed-forgetting paradigms (Andres et al., 2007; Andres & Van der Linden, 2002; Schmitter-Edgecombe et al., 2004). However, Anderson et al. has argued that the Think/No-Think task may require a greater amount of cognitive control than that needed for standard directed forgetting tasks, so may yield different results (Anderson et al., 2011).

Here, we combine behavior and EEG recordings in lateral PFC patients to examine the extent to which LPFC contributes to the ability to directly inhibit memories. The results should provide insight into how we can (or fail to) intentionally modulate our memory.

MATERIALS AND METHODS

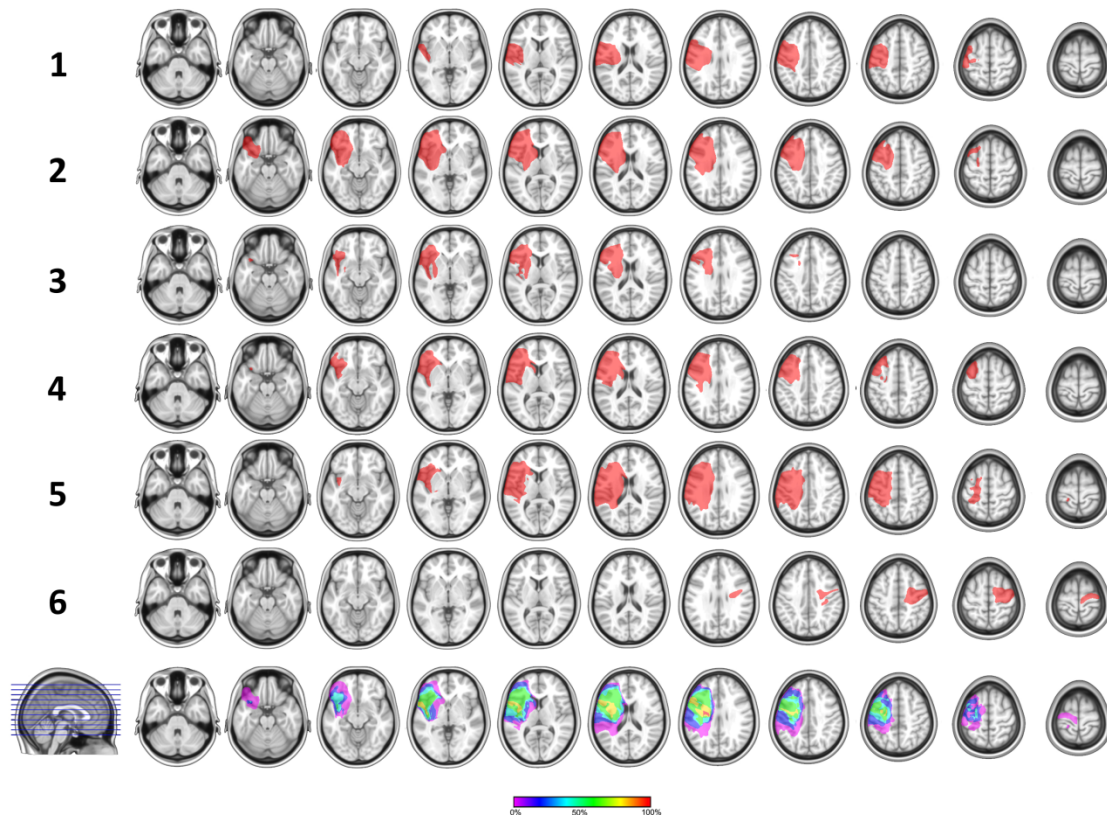
PARTICIPANTS

A total of 6 patients (5 F; mean age: 58.8, SD=7.9 years old) with focal one-sided lateral prefrontal cortex lesions (5 left, 1 right; see Figure 4-1) were recruited for participation in the study. The lesion location for each patient and the group lesion overlap for the 6 patients is presented in Figure 4-1. The single right lesion patient's lesion is mapped to the left hemisphere for demonstration purposes. Lesions were delineated using MRlcro software (Rorden & Brett, 2000) by a neurologist (RTK) using input from T1, T2, and Flair scans acquired at least 6 months post-stroke on a Siemens 3T scanner for all 6 patients. Lesion reconstruction on horizontal slices, determination of lesion volume, and putative cytoarchitectonic areas damaged were computed using MRlcro.

One patient with marked aphasia was unable to perform the subsequent memory tests at the speed used for the rest of the patients. We compensated for this by increasing the response duration allowance, such that if a response attempt was initiated within the normal time, the experiment was paused until the patient had completed the response, and then the next trial proceeded in the same manner.

All patients provided written informed consent approved by the University of California, Berkeley Committee for Protection of Human Subjects.

Figure 3-1. Lesion reconstructions for prefrontal patients. Each row shows the extent of damage in an individual patient. Averaged lesion area is shown in the bottom row, and color represents the number of subjects with a lesion at each specific site. Both left and right lesions are normalized to the left hemisphere for comparison. Maximal lesion overlap (>50%) was observed in Brodmann areas 6, 8, 9, and 46.



STIMULI AND DESIGN

We developed a modified version of Anderson and Green's (2001) visual Think/No-Think (TNT) paradigm, adapted to the auditory sensory modality and to be compatible with ERP analysis. In this version all word stimuli were presented in the auditory domain, and only the instruction cue items were presented visually (see Figure 4-2).

Stimuli consisted of 48 pairs of English words developed for this experiment, which paralleled the procedures used in previous TNT studies, and were presented auditorily. Of the 48 word pairs, 6 were used for practice, and the remaining 42 were split evenly into 3 groups for Think, No-Think, and Baseline conditions. Each of the Think and No-Think items were presented 18 times during the Think/No-Think phase of the experiment.

PROCEDURE

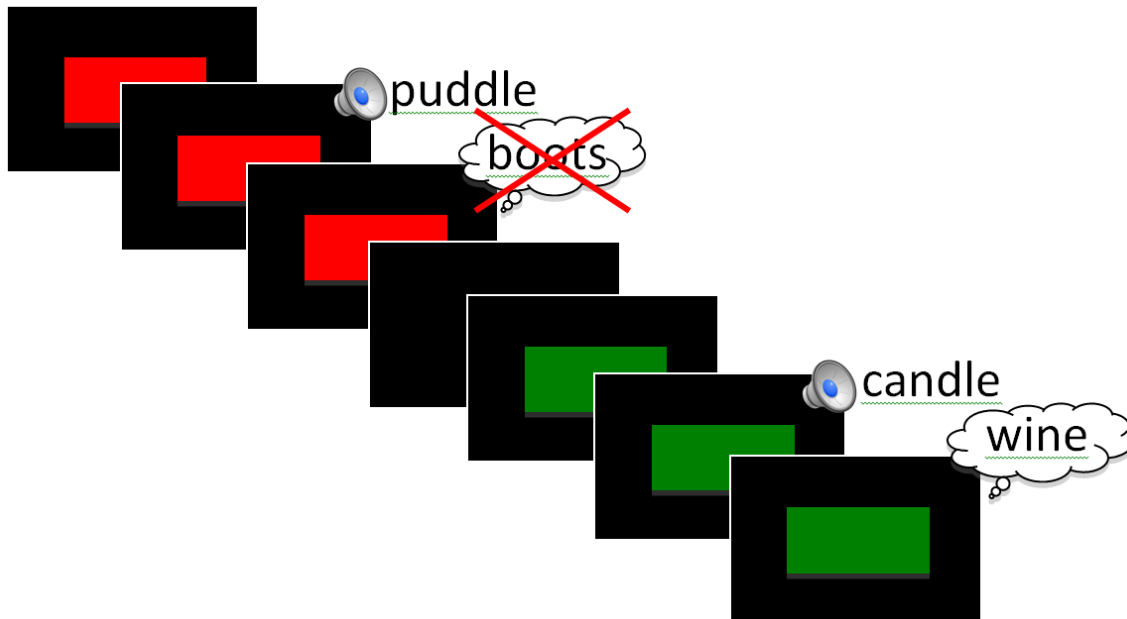
Learning: In the initial learning phase of the experiment, all 48 word pairs were presented with 1000 ms between the onset of the first and second word of each pair and a 6600 ms inter-trial interval. Participants were asked to try to learn the pairs such that if they are given the first word, or "cue word", they will be able to respond with the second, or "target word". They listened to each pair once before moving on to the recall phase of the experiment.

Recall: Recall memory was tested immediately following the initial study phase. Subjects were given the cue word of each pair and asked to respond with the target word, receiving feedback on each trial. They were asked to continue studying unlearned word pairs until they reached 100% accuracy, such that each target word was recalled correctly exactly once. Recall for this phase was self-paced.

TNT: Think and No-Think cue words were presented with their corresponding Think or No-Think instruction cue 18 times per word during this phase of the experiment. On each trial, subjects viewed a visual instruction cue that appeared centered on the screen preceding the auditory presentation of the cue word. We separated the cue and word presentation because anticipation of to-be-inhibited item has been shown to have differential effects on ERPs (Hanslmayr et al., 2009) and to also increase later forgetting of items (Hanslmayr et al., 2010). Participants were instructed to either silently recall (green box; Think words) or inhibit (red box; No-Think words) the target word of each pair after hearing the cue word. It was stressed to all participants that on No-Think trials, it was important to keep the target word out of mind and not to think about it even after the trial was over. This was instructed since intentional forgetting can be achieved with either thought substitution (by which a new word is mentally used to replace the target word in the original pairing), or by direct suppression of items (Hertel and Calcaterra, 2005, Bergstrom et al, 2009), which produce differing brain mechanisms (Benoit & Anderson, 2012). Given we were interested in direct suppression all participants were instructed to directly suppress, and not merely to substitute the to-be-suppressed word with an alternate item. In each trial, the instruction cue appeared for 900 ms with a 100 ms jitter before the first word of each Think or No-Think pair was presented (Figure 4-2).

The instruction cue remained on the screen for the entirety of the word presentation. Inter-trial interval was 3600 ms with a 500 ms uniformly distributed jitter.

Figure 3-2. Schematic of the TNT phase of the experiment for an example No-Think (red) and Think (green) trial. See text for stimulus timing.



Subsequent Memory: Subsequent memory was tested using both the independent and the same probe method developed from Anderson and Green's (2001) TNT visual paradigm. In the independent-probe test, subjects were given a semantic category followed by a letter and were instructed to respond with a word that fit into that category and began with that letter. Participants were given 5000 ms to respond before the automatic advancement to the next trial. Each semantic category corresponded to a target word from the earlier learned list, and was also primed with the letter the target word began with. In the same probe test, subjects were auditorily presented with the first word of each pair and asked to respond with the second word of the pair. They were given 5000 ms to respond before the automatic advancement to the next trial. An exception was made for a patient with marked aphasia. In her case, if a response attempt was initiated during the allotted time, the experiment was paused in order to let her complete her answer, after which, the next trial began.

EEG RECORDING AND ANALYSIS

Scalp EEG was recorded at 1024 Hz from a 64 channel active electrode system (Biosemi; 10-20 system positions). Additional electrodes were used for reference (earlobes), and to record ocular (EOG) activity.

Offline, the data were preprocessed and analyzed using MATLAB 2011b, custom scripts and the EEGLAB toolbox (Delorme & Makeig, 2004). Independent-component analysis (ICA) was used to remove vertical and horizontal EOG activity. Excessively noisy electrode channels were determined by visual inspection and replaced using spherical spline interpolation of the voltage from surrounding electrodes. The data were re-referenced using current source density (CSD). We used a CSD reference using the Matlab implementation of a spherical spline algorithm (Perrin et al, 1989, Kayser and Tenke, 2006) to obtain the second spatial derivative of the scalp voltage ($\mu\text{V}/\text{m}^2$ units; flexibility parameter $m = 4$; smoothing parameter $\lambda = 5 \times 10^{-5}$). Positive values of the CSD indicate local current flow out of the skull and negative values indicate current flow into the skull. The CSD transformation allows for a greater degree of independence from the location of reference electrode(s) (Luck, 2014; Kayser & Tenke, 2012) and provides a more focal spatial estimation of the underlying cortical activity (Gevins, 1989; Nunez & Pilgreen, 1991). The data were then bandpass filtered between 0.1 and 35 Hz and downsampled to 120 Hz.

All EEG analysis was performed on the TNT phase of the experiment. Epochs were created for both cue-locked and word-locked activity for Think and No-Think conditions. All trials containing activity greater than 100 μV were removed and the remaining trials were subjected to an iterative artifact rejection process that removed any trials containing data that exceeded 5 standard deviations from the mean of all data at each time point. This was done iteratively until no trials remained that fit that criterion.

Event-related potentials: Think and No-Think ERPs were created from the data after artifact-rejection. Both Word and Cue locked trials were baseline corrected from -100 to 0 ms prior to stimulus onset and then averaged within each subject.

ERP STATISTICAL ANALYSIS

A multi-step permutation method was used to determine differences in ERPs between the Think and No-Think conditions. The null hypothesis that we are testing against is that there is no difference in scalp evoked activity due to condition.

For each subject, we first computed 2000 null ERPs for each condition at each channel. These null ERPs were obtained from subsets of trials independently drawn from the larger set of the combined trials from both conditions. The number of trials drawn from the combined set for each condition was the same as the number of trials in that condition. Each of the 2000 subsets of trials in each condition was baseline corrected and averaged to obtain a null ERP.

Following this, a set of 50,000 null difference waves (No Think-Think) was computed for each subject at each channel. These difference waves were obtained by subtracting one randomly selected null Think ERP from another randomly selected null No Think ERP. True difference waves were also obtained for each subject using unshuffled trials.

The true and null data were then submitted to a two-tailed test based on the cluster mass statistic (Bullmore et al., 1999). All time points between 0 and 750 ms following Cue stimuli and 0 and 1500 ms following Word stimuli at all 64 scalp electrodes were included in the test (5760 and 11520 total comparisons for Cue and Word, respectively). First, 50,000 across subject averages were computed using the 50,000 null difference waves in each subject. T-scores were then computed for each null grand average difference wave by comparing it to the entire distribution of null grand average difference waves at every time point. This results in 50,000 sets of 5760 (64 channels x 90 time points) and 11520 (64 channels x 180 time points) t-scores for Cue and Word stimuli, respectively.

For each set, all t-scores corresponding to uncorrected p-values of 0.01 or less were formed into clusters with any neighboring such t-scores. Electrodes within approximately 5 cm of one another were considered spatial neighbors and adjacent time points were considered temporal neighbors. The sum of the t-scores in each cluster is the "mass" of that cluster and the most extreme cluster mass in each of the 50,000 sets of tests was recorded and used to estimate the distribution of the null hypothesis.

Clusters were then obtained from the true data and the percentile ranking of the mass of each cluster from the true data was used to derive its corrected p-value. The p-value of the cluster was assigned to each member (time-channel point) of the cluster and points that were not included in a cluster (due to small t-score) were given a p-value of 1. Differences between conditions with a corrected p-value less than 0.05 were considered significant.

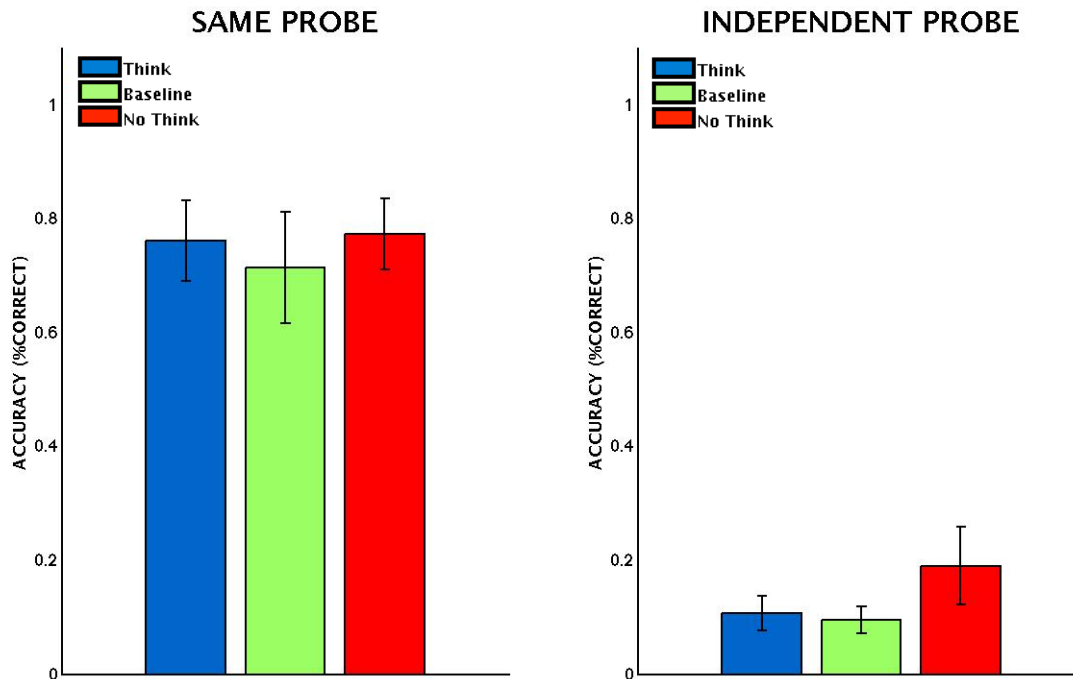
This permutation test was used instead of mean amplitude ANOVAs because it provides much better spatial and temporal resolution than conventional ANOVAs while at the same time maintaining weak control of the family-wise alpha level at 0.05. The cluster mass statistic was chosen for this permutation test because it has been shown to have relatively good power for ERP effects (Groppe et al., 2011). See Luck (2014) as well as Maris and Oostenveld (2007) for further review of this method.

RESULTS

Behavioral Results

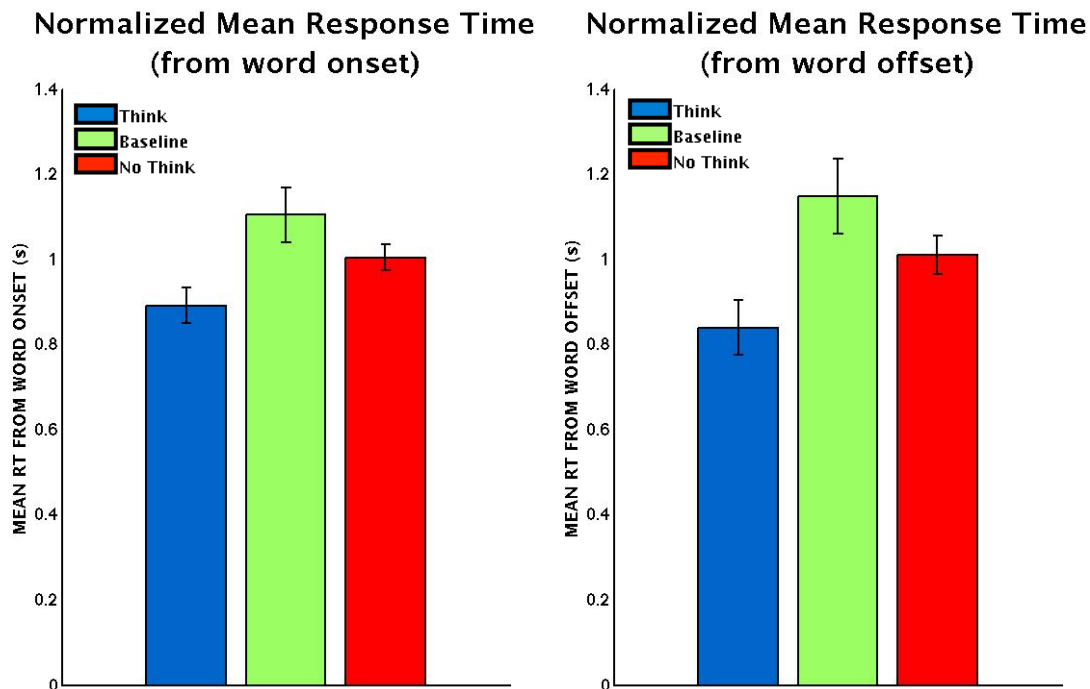
Accuracy: We conducted one-way repeated measures analyses of variance (rmANOVAs) on accuracy for both the same-probe and independent-probe subsequent memory tests (Think, Baseline, No-Think), see Figure 4-3. Accuracy was defined as the proportion of items responded to with the appropriate target word. There was no difference between conditions for either the Same-Probe or Independent-Probe test. It is conceivable that the sample size ($n=6$) precluded observing an effect. However, similar PFC lesion analysis in memory tasks using this cohort has produced robust behavioral effects (see Voytek & Knight, 2010; Fogelson, Shah, Scabini, & Knight, 2009).

Figure 3-3. Accuracy (% correct) for Think (blue), Baseline (green), and No-Think (red) items for same and independent probe tests, which found no significant difference between conditions.



Response time: We examined response times for correctly recalled items in the same probe test to determine if there was any evidence of inhibition for correct trials. The overall ANOVA was significant for mean onset ($F(1,5)=9.59, p<0.05$ and approached significance for mean offset ($F(1,5)=6.49, p=.051$), see Figure 4-4 We found evidence for enhancement of memory in the Think condition, but no indication of inhibition in the RT measure. For mean onset, there was a significant difference between Think and No-Think ($p=0.027$), and a marginal difference between Think and Baseline ($p=0.097$). There were no other significant differences for the No Think condition.

Figure 3-4. Mean normalized response time for correct Think (blue), Baseline (green), and No-Think (blue) items from word onset and offset in the same probe test. Mean Onset: $F(1,5)=9.59$, $p<0.05$; Think response time was faster than Baseline ($p<0.05$) and marginally faster than No-Think ($p<0.10$).



EEG Results

Cue: The permutation and cluster analysis revealed a few periods of significant condition differentiation (see Figure 4-5). First, we observed an N1 effect as in previous versions of this task, such that No-Think cues produced a more negative potential around 130 ms that was significant at anterior and posterior electrode channels ($p<0.05$). This suggests that frontal patients are initially processing the instruction cue differentially. Second, we observed a No-Think positivity at approximately 260 ms in occipital areas ($p<0.05$). Last, we found an ipsi-lesional occipital positivity that peaked at 380 ms ($p<0.05$). The cue findings indicate that patients exhibit differential instruction cue responses, but since they are located in visual areas, it is likely that this simply reflects some sort of bottom-up attention capture specific to the cue boxes.

Word: The permutation and cluster analysis demonstrated brief and minimal condition differences which emerged around 600 ms ($p<0.05$), see Figure 4-6. This condition difference, showing a significant increase in parietal positivity for Think compared to No-Think words, may reflect the memory retrieval effect (Alan & Rugg, 1997). Importantly, though there is a significant difference between conditions, the positivity is present for both Think and No-Think word ERPs, suggesting that No-Think words are also being retrieved.

Figure 3-5. Cue-locked grand average ERP data. (A) ERP waveforms from three anterior (AF3, AFz, AF4) and three central (C3, Cz, C4) electrode channels. (B) No-Think – Think significant t-scores at all electrodes and time points. (C) Topographies at four time points showing significant condition differences. Electrodes that show a significant difference at $p < 0.05$ are marked with an asterisk. Note that the right hemisphere lesion patient's data has been mirrored across the midline electrodes so that all lesions are presented on the left.

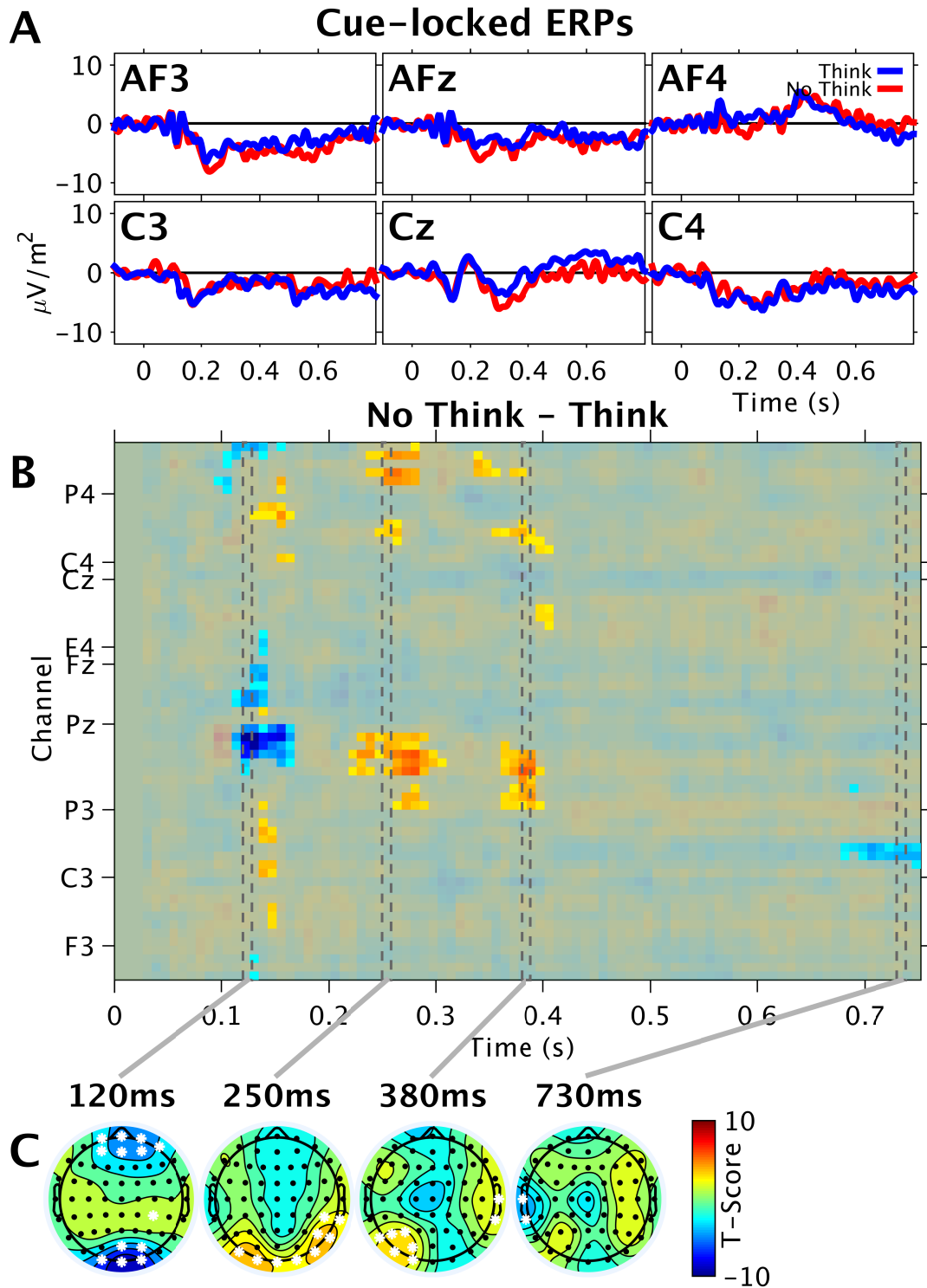
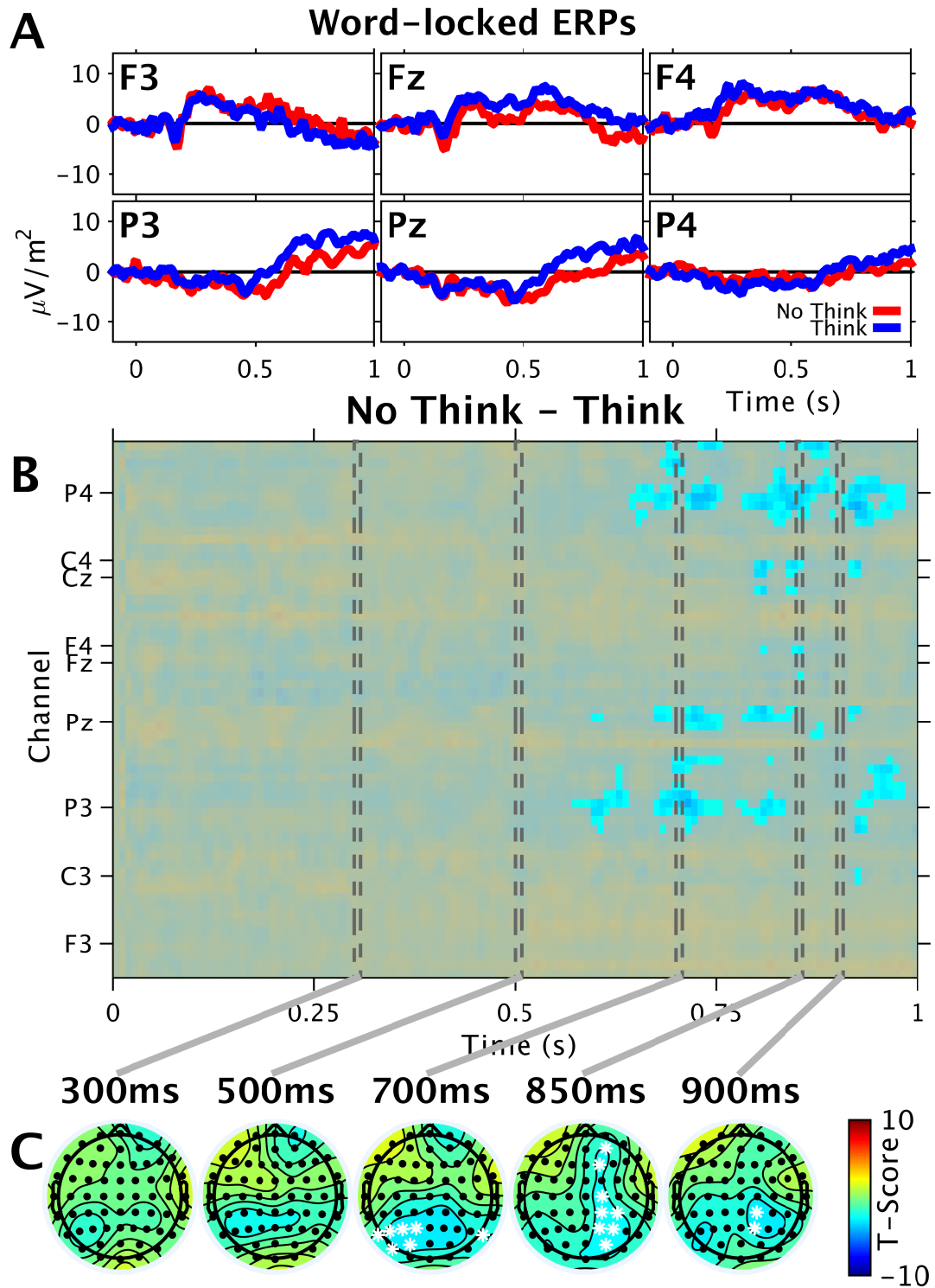
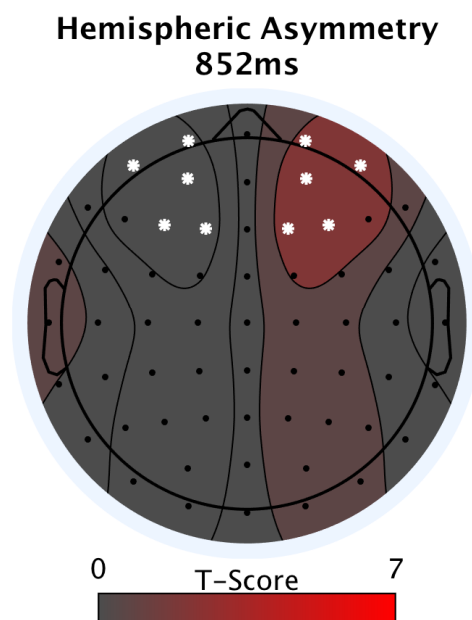


Figure 3-6. Word-locked grand average ERP data. (A) ERP waveforms from three frontal (F3,Fz,F4) and three parietal (P3,Pz,P4) electrode channels. (B) No-Think – Think significant t-scores at all electrodes and time points. (C) Topographies at five time points showing significant condition differences. Electrodes that show a significant difference at $p < 0.05$ are marked with an asterisk



We also tested for any parietal laterality effects during the word period because successful inhibition may rely on suppression of the parietal retrieval memory effect that is typically lateralized to the left hemisphere. We did a second permutation analysis to address this issue. The methodology was exactly the same as for the previous analysis, except the two conditions compared were 1) difference waves between Think and No Think words and 2) these same difference waves mirrored across the midline electrodes. No parietal lateralization was observed. However, we did observe a late onset frontal contra-lesional laterality maximal at 852 ms ($p < 0.05$; see Figure 4-7). We determined this time point by summing the absolute value of the t-scores across channels for every time point during the Word epoch and selecting the time point with the greatest value after smoothing using a 100 ms moving average. Areas on the plot colored red have a bigger condition difference in that hemisphere compared to the other. All electrodes with a significant laterality difference ($p < 0.05$) are marked with a white asterisk.

Figure 3-7. Word trials at 852 ms. Areas where the difference between conditions is larger on that hemisphere compared to the other are depicted in red. Electrodes with significant differences < 0.05 are indicated with an asterisk.



DISCUSSION

Behaviorally, we observed evidence for memory enhancement for Think items based on response time analysis, but found no suggestion of inhibition for No-Think items with any analysis method employed. Although overall memory was somewhat impaired relative to what is found in older adults using the auditory TNT paradigm, the ability to enhance memory remained partially intact, while memory inhibition was absent. This

behavioral pattern provides support for a key role of the lateral PFC in directed forgetting and is in accord with previous fMRI work implicating this region in intentional forgetting.

Although we found some similarities in the effects elicited by instruction cues, there was an overall lack of cue-related responses compared to what we have seen in young and older adults using the same paradigm. Early responses were localized in occipital and anterior electrode sites, which may reflect early selective attention to No-Think cues (Luck et al., 2000). We also observed later posterior positive components that were again greater for No-Think cues, but none of these effects were sustained as in previous studies explored in this thesis. Given the absence of any prolonged effects, it may be that an inability to maintain a preparatory state contributes to the memory inhibition deficit seen in these patients (see Padilla, Wood, Hale, & Knight, 2006; Otten, Quayle, Akram, Ditewig, & Rugg, 2006).

We observed late condition differences during the word-locked period, although the memory retrieval component appeared to be present for both Think and No-Think words. Although the overall ERP condition difference and widespread ERP effect may appear similar to that seen in older adults, the Word ERP response differed in several ways. First, the significant activity was sparser and emerged later than that seen in older adults (older adults 500 ms onset; PFC patients 600 ms). Second, though there was a difference between conditions, the memory retrieval component was present for both Think and No-Think trials, suggesting that No-Think items were still being retrieved. The fact that there was a difference may represent stronger remembering for Think items, as reflected in our response time analysis. Third, the lateralized effect we found was frontal, and localized to the contra-lesional hemisphere. Some evidence has shown that frontal patients are impaired at cued recall (Swick & Knight, 1996), and it is possible that this is a compensatory (Voytek et al., 2010) response that enables patients to successfully retrieve a Think target word. Although it is difficult to distinguish between Think enhancement and No-Think inhibition using the ERP data, the observed effect in these patients likely only reflects successful memory retrieval, but not that of memory suppression given the observed behavioral impairments in memory inhibition.

Although it is the right PFC that has been implicated in stopping a prepotent response and in maintaining inhibitory control (e.g. Aron et al., 2003), and in modifying a current motor plan in target reaching tasks (e.g. Mutha, Stapp, Sainburg, & Haaland, 2014; Schaefer, Mutha, Haaland, & Sainburg, 2012), our findings suggest that impairment in either hemisphere leads to an intentional memory suppression deficit. This is in accord with other lesion evidence that both the left and right PFC are engaged in inhibitory processing (Kramer et al., 2013). However, given we had only one right hemisphere lesion we cannot make any strong claims about hemispheric laterality. Future work directly comparing right and left hemisphere PFC lesions might elucidate any hemispheric differences regarding memory suppression. Nevertheless, the current study adds to the increasing evidence that the PFC is crucial to the ability to inhibit the recollection of unwanted memories.

CHAPTER 5

Conclusions

The act of forgetting is so pervasive in our daily lives, that it is surprising that it hasn't garnered more scientific attention. It is commonly thought of, both in lay terms and academic circles, as simply a failure to remember. In this view forgetting is a passive process simply viewed as a failure to properly encode and reinforce events. However, understanding the mechanisms by which we actively forget has begun to receive increasing attention in the memory literature, as it has become apparent there are beneficial aspects of forgetting. Although the way we passively forget remains an important topic, the way we can actively *control* our forgetting has significant clinical implications, and has been the focus of this thesis.

In three experiments comprising this dissertation, I examined the behavioral and electrophysiological effects of intentional memory inhibition in the auditory modality. Most studies investigating intentional forgetting, particularly those using the Think/No-Think paradigm, have utilized visual stimuli. I aimed to broaden the field by addressing the same question, but applying it to a different sensory domain. While much of our brain is organized to process incoming visual inputs, our memories, like our experiences, are multisensory. Therefore, it is important to understand how intentional forgetting of memories from all sensory modalities might take place. While the studies examined in this thesis do not directly compare and contrast visual and auditory behavioral and electrophysiological measures, the present findings add to the growing memory inhibition literature to help form a more complete picture of how we intentionally forget.

In Chapter 2, I investigated the behavioral and electrophysiological effects of repetition on auditory directed forgetting in young adults. I found that five repetitions per word were enough to produce facilitation of memory, but showed no indication of memory suppression. The ERP data was in accord with the behavioral findings, showing that auditory words were not suppressed during inhibition attempts, though frontal activity suggested that efforts toward inhibition were made. In a second study I increased the number of repetitions to eighteen. Though accuracy measures did not reflect successful inhibition, a detailed analysis of the behavior led to demonstrable signs of memory suppression, in response time measures. The lack of a suppression effect in the same probe measures may be a result of near-ceiling performance exhibited by the young adults that took part in the experiment. Since many Think/No-Think studies have produced accuracy effects at repetitions equal to or fewer than 18, my findings also suggest that auditory memory may be more difficult to inhibit.

The ERP responses were in accord with the behavioral findings, showing a diminished parietal memory-retrieval effect to the attempted suppression of the recollection of auditory words, an effect that was not found in the five-repetition experiment. As in the initial study, an increase in frontal activity was observed for to-be-inhibited items, implicating the prefrontal cortex in the intentional suppression of memory. In sum, the

behavioral and ERP evidence indicate that while auditory directed forgetting can be achieved using the current methods, greater practice may be needed in order to produce effects similar to what is seen in the visual domain.

In Chapter 3, I focused on the effect of aging on auditory directed forgetting using the 18 repetition paradigm developed in Chapter 2. This is particularly important given the well know problems with memory associated with aging. I found clear behavioral and ERP evidence that older adults are able to successfully inhibit unwanted auditory memories. Surprisingly, when cued with the same item that the to-be-inhibited word was initially learned with, older adults showed a stronger forgetting effect with accuracy-based measures than that found in the young adult 18-repetition experiment. Note that this may be due in part to near-ceiling performance in the younger adults. Response time measures also revealed effects of successful inhibition of to-be-forgotten items, further supporting the idea that inhibitory control of memory remains intact with age.

The ERP findings in older adults were similar to those found in the 18 repetition young adult study. Specifically, older adults exhibited a classic TNT reduction of the parietal memory retrieval effect for to-be-inhibited words, which was accompanied by a frontal activity increase, bolstering the claim that older adults retain the capacity to inhibit their memories. This is somewhat at odds with the cognitive aging literature, which has demonstrated a decline in some inhibitory functions with age. A paradigm that produced equivalent levels of recall between young and older adults would be required to determine if inhibition levels were equal between groups.

In chapter 4, I explored a potential causal role of the prefrontal cortex in active memory inhibition in the auditory domain. I observed that patients with focal frontal lesions have a reduced or absent ability to intentionally inhibit the recollection of memories. The only behavioral evidence of condition differences (i.e. Think vs No-Think) was obtained from our response time analysis, which revealed a facilitation effect for to-be-remembered items, but no evidence of memory suppression.

The ERP results were in agreement with the behavior. During repeated retrieval and inhibition practice, suppression of memory items would be expected to be reflected in a reduction of the parietal memory retrieval effect, as shown in Chapter 2 and 3. Frontal patients produced robust ERP retrieval responses for both to-be-remembered and to-be-forgotten items, coupled with the absence of a parietal laterality condition effect, signifying that they were unable to successfully prevent the retrieval of words that they were instructed to keep out of mind. This adds support to the increasing evidence that the prefrontal cortex is necessary for inhibitory control of memory.

Taken together, the studies in this thesis lend support to the following claims: 1) Based on behavioral and electrophysiological evidence, auditory memories can be intentionally suppressed in much the same way as visual memories, though they may be more difficult to inhibit. 2) While frontal-mediated inhibition has been shown to decrease with age in some tasks, auditory memory inhibition can still be elicited in older adults. 3) The prefrontal cortex plays a causal role in the ability to actively inhibit unwanted memories.

Although the studies in this dissertation provide answers to many open issues in active forgetting, there are still many open questions in this line of research. For instance: *Can multisensory memories be inhibited in the same way? How long will inhibition effects last? Does training inhibition over longer periods of time produce longer lasting effects?* Answers to these questions may clarify whether an active forgetting task can potentially be useful in a clinical setting. Since many people suffer from disorders in which failure of memory inhibition is central to the clinical syndrome (e.g., post-traumatic stress disorder, anxiety, depression), finding reliable long-lasting ways to inhibit unwanted memories would be of substantial benefit. Further research into how we are able to successfully control our forgetting under normal circumstances will shed light into how memory inhibition is disrupted in these disorders. Development of a better understanding of this inhibitory cognitive function, may lead to better methods to treat patients who have deficits in their ability to inhibit unwanted memories.

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