Memory, Interference, and Depression

By

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A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
(Industrial and Operations Engineering and Psychology)
in The University of Michigan
2010

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Dedication

To my sister, parents and grandparents. Your lives, your stories, and our conversations got me interested in studying the mind, and you kept my mind at ease when trying to study it.

Acknowledgements

First, I'd like to thank my committee members. Nadine thanks for your help throughout the dissertation process and for your professionalism. I very much enjoyed taking your Cognitive Ergononomics classes. Concepts I learned from those courses are not limited to nuclear power plants, but can be applied to many aspects of daily life.

Steve, taking Neural Models with you changed my whole research trajectory and my life. Our conversations vary from research to general life problems. Your advice is always so spot-on, and you know me so well. I hope one day that I can help someone out as much as you have helped me. You have brought out the best in me.

Yili, I would not be in grad school without you. You showed an interest in me at a time when I was struggling to find my way. You helped me to find my passions, and your support has been very important to me. I know you care a great deal about my well-being, and I am so very appreciative of that. I cannot thank you enough.

John, you've watched me grow and nurtured me from a naïve undergrad, to a less naïve Ph.D. We have so many stories, so many laughs, and we've had so much fun along the way. You've opened my eyes to a world of seemingly endless possibilities and helped me so very much to reach my goals. John, I couldn't have done it without you. I'm proud to be one of your students, John, and I hope to follow in your large footsteps, even though you like to take little steps with little feet.

Friends and colleagues: SteveO, Evan, Rique, Beez, Brucey, Teddy, Eric, Ant, Dom, Lee, Ellen, Travis, Alex, Michael, Martin, Susanne, Jamaal, Allyson, Emre, Rich, Rick, Joon, Katie A., Ethan, Patty, Court, LJ, Katie R., Laura, and Katie PM. Mentioning your names here does not do justice for how much you have helped me over the years. I can't express how grateful I am to have you in my life.

Finally, my parents, my sister and my grandparents. Mom and Dad, what can I say. I could only accomplish what I have because of your love and support. Mom, you never thought someone who hated school, even first grade, so much would stay there so long, but grad school has been one of the best experiences of my life.

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List of Abbreviations

ACC	Accuracy
ANOVA	Analysis of Variance
BA	Brodmann's Area
fMRI	functional magnetic resonance imaging
HC	Healthy Control
ISI	Inter-Stimulus Interval
ITI	Inter-trial Interval
LiFG	Left Inferior Frontal Gyrus
MDD	Major Depressive Disorder
ms	milliseconds
NRN	Non-recent Negative
PCC	Posterior-Cingulate Cortex
RN	Recent Negative
RT	Reaction Time
SCC	Subgenual-Cingulate Cortex
STM	Short-term Memory

Chapter 1

Introduction

"*In the practical use of our intellect, forgetting is as important as remembering*."
William James

Why is it that people tend to forget what they want to remember, and remember what they want to forget? It seems that in our daily lives, where we are constantly bombarded with information which we wish to remember, we tend to have difficulty holding on to some important material. Most people have had the experience of getting up to go the kitchen only to forget what one wanted upon entering the kitchen. Why is this so?

On the other hand, many of us have had the experience of wanting to let go of some thoughts and memories, which are painful and hurt us cognitively making it difficult to concentrate on daily tasks. It seems that many of these memories are negative in nature. Why is it so difficult to let go of and ignore these thoughts and memories, when we desire to forget them?

This dissertation centers on these two themes, which have significant implications both for theoretical psychology and daily life and systems design. In Chapter 2: "In search of Decay in Verbal Short-term Memory" a series of experiments are conducted aimed to uncover the major cause of forgetting in short-term memory. From a series of seven experiments, it was found that newly formed memories can overwrite past information, thus causing forgetting. However, memories appear not to decay via the mere passage of time. These studies showed the overwhelming contribution of interference (where new information can overwrite old information, but old information can also prevent the learning of new information) on forgetting in short-term memory. As the James quote suggests, this is not necessarily a bad thing. Forgetting information is critical to effective cognitive performance. Consider how debilitating life would be if we remembered minute daily details, it would be burdening. In fact, recent research has shown that less hippocampal neurogenesis is related to better short-term memory (i.e., limited neural capacity may actually help to filter out useless information and prevent the system from being overwhelmed; Saxe et al., 2007). Perhaps, then, interference plays the role of wiping out information so that we are not inundated with details. This only becomes problematic when it interferes with memories that we actually want to keep. Chapter 2 has been published in Berman, M.G., Jonides, J., & Lewis, R.L. (2009). "In Search of Decay in Verbal Short-term Memory." *The Journal of Experimental Psychology: Learning, Memory and Cognition* 35(2):317-333.

Chapters 3 and 4 of this dissertation focus on applying basic research on interference and short-term memory to major depressive disorder (MDD) and rumination, a process by which individuals perseverate on negative self-referential information.

Chapter 3 utilizes a directed-forgetting task that is similar in spirit to the recent-probes task that is used throughout Chapter 2. In fact, Nee, Jonides & Berman (2007) showed that the two tasks activate overlapping neural networks suggesting similarities between the two tasks. Chapter 3 explores whether people suffering from major depressive disorder have a selective deficit in removing negatively valenced information from short-term memory; Is negative information in short-term memory more interfering for people suffering from depression than healthy controls (HC)? Alternatively, people suffering from major depression may show a more general deficit in resolving interference, but Joormann et al., (2010) suggest that the deficit may be selective to negative valence. Chapter 3 also explores the neural mechanisms that may underlie these deficits in resolving interference from negatively valenced information and their relation to ruminative processes. Chapter 3 is currently a manuscript that was reviewed for publication and is now being revised for resubmission.

While the focus of Chapter 3 was on a short-term memory task involving valenced stimuli, Chapter 4's focus is on off-task behavior and neural activity for MDDs and HCs. One can conceptualize rumination as an internal form of interference. One can imagine it being difficult to work and concentrate if many attentional resources are devoted to thinking and perseverating about past negative episodes (e.g. a break-up with a romantic partner). What's interesting is that it appears that MDDs ruminate more strongly when they are not engaged in a task, and that being engaged in a task may disrupt neural networks that may mediate ruminative tendencies. The results from Chapter 4 suggest that the study of depression should not only center on on-task performance, but also on off-task performance, when MDDs may have the opportunity to

engage in ruminative processes, which may be disrupted both neurally and behaviorally by engaging in a task. It is of note that the word interference does not appear in Chapter 4, and yet rumination does act as internal interference for these participants who suffer from depression; it is the background noise that hurts their ability to concentrate. Chapter 4 was reviewed for publication and is currently under revision for resubmission.

Understanding the underlying mechanisms of depression has important implications, especially when considering that nearly 20% of Americans will experience a major depressive episode during their lifetime (Andrade et al., 2003; Kessler et al., 2003). According to the World Health Organization (2001), depression is the 2nd most damaging cause of Disability Adjusted Life Years, and greatly hurts economic productivity. Therefore, understanding more about this disease will potentially have important impacts on society.

Chapter 5 summarizes this work, and also suggests some future directions to take this research. In addition, Chapter 5 suggests some therapeutic interventions that may be useful to alleviate depressive symptoms including interacting with nature.

Chapter 2

In Search of Decay in Verbal Short-term Memory

Abstract

Is forgetting in the short-term due to decay with the mere passage of time, interference from other memoranda, or both? Past research on short-term memory (STM) has revealed some evidence for decay and a plethora of evidence showing that STM is worsened by interference. However, none of these studies has directly contrasted decay and interference in STM in a task that rules out the use of rehearsal processes. In this paper we present a series of studies using a novel paradigm to address this problem directly, by interrogating the operation of decay and interference in STM without rehearsal confounds. The results of these studies indicate that short-term memories are subject to very small decay effects with the mere passage of time, but that interference plays a much larger role in their degradation. We discuss the implications of these results for existing models of memory decay and interference.

Introduction

Why do we forget when the information to be remembered is modest in amount and the retention interval is short? That is, what causes forgetting of information in short-term memory? This is a question that has engaged psychology for over a century, and yet its answer remains elusive.

One theory that has a long history in accounting for forgetting is decay. The claim of this theory is that as time passes, information in memory erodes and is therefore less available for later retrieval. Decay has been a popular concept with respect to short-term memory, especially with the emergence and influence of Baddeley's short-term memory architecture (Baddeley and Hitch, 1974; Baddeley, 2000). However, the concept of decay is not without problems. For one, the concept doesn't make much sense without elaboration. After all, the mere passage of time alone cannot cause forgetting. For a decay theory to be of value, it must lay claim to some process or processes that occur more and more as time passes.

Finding the mechanism or process of decay is one problem, but finding empirical evidence for decay is an even greater problem. In principle, it seems relatively straightforward to conduct an experiment to examine whether decay is a cause of forgetting: Provide a participant with some material to memorize, allow a varying short period of time during which the material must be maintained in memory, and then probe the participant to determine how much information was retained. If decay is operating, then as the length of the retention interval increases, there should be worse retrieval of the retained information. Although this experiment is in principle straightforward, in practice it is difficult to execute convincingly in a way that rules out alternative accounts.

Consider the classic study of Peterson and Peterson (1959), originally thought to provide strong evidence for decay. In this experiment, participants were given a letter-trigram to store, followed by a retention interval that varied from 3 to 18 sec. During the retention interval, participants were required to count backwards by 3's to prevent rehearsal of the memorandum. Following the retention interval, participants recalled the item in memory. Peterson and Peterson (1959) found that performance declined as retention intervals increased, and the authors attributed this decline to increasing decay of the memory trace with increasing time. The attribution of this effect to a decay mechanism is, however, suspect.

First, Peterson and Peterson argued that counting backwards could not be a source of interference because their secondary task materials differed sufficiently from the item to be stored in memory (letters vs. numbers). Yet, it is surely the case that the counting task requires short-term retention of material just as does the main memory task (e.g., you have to remember the number 743 to do a subtraction of 3 from it to yield the next number in the series). So, retroactive interference (RI) is a likely contributor in this task. Also, others have shown that interference can be produced by other verbalizable items that are not similar to the to-be-remembered material (Wixted, 2005; Postle, D'Esposito and Corkin, 2005), blunting Peterson and Peterson's interference argument. Therefore, Peterson and Peterson's claim that the materials are sufficiently distinct to avoid interference may not be appropriate.

Second, Keppel and Underwood (1962) showed that on the very first trial of an experiment like that of Peterson and Peterson (1959), there is little or no forgetting as a function of retention interval even though there is such forgetting on later trials. Keppel and Underwood (1962) interpreted this contrast between first and later trials as evidence that Proactive Interference (PI) plays a major role in the experiment and worsens memory performance. These findings substantially question whether a decay mechanism needs to be trotted out to account for any forgetting in this sort of experiment (Nairne, 2002). In short, proactive and retroactive interference accounts may provide a better explanation of the forgetting phenomenon that Peterson and Peterson (1959) attributed to decay.

Another important problem in assessing the role of decay on short-term memories for verbal material is the habitual tendency of people to rehearse material that they are to retain. This is evident in the laboratory and in everyday life. When we look up a phone number in the directory and then walk over to the phone, we rehearse the now-memorized number until it is dialed. This happens so habitually that it is often not noticed and is difficult to disengage. The technique that investigators have used most often to prevent rehearsal (so that they could get an accurate gauge of whether decay was exerting an effect on memory) is to have subjects engage in a secondary task that prevents rehearsal.

The Petersons used counting backwards as their secondary task, but we have already seen that this task, in itself, requires short-term retention, and so it does more than just prevent rehearsal; it produces interference. Others have tried different methods, such as tone detection, as a secondary task to prevent rehearsal. The idea here is to find a task that is taxing of mental capacity and therefore prevents rehearsal, but does not tap

short-term retention; and it must use items sufficiently dissimilar from the memoranda to render interference immaterial. Although early evidence from such experiments suggested that under these conditions there was no forgetting of primary material, and hence no influence of decay (Reitman, 1971; Shiffrin, 1973), later research discovered that the early work may not have taxed processing capacity sufficiently (Reitman, 1974).

Indeed, a careful analysis of these studies by Roediger, Knight, and Kantowitz (1977) makes one wonder whether the use of a secondary task is appropriate to prevent rehearsal at all. They compared conditions in which a retention interval was filled by nothing, by a relatively easy task, or by a relatively difficult one. Both conditions with a filled interval led to worse memory performance, but the difficulty of the intervening task had no effect. Roediger et al. (1977) concluded that the primary memory task and the interpolated task, although demanding, used different processing pools of resources, and hence the interpolated tasks may not have been effective in preventing rehearsal. So, they argued, this sort of secondary-task technique may not prevent rehearsal and may not allow for a convincing test of a decay hypothesis.

Posner and Rossman (1965) explored the difficulty of interpolated tasks on memory performance and *did* find that the more difficult the interpolated task, the more forgetting ensued. However, in their experiments the interpolated tasks operated on the actual memoranda. More importantly, though, like Roediger et al. (1977), Posner and Rossman (1965) did find increases in memory errors even for simple interpolated tasks, suggesting that these tasks produce interference also. These data indicate that secondary tasks fail on two counts: by not eliminating rehearsal and by producing interference.

Other potential evidence for decay comes from studies of serial recall accuracy, which is better for words that have shorter articulatory durations compared to longer durations (known as the *word-length effect*; Baddeley et al., 1975; Schweickert and Boruff, 1986; Mueller et al., 2003). The word-length effect, however, is not without criticism. In a review by Lewandowsky and Oberauer (2008), the authors explain that the word-length effect is inherently correlational, dependent on specific stimulus materials and subject to other non-verbal rehearsal strategies such as refreshing (Raye et al., 2007). In addition, the number of times that items are rehearsed in these studies is not controlled, so items with shorter articulatory durations may be rehearsed more often than those of longer durations, which may lead to stronger memory representations independent of decay. All of these lines of evidence eliminate the word-length effect as viable evidence supporting decay.

More recently, research on serial recall has shown no evidence of time-based decay in verbal short-term memory. Lewandowsky, Duncan, and Brown (2004) have shown that altering recall speeds (by either speeding or slowing recall) had no impact on serial recall performance. This would not be predicted by decay models of short-term memory, which would hypothesize worse serial recall accuracy with slower recall speeds. The authors also eliminated rehearsal with articulatory suppression (e.g., having participants repeat a non-memory word aloud to eliminate the ability to rehearse memoranda) during the delays between stimulus presentations, which eliminates rehearsal confounds. In addition, the authors modeled their data and found that adding a time-weighting parameter did not improve the fits, as output interference alone could model the behavioral data (Lewandowsky, Duncan and Brown, 2004).

It appears, then, that standard behavioral paradigms have not provided compelling evidence for the role of decay in forgetting of intentionally stored verbal material. Are there other approaches to the study of decay that may be more convincing?

One move is to examine the role of decay in the forgetting of nonverbal material, under the rationale that if the nonverbal material is not itself easily subject to a verbal code, participants will not be able to engage in rehearsal as a technique to maintain memory. This is a slippery route to take. First, there are many sorts of nonverbal materials that are themselves subject to verbal coding. For example, research by Meudell (1977) used 4 x 4 matrices, four of whose cells were filled, with the filled cells being the memoranda in the experiment. These sorts of stimuli seem quite susceptible to verbal coding. This problem can be avoided, however, as indicated by Harris (1952) who used auditory pitches as memoranda that differed subtly in frequency, so subtly that an effective verbal code would have been difficult to create. Harris (1952) varied the retention interval between a target tone and a probe tone from 0.1 to 25 sec. and found an orderly decline in performance in decisions about whether the tones matched with increasing retention intervals. A study of this sort seems more convincing about the value of decay as a mechanism of forgetting, at least on the face of it.

Even this study, however, may be subject to the interpretation that during the otherwise quiet retention interval, participants were engaged in some sort of thinking that made use of short-term retention processes, and so exerted a retroactive interference effect on the experiment. Cowan, Saults, and Nugent (1997) also showed evidence of decay in a tone-matching task, i.e., worse performance with increased time between tones. However, these results are open to reinterpretation. In their experiment Cowan,

Saults and Nugent (1997) varied two intervals, the time between tones to be judged (Inter Stimulus Interval - ISI) and the time between tone pairs (Inter Pair Interval – IPI). The authors found that even when the ratio of IPI:ISI was controlled, increased forgetting ensued with increased ISI thus supporting decay (Cowan, Saults, and Nugent, 1997). However, when the authors re-analyzed these data and considered the IPI from the previous trial and the ISI from the previous trial, different conclusions were drawn. For example, on trials where the previous trial's IPI and ISI were long (24 sec and 12sec) and the current IPI was long (24 sec), no forgetting ensued across the current trial's ISI, which varied from 1.5 – 12 seconds, thereby not supporting decay (Cowan, Saults, and Nugent, 2001). These results can be interpreted in terms of tones from the current trial being more distinct from one another and from previous tones at these longer time scales (Cowan, Saults, and Nugent, 2001) thereby mitigating proactive interference from past tones.

Additionally, Brown, Neath and Chater (2007) simulated Cowan, Saults, and Nugent's (1997) original decay findings with their SIMPLE model, which is not dependent on time-based decay. The intuition behind this model is the following. When the ISI between the current pair of tones is longer, these tones are more susceptible to proactive interference from previous tones, even when the current IPI is increased to account for the longer current trial's ISI. As such, the model successfully simulated the results from Cowan, Saults and Nugent, (1997) leading the author's to conclude that the apparent effect of decay with increasing ISI may in fact be due to increased Proactive Interference from past tones with increased ISI (Brown, Neath and Chater, 2007).

Another move to study decay is to encase the study of this mechanism in a task that does not overtly require memory, such as an incidental or implicit memory task. This is an important point because even with the compelling evidence against decay by Lewandowsky et al. (2004), participants were still required to recall all presented stimuli and thus could have performed more covert forms of rehearsal, such as refreshing (Raye et al., 2007), that could mask potential decay effects. In addition, articulatory suppression may not prevent such refreshing processes (Raye et al., 2007; Hudjetz and Oberauer, 2007). Since the task required repeating back all presented items, such refreshing strategies would be advantageous and would lead to better serial recall. More recently, however, Oberauer and Lewandowsky (2008) and Lewandowsky, Geiger, and Oberauer (2008) *blocked* refreshing with a choice reaction time task and found no forgetting in serial recall at long delays vs. short delays; again showing that memory does not decay with the mere passage of time.

In all of these studies which we have cited exploring decay, the participants are aware that they must remember stimulus items on which they will be tested at some later time. While many researchers have been careful to prevent rehearsal and refreshing, which may have masked decay phenomena, it would be better if participants had no motivation to rehearse/refresh memoranda. This requires moving to a paradigm that tests memory more implicitly, thereby removing the motivation to rehearse memoranda. McKone (1995, 1998) tested decay in such a paradigm that explored decay in implicit short-term memory by varying the time between successive repetitions of an item in a lexical decision task. The issue was whether there was a savings in decision time, with more savings related to less time between item repetitions. What is most interesting

about this experiment is that there was no overt memory task involved, so there was no reason for subjects to rehearse each item after a trial had been completed. McKone (1998) found that when the amount of time between repeated items increased (the lag interval varied from 2 to 16 sec. in increments of 2 sec. [1]) lexical decision time increased, suggesting the decay of these short-term memory representations. McKone (1995, 1998) also varied the number of intervening items between repetitions which also increased lexical decision time of the repetitions, and interestingly, this interference effect was stronger than the decay effect.

In our view, McKone's (1998) study provides good evidence for decay: the paradigm provides no encouragement for rehearsal, and decay and interference were independently manipulated. Of course, one may argue that the technique used by McKone (1998) does not tap the role of decay in explicit short-term memory in that her measure of memory depended on the facilitation of a lexical decision. Therefore, these results may be tangentially related to the exploration of decay in short-term memory, because it could be argued that McKone's stimuli never entered the explicit focus of attention (i.e., they were never maintained or retrieved) and rather were processed without an intentional memory component. Nevertheless, this technique is an effective one for controlling for other issues, as we argue, and so it bears further exploration.

Taken together, the evidence supporting decay is equivocal. Studies of explicit memory provide some substance to the notion that decay is a source of forgetting, but these results are often difficult to interpret for two reasons. First, participants have a

[1] In her study all the lag intervals varied by 2 sec., except for the last lag that jumped from 10 to 16 sec.

habitual tendency to rehearse during unfilled intervals; and second, preventing rehearsal with a secondary task has the potential to interfere with memory performance in the primary task. We now describe a new paradigm intended to avoid both problems.

Exploring Decay and Interference in Explicit Short-Term Memory

To contrast decay and interference as causes of forgetting in STM, we used a Recent-probes task that is a variant of the item-recognition task introduced by Sternberg (Sternberg, 1966; Monsell, 1978). As we describe below, this task has the virtues of testing explicit short-term memory, avoiding any encouragement for rehearsal, and supporting precise and orthogonal manipulations of retention intervals and item-based interference.

In this task the participant is shown 4 target words to remember for a brief retention interval of several seconds. A probe word is then presented and the participant is instructed to respond affirmatively if the probe is one of the words in the stimulus set, or negatively if it is not. The manipulation of interest has to do with pairs of trials in which the probe does not match any member of the current target set, but does match a member of the set shown on the previous trial. On these trials, participants are delayed in responding 'No' to the probe compared to a novel probe that has not appeared recently. This delay in responding is due to the high familiarity of the recent probe, it having been presented on the previous trial. These two "No" response trial-types (recent and non-recent) are the trials of interest in this paradigm and are portrayed in Figures 2-1 and2-2.

The extra time taken to negate a recently presented "No" probe (RN trial) is typically 50-100ms more than a non-recent "No" probe (NRN trial). This effect is highly reliable in both response time (RT) and accuracy (ACC), but is typically more robust in RT due to high accuracy overall in this paradigm. The effect has been replicated many times, and there are neuroimaging data localizing the brain mechanisms that are engaged by the interference produced by the recent probes task (Nee, Jonides and Berman, 2007; Jonides et al., 1998; Nelson et al., 2003; Mecklinger et al., 2003; D'Esposito et al., 1999; Badre and Wagner, 2005; Jonides and Nee, 2006; Bunge et al., 2001). In summary, the Recent-probes task provides robust interference effects of previously seen items affecting recognition performance, both behaviorally and neurally.

The epoch of time in the Recent-probes task that interests us is the inter-trial interval (ITI). We seek to examine whether variations in the length of this interval or in the insertion of other tasks during this interval has an effect on the size of the Recent-probes effect. This task is ideal for investigating causes of forgetting because once any trial has ended in this task, participants have little reason to rehearse items on that trial or any previous trials. Therefore, this task avoids the problem of having rehearsal occur during an interval (the ITI) when a representation may be decaying.

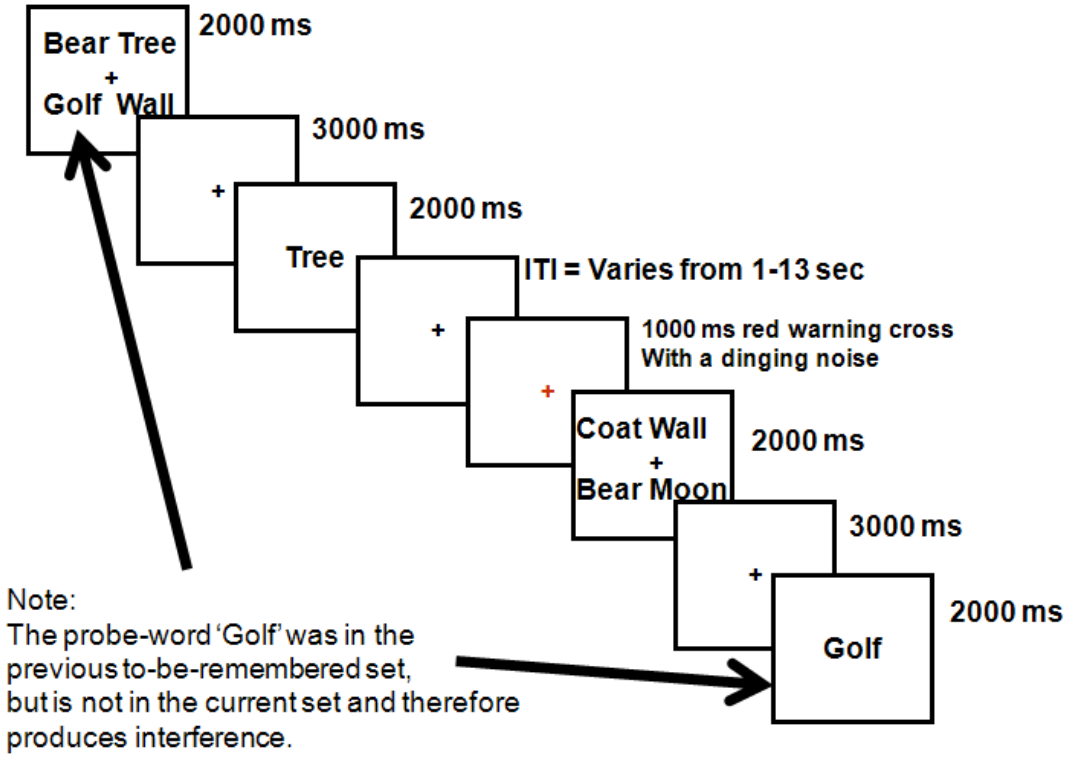

Figure 2-1: Interference Trial from the Recent Probes Task

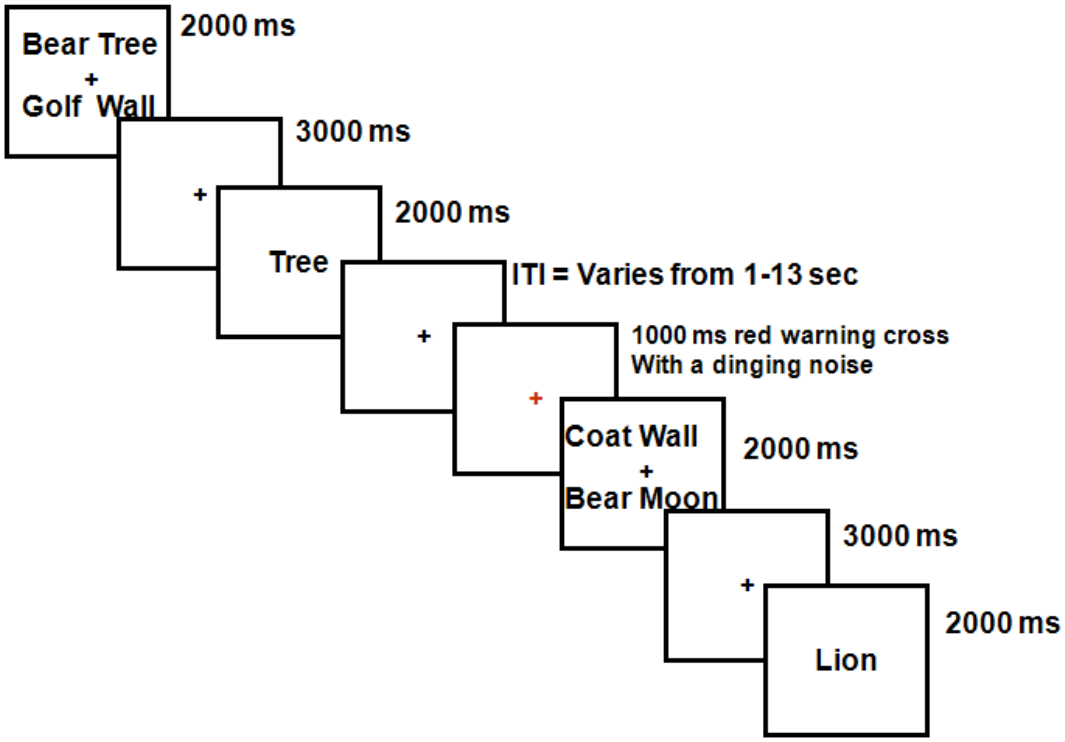

Figure 2-2: Non-Interference Trial from the Recent Probes Task

Exploring Decay in STM

The aim of these experiments was to document whether short-term memories show evidence of decay in the Recent-probes task. We varied the ITI that separated adjacent trials; if memories decay with the mere passage of time, then RN probes taken from trials that had longer preceding ITIs should not be as interfering compared to RN probes that were taken from previous trials that had shorter ITIs. Here we measure the effect of time from the end of the previous trials (i.e., from the previous trial's probe) when the previous trial's items were last refreshed. Therefore, with ITI's of 1, 5, 9, and

13 seconds, the total time from the previous trial could be 7, 11, 15, and 19 seconds. These timelines are outlined in Table 1 for all of our experiments.

The Delay Time Values (in Seconds) for Experiments 1–5 and 7

Experiment	Delay time lines				
	ITI	Warning cross	Stimulus set	Retention	Probe
1: Low proactive interference					
Duration	1, 5, 9, or 13	1	2	3	Terminates with response
Onset	0	1.0–13.0	2.0–14.0	4.0–16.0	7.0–19.0
2: Lowest proactive interference					
Duration	1, 5, 9, or 13	1	2	3	Terminates with response
Onset	0	1.0–13.0	2.0–14.0	4.0–16.0	7.0–19.0
3: Fast ITI					
Duration	0.5, 2, 3.5, or 5	0.5	2	1	2
Onset	0	0.5–5.0	1.0–5.5	3.0–7.5	4.0–8.5
4: Fastest ITI					
Duration	0.3, 0.8, 1.3, or 1.8	No warning	2	1	2
Onset	0	n/a	0.3–1.8	2.3–3.8	3.3–4.8
5: No articulatory suppression					
Duration	1, 5, 9, or 13	1	2	3	Terminates with response
Onset	0	1.0–13.0	2.0–14.0	4.0–16.0	7.0–19.0
5: Articulatory suppression					
Duration	1, 5, 9, or 13	1	2	3	Terminates with response
Onset	0	1.0–13.0	2.0–14.0	4.0–16.0	7.0–19.0
7: Blank ITI versus filled					
Duration	1 or 10[a]	1	2	3	Terminates with response
Onset	0	1.0–10.0	2.0–11.0	4.0–13.0	7.0–16.0

Note. The delay times are broken down by different durations of the different components of a recent-probes trial. ITI = intertrial interval; n/a = not applicable.
[a] On some trials there was an entire trial that separated trials that lasted for 10 s rather than a blank 10-s delay. This trial was equated in total time with the blank 10-s interval. On these trials the recent negative probe was taken from the two-back set.

Table 2-1: The delay time values for Experiments 1-5 and 7. The delay times are broken down by different durations of the different components of a recent probes trial.

Experiment 1:

Methods:

Twenty participants (18 females, mean age = 25.2) were recruited from the University of Michigan to participate in the study. All participants gave informed consent as reviewed by the University's Institutional Review Board. Participants were paid 10 dollars per hour for their participation plus bonuses for fast and accurate responding throughout the experiment. Bonus scores were calculated on a trial by trial basis and were calculated

with following equation: TrialScore = Probe ACC * (700 - Probe RT); where probe accuracy is a binary variable, '1' if correct and '0' if incorrect. Individual trial scores were summed together to yield a total score. Participants were paid a penny for each point of their total score.

Procedure: We used the Recent-probes task to assess decay by varying the ITI between adjacent trials. There were four ITI values: 1 sec., 5 sec., 9 sec. and 13 sec. On each trial the participant was shown four target words for 2 seconds. Following a 3-second blank delay (retention interval), the participant was shown one of four possible probe-words (which defined the trial-types variable that we analyzed): a non-recent positive (NRP) probe that was a member of the current stimulus set, but was not a member of the past stimulus set, a recent positive probe (RP) that was a member of the current set and the previous set, a non-recent negative (NRN) probe that was not a member of the current target set and was novel (i.e., never seen in the experiment), and a recent negative (RN) probe that was not a member of the current set, but was a member of the previous trial's set. For each target set, two words overlapped with the previous set so that recency of appearance could not be used to predict the type of trial that would be encountered (a positive or negative trial). There were 192 trials total, with 48 RN, 48 NRN, 48 RP, and 48 NRP trials. Of the 48 trials, 12 were from each of the different ITI values. Trials were presented in random order, with an equal number of each trial-type were presented in each block of the experiment. There were 4 blocks total.

Materials: We used 440 words in this experiment. Words ranged from 4-6 letters and 1-2 syllables with a mean frequency of 118.96 per million (*SD* = 109.042).

Design and Analysis: In these studies we were interested in only three dependent measures: NRN response-time, RN response-time, and the effect of contrasting RN and NRN response time. We report positive trial accuracy only to show that participants took the task seriously; positive trial performance was not important theoretically. In addition, overall accuracy for this task is near ceiling, therefore accuracy data are not explored in great detail. A repeated measures ANOVA 4(time intervals) x 1(trial-type) design was used in this experiment. There were three dependent variables: NRN response time, RN response time, and the RN – NRN contrast. Of most interest was whether the response time to RN trials and the RN - NRN contrast decreased with increasing time. In the analysis of response time, only the means of correct trials were used. Planned-comparison paired t-tests were later performed to test contrasts of interest as well as linear contrasts to test linear response time decreases as a function of increasing ITI.

Results and Discussion:

In this experiment we found no evidence for decay in short-term memory. Time did not reliably alter RN response time ($F(3, 57) = .626$, n.s.) the RN – NRN contrast ($F(3, 57) = 2.469$, $p = .07$) or NRN response time ($F(3, 57) = 2.744$, $p = .051$). However, the RN – NRN contrast showed a borderline reliable effect that seemed to be driven by

increases in NRN response time with increasing delay time. As can be seen from Figure 2-3, response time to RN trials does not decrease with increasing delay time and stays rather constant at 670 ms., a finding that does not support decay. In addition, not one of the linear contrasts was reliable, which tested a linear decline in response time with increasing ITI (though there was a borderline reliable increase in NRN response time). Moreover, there were no effects on accuracy, and accuracy for all trial-types, including positive trials, was above 94%. Lastly, with paired t-tests we found that the RN – NRN contrast was highly reliable at all time intervals. In sum, Experiment 1 yielded little to no evidence for decay. Had decay played a role, response time should have decreased with increasing time for RN trials and the RN – NRN contrast. The results from Experiment 1 can be seen in Figure 2-3 and in Tables 2-2 thru 2-4.

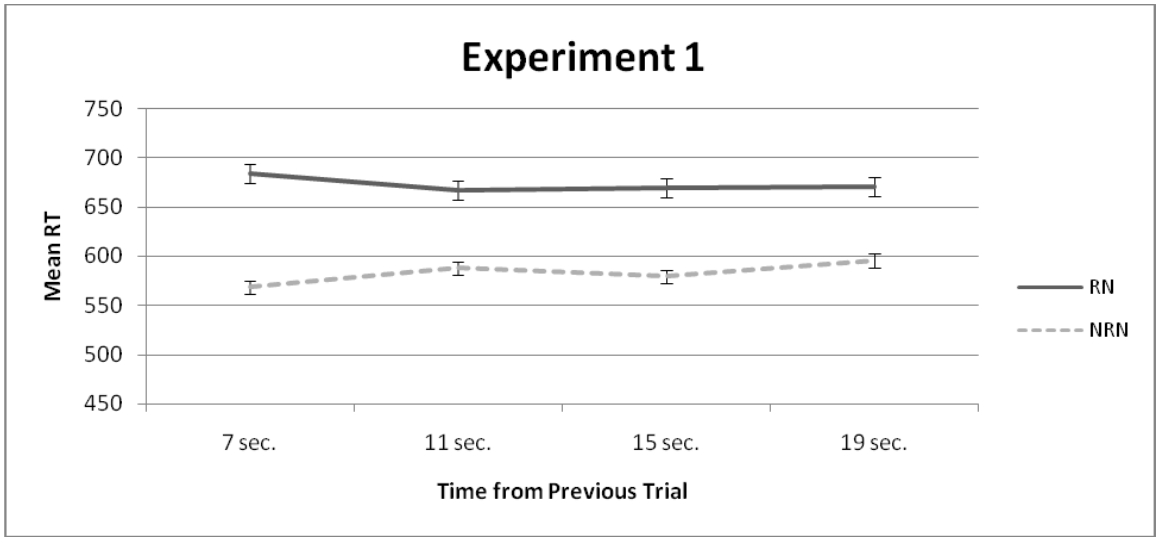

Figure 2-3: Results from Experiment 1 displaying RN and NRN RT by ITI[2].

[2] 95% Confidence Intervals of this plot were based on calculation from Loftus and Masson 1994.

There is one additional point to consider from Experiment 1. In this experiment, there were occasions when an RN probe could have been seen repeatedly on many previous sets because the RN probe was chosen randomly from the previous set. This repetition occurred on roughly 50% of the RN trials. This repetitive stimulus presentation could have raised the familiarity of RN items, which may have prevented them from decaying as quickly with time if the traces had stronger activation from the beginning. When we explored post-hoc (with a repeated measures ANOVA) those RN trials in which the probe was from the previous trial only we found that response time for RN trials ($F(3, 57) = .827$, n.s.), NRN trials ($F(3, 57) = 1.721$, n.s.) and the RN-NRN contrast ($F(3, 57) = 1.578$, n.s.) did not change with increasing time. Accuracy also did not change with time for these trials as accuracy for RN trials ($F(3, 57) = 1.290$, n.s.), NRN trials ($F(3, 57) = 1.260$, n.s.) and the RN-NRN contrast ($F(3, 57) = 1.815$, n.s.) did not change with increasing delay times. Therefore, when we analyzed the trials of Experiment 1 with the lowest familiarity levels, we still found no evidence for decay with the mere passage of time. Although this analysis yielded no evidence of decay for the purest trials in Experiment 1, we thought it wise to control this variable experimentally. This issue motivated Experiment 2.

Experiment	Total delay time			
1: Low proactive interference				
Trial type	7 s	11 s	15 s	19 s
NRN	568 (18)	588 (24)	579 (23)	596 (24)
RN	684 (26)	667 (32)	670 (27)	670 (27)
RN–NRN	116 (12)	79 (15)	91 (12)	74 (14)
2: Lowest proactive interference				
Trial type	7 s	11 s	15 s	19 s
NRN	586 (20)	615 (23)	609 (22)	610 (23)
RN	686 (27)	662 (24)	669 (26)	680 (21)
RN–NRN	100 (18)	48 (14)	60 (13)	70 (11)
3: Fast ITI				
Trial type	4 s	5.5 s	7.0 s	8.5 s
NRN	533 (18)	544 (16)	537 (19)	541 (17)
RN	615 (19)	637 (22)	600 (23)	612 (25)
RN–NRN	81 (8)	93 (14)	63 (14)	71 (17)
4: Fastest ITI				
Trial type	3.3 s	3.8 s	4.3 s	4.8 s
NRN	571 (38)	572 (41)	561 (41)	563 (34)
RN	632 (44)	640 (40)	632 (46)	658 (53)
RN–NRN	61 (17)	68 (14)	71 (11)	95 (23)
5: No articulatory suppression				
Trial type	7 s	11 s	15 s	19 s
NRN	613 (38)	625 (46)	651 (56)	647 (50)
RN	711 (47)	687 (41)	707 (62)	694 (56)
RN–NRN	97 (34)	62 (22)	56 (16)	47 (17)
5: Articulatory suppression				
Trial type	7 s	11 s	15 s	19 s
NRN	720 (75)	725 (73)	739 (78)	730 (79)
RN	832 (89)	833 (80)	815 (91)	803 (87)
RN–NRN	112 (38)	108 (18)	76 (34)	73 (29)

Note. Standard errors in parentheses. ITI = intertrial interval; NRN = nonrecent negative; RN = recent negative.

Table 2-2: Mean Correct response-time for Experiments 1-5. Standard Errors in parentheses

Experiment	Total delay time			
1: Low proactive interference				
Trial type	7 s	11 s	15 s	19 s
NRN	99.6% (0.4)	100.0% (0.0)	98.8% (0.7)	99.2% (0.6)
RN	96.8% (0.9)	94.7% (1.3)	95.1% (1.6)	95.5% (1.9)
RN–NRN	−2.8% (0.9)	−5.3% (1.3)	−3.7% (1.8)	−3.7% (2.1)
2: Lowest proactive interference				
Trial type	7 s	11 s	15 s	19 s
NRN	98.1% (0.7)	99.2% (0.5)	99.6% (0.4)	98.8% (0.9)
RN	98.3% (0.8)	96.1% (1.3)	97.5% (1.0)	97.0% (1.0)
RN–NRN	0.2% (1.2)	−3.1% (1.5)	−2.1% (1.0)	−1.8% (1.0)
3: Fast ITI				
Trial type	4 s	5.5 s	7.0 s	8.5 s
NRN	99.3% (0.7)	97.9% (2.1)	100.0% (0.0)	99.3% (0.7)
RN	98.7% (0.9)	98.7% (0.9)	97.3% (1.6)	97.3% (1.1)
RN–NRN	−0.7% (1.2)	0.8% (2.4)	−2.8% (1.6)	−2.0% (1.0)
4: Fastest ITI				
Trial type	3.3 s	3.8 s	4.3 s	4.8 s
NRN	97.9% (1.5)	99.3% (0.7)	99.3% (0.7)	99.3% (0.7)
RN	93.1% (3.0)	91.8% (2.9)	95.2% (1.9)	93.1% (2.5)
RN–NRN	−4.8% (2.2)	−7.6% (2.8)	−4.2% (1.6)	−6.3% (2.3)
5: No articulatory suppression				
Trial type	7 s	11 s	15 s	19 s
NRN	96.7% (2.6)	96.3% (3.9)	96.7% (2.6)	96.3% (3.9)
RN	91.8% (3.9)	93.0% (2.9)	92.0% (3.1)	94.4% (4.1)
RN–NRN	−4.9% (1.7)	−3.3% (2.8)	−4.7% (3.0)	−1.9% (2.0)
5: Articulatory suppression				
Trial type	7 s	11 s	15 s	19 s
NRN	99.1% (0.9)	98.1% (1.9)	98.2% (1.2)	100.0% (0.0)
RN	96.3% (2.0)	94.4% (2.4)	98.2% (1.2)	99.1% (0.9)
RN–NRN	−2.8% (2.4)	−3.7% (3.5)	0.0% (1.3)	−0.9% (0.9)

Note. Standard errors in parentheses. ITI = intertrial interval; NRN = nonrecent negative; RN = recent negative.

Table 2-3: Accuracy values for Experiments 1 – 5. Standard Errors in parentheses

Experiment 2: Lower Proactive Interference

In Experiment 2 we ensured that all RN probes were presented only in the immediately previous set[3] and were not members of many previous target-sets consecutively. In addition, we ensured that RN probes were not probed items on the previous set. We felt that this arrangement would reduce ambient proactive interference levels even lower than in Experiment 1. We still maintained the same hypothesis as in the previous study that response time to RN trials would not vary with increasing time between trials.

Methods:

Twenty-Two participants (17 females; mean age = 20.3) were recruited from the University of Michigan to participate in the study. One participant was excluded for having very low accuracy (below 50% on some trial-types). Other than that change, this experiment was the same in all respects as that of Experiment 1.

Results and Discussion:

Experiment 2 replicated the findings of Experiment 1; there were no changes in response time and accuracy with increasing delay time, again suggesting that short-term

[3] On each trial of the experiment 2 words overlapped from the previous set, which meant that each RN probe was actually taken from the past set and the one before it. Keeping this overlap prevented us from being able to take the probe word from the past set only.

memories in this paradigm do not decay with the passage of time. Delay time did not reliably alter RN response time ($F(3, 60) = .911$, n.s.), but the RN – NRN contrast did vary reliably with time ($F(3, 60) = 3.048$, $p < .05$). However, this change in the contrast was due to idiosyncratic changes in NRN response time with changes in time ($F(3, 60) = 5.471$, $p < 0.001$). When we explored this effect further, by separating participants according to working memory spans (as measured with operation-span[4] Turner and Engle, 1989; Unsworth et al., 2005), we found that only the low-span participants showed these reliable changes in NRN response time and RN response time[5], suggesting that they may not have been as vigilant and may have had more task-unrelated-thoughts throughout the study, especially during long ITIs (Kane et al., 2007).

In addition, not one of the linear contrasts was reliable, except for NRN response time. This is important because the reliable changes did not produce any systematic effects with increased time; rather the changes were more idiosyncratic and would not be predicted by decay theories (that pattern was non-monotonic). Moreover, there were no effects on accuracy; accuracy for all trial-types, including positive trials, was above 95%. Lastly, with paired t-tests we found that the RN – NRN contrast was highly reliable at all delay intervals. In sum, Experiment 2 yielded little evidence for decay. Had decay played a role, response time should have decreased monotonically with increasing delay time for RN response time and the RN – NRN contrast. The changes in the RN – NRN

[4] In the operation span task that was used was the automated operation span task (Unsworth et al., 2005). Here subjects need to remember words while simultaneously solving math problems. We defined high and low span participants by performing a median split on their operation span scores.

[5] Low span participants showed a reliable difference in RN response-time when comparing the 1 sec. ITI to the 5 sec. ITI ($t(10) = 2.29$, $p < .05$).

contrast were due to idiosyncratic changes in NRN response time with increasing time. These reliable NRN response time changes with increasing delay time concerned us and motivated Experiments 3 and 4. The results from Experiment 2 can be seen in Tables 2-4.

Experiments 3 and 4: Shorter ITIs

Experiments 1 and 2 showed that short-term memories do not decay reliably with the mere passage of time. However, concerns arose regarding participants' vigilance at longer delays for NRN trials, which produced borderline reliable changes in the RN – NRN effect for Experiment 1 and reliable changes for Experiment 2. In addition, viewing Table 1, these changes in the RN – NRN effect seemed to be driven by delay times between 7 and 11 seconds. These concerns led us to quicken the pace of the experiment and focus on time delay values that were near 7 and 11 sec. This achieves two goals. First, a quicker pace to the experiment and shorter ITI values should eliminate any vigilance problems that may have arisen in Experiments 1 and 2. Such vigilance problems may have been related to task unrelated thoughts that could have produced interference at longer time delays. Second, exploring decay at shorter delay times allowed us to examine whether decay processes happen quite early in the delay interval and may have been largely completed by the time we began measurements at the shortest time delay of 7 seconds in our earlier experiments.

Experiment 3

Methods:

Twelve participants (7 females; mean age = 20.8) were recruited from the University of Michigan. All subject procedures were the same as in Experiments 1 and 2.

Procedure: The procedure for this experiment was similar to that of Experiment 2 except for two changes. First, the retention interval between the stimulus display and the probe word was shortened from 3 seconds to 1 sec. This was done to reduce the total time that separated contiguous trials so that decay could be explored at shorter intervals. Second, the ITIs that were used were shortened to 500 ms, 2000 ms, 3500ms, and 5000ms. In addition, there was a 500 ms warning that alerted participants that the next trial was approaching. Therefore, our total delay times in this experiment were 4, 5.5, 7 and 8.5 seconds, which can be seen in Table 1. Lastly, the probe in this experiment remained on the screen for 2000 ms independent of the participant's response time. Other than these changes this experiment was the same in all respects to that of Experiments 1 and 2.

Results and Discussion:

Experiment 3 replicated the key findings of Experiments 1 and 2 (modulo the changes in NRN response time from those studies): There were no changes in response

time with increasing delay, again strongly suggesting that short-term memories in this paradigm do not decay with the mere passage of time. Delay time did not reliably alter RN response time ($F(3, 33) = 1.605$, n.s.) the RN – NRN contrast ($F(3, 33) = 1.150$, n.s.) or NRN response time ($F(3, 33) = 0.844$, n.s.). In addition, none of the linear contrasts was reliable, and no effects were found on accuracy as accuracy for all trial-types was above 93%. Lastly, with paired t-tests we found that the RN – NRN contrast was highly reliable at all ITI intervals. Therefore, Experiment 3 replicated the findings of Experiments 1 and 2, but did so in two important ways. First, by shortening the delay intervals, we removed potential vigilance effects. Second, we verified an absence of decay around the shorter time delays of Experiments 1 and 2 (i.e., 7 and 11 seconds) by sampling more delay time points around those delay time values.

Experiment 4

In Experiment 4 we shortened the delay times even further than in Experiment 3 to explore decay at even shorter intervals. It may have been that at longer delay intervals we missed opportunities to find decay, especially if decay in STM exists on a much shorter time scale. Experiment 4 was designed to explore this very issue.

Methods:

Twelve participants (8 females; mean age = 21.4) were recruited from the University of Michigan to participate in the study. All subject procedures were the same as in the previous experiments.

Procedure: The procedure for this experiment was similar to that of Experiment 3, the only difference being the shortening of the ITIs even further. In this study the ITIs that were used were 300 ms, 800 ms, 1300ms, and 1800ms, which translated into delay times of 3.3, 3.8, 4.3 and 4.8 seconds that can be seen in Table 1. For this study there was no warning fixation cross indicating that the next trial was approaching as it was unnecessary with such short ITIs. All other aspects of this Experiment were the same as the three previous experiments.

Results and Discussion:

Experiment 4 replicated the findings of the previous three experiments as there were no changes in response time with increasing ITI as shown in Tables 2, 3 and 5. Delay time did not reliably alter RN response time ($F(3, 33) = 1.124$, n.s.) the RN – NRN contrast ($F(3, 33) = 0.954$, n.s.) or NRN response time ($F(3, 33) = 0.316$, n.s.). In addition, none of the linear contrasts was reliable, and no effects were found on accuracy as accuracy for all trial-types was above 92%. Lastly, with paired t-tests we found that the RN – NRN contrast was highly reliable at all delay time intervals. Therefore, Experiment 4 replicated the findings of Experiments 1-3, and did so by eliminating

vigilance effects and by testing decay at much shorter time intervals, where decay may have had a better chance to exist.

	Univariate tests					
	Measure			Linear contrasts		
Experiment	NRN	RN	RN–NRN	NRN	RN	RN–NRN
1: Low PI						
F	2.74	0.63	2.47	4.20	0.65	3.76
Significance	0.05	0.60	0.07	0.05	0.43	0.07
η_p^2	0.13	0.03	0.12	0.18	0.03	0.17
Observed power	0.63	0.17	0.58	0.49	0.12	0.45
2: Lowest PI						
F	5.47	0.91	3.05	7.19	0.05	1.99
Significance	0.00	0.44	0.04	0.01	0.82	0.17
η_p^2	0.21	0.04	0.13	0.26	0.00	0.09
Observed power	0.92	0.24	0.69	0.72	0.06	0.27
3: Fast ITI						
F	0.84	1.60	1.15	0.28	0.78	1.51
Significance	0.48	0.21	0.34	0.61	0.40	0.25
η_p^2	0.07	0.13	0.09	0.02	0.07	0.12
Observed power	0.21	0.38	0.28	0.08	0.13	0.20

Note. Univariate tests test the reliability of intertrial interval (ITI) as a predictor of response time for the different dependent variables. Linear contrasts test the linear contrast or monotonic decrease of response time as a function of ITI. NRN = nonrecent negative; RN = recent negative ; PI = proactive interference.

Table 2-4: ANOVA results on response-time for Experiments 1 – 3. Univariate tests test the reliability of ITI as a predictor of response time for the different dependent variables. Linear contrasts tests the linear contrast or monotonic decrease of response-time

Experiment 5: Preventing potential covert rehearsal

Experiments 1-4 were built around the rationale that the Recent-probes task is a good platform to examine the influence of decay because the task doesn't just discourage

rehearsal during the critical delay interval; there is no reason at all for subjects to rehearse past trial items. Nonetheless, while there is no reason for participants to rehearse the items from the previous trial during the ITI, it could be that participants covertly rehearse these items anyway. If this were the case, of course, our paradigm would not be the ideal platform to test decay as a theory of forgetting that we have billed it to be. To address this issue, in Experiment 5 we had participants perform articulatory suppression during the ITI to prevent covert rehearsal. If participants were covertly rehearsing during the ITI, then those who engaged in articulatory suppression should be more susceptible to decay in STM than those who did not have articulatory suppression during the ITI.

Methods:

Twenty participants (12 females; mean age = 21.65) were recruited from the University of Michigan to participate in the study. Two participants were removed: one for having inadvertently been a participant previously and another for having extremely low accuracy scores (33% on some trial-types). All subject procedures were the same as in the previous experiments.

Procedure: The procedure for this experiment was similar to that of Experiment 1 as the same ITIs were used. However, half of the participants were randomly chosen to be in the articulatory suppression condition, where participants had to count aloud "1, 2, 3" repeatedly during the ITI. The other participants performed the task in its original form. Experimenters were within earshot to ensure that the participants were performing the articulatory suppression task aloud.

Design and Analysis: Our design and analysis were similar to Experiments 1-4 except that we added a between-subject variable for whether the participant engaged in articulatory suppression or not.

Results and Discussion:

Experiment 5 replicated the findings of the previous four experiments as there were no changes in response time and accuracy with increasing delay time. This was true both for participants who replicated the procedure of Experiment 1 and for those who engaged in articulatory suppression. In short, the addition of articulatory suppression had no effect in revealing evidence for the operation of decay.

In Tables 2, 3 and 5 one can see that delay time played no role in altering response time for any of the dependent variables for the both the articulatory suppression and non-articulatory suppression conditions. Of most interest was whether articulatory suppression interacted with delay time. We found that it did not, as RN response time did not change with increasing delay time depending on the articulatory suppression condition ($F(3,48) = 0.400$, n.s.), nor did the RN – NRN contrast ($F(3,48) = 0.161$, n.s.) or NRN response time ($F(3,48) = 0.295$, n.s.). As expected, articulatory suppression did slow participants overall, because articulatory suppression may hinder participants from being as prepared to encode upcoming stimulus sets and because having to engage in articulatory suppression essentially makes this a task-switching paradigm. Additionally, no effects were found in accuracy and accuracy for all trial-types was above 93%. Thus,

Experiment 5 replicated the findings of Experiments 1-4 even when any possible covert rehearsal of the previous trial's items was mitigated by articulatory suppression.

Experiment 6: Testing the Effects of Executive/Conscious Control

With Experiments 1 – 5 we have shown no evidence of short-term memory degradation with the mere passage of time. With Experiment 5 we showed that participants were not rehearsing previous items during the ITI, because articulatory suppression during the ITI had no influence. However, there have been recent proposals for *refreshing* processes that are not based on articulatory rehearsal, and these could potentially be used to re-activate past items (Raye, et al., 2007). Such refreshing may allow participants to strategically tag past items with a context code (i.e., this word is on stimulus set 'n-1' that was just seen), and therefore re-activating them could potentially help participants determine the correct negative response to recent negative foils (i.e., thereby counteracting familiarity of the recently seen items). Experiment 6 was aimed at manipulating such conscious strategies by instructing participants to ignore past lists once a trial had ended. If participants have some executive control over this effect, we would expect to see a change in the RN – NRN effect for participants who were instructed to ignore past sets versus those who were not. As stated above, such instructions could mitigate the RN – NRN effect if participants are able to tag past items as being foils. However, such instructions could also increase the RN – NRN effect if these instructions make past items more salient or familiar, and therefore more interfering. In addition, the instructions may change the effect variably from subject to subject, which would be uncovered by an increase in variance in the RN – NRN effect.

Methods:

Forty participants (24 females; mean age = 21) were recruited from the University of Michigan to participate in the study.

Procedure: The procedure for this experiment was similar to that of Experiment 1, but only the 5000 ms ITI was used. However, half of the participants were in the instruction condition, in which participants were warned to ignore previous sets. The other participants performed the task with its original instructions[6].

Materials: A subset of 30 words from Experiment 1 was used in this experiment.

Design and Analysis: A between-subjects ANOVA was conducted comparing RN, NRN and RN – NRN response times for subjects who were and were not instructed to ignore previous stimulus sets.

[6] The subjects that ran on the instruction version only had ITIs of 5000 ms. Those that ran on the no instruction condition had all 4 ITI conditions, but only the 5000 ms ITI was analyzed. Accuracies for all other trialtypes was above 95% and the mean correct RT values for the ITI values of 1, 5, 9 and 13 seconds for NRN trials were: 579, 586, 585, 576 and for RN trials were: 638, 643, 655, and 646. There were no reliable differences found between these different ITI values.

Results and Discussion:

We found that instructing participants to ignore past sets had no impact on RN response time ($F(1,38) = 0.158$, n.s.), NRN response time ($F(1,38) = 0.062$, n.s.) or the RN – NRN contrast ($F(1,38) = 0.032$, n.s.) as corroborated with a between-subjects ANOVA (see Figure 2-4). These data indicate that participants may not be able to consciously remove past sets from mind to mitigate the interference that past items produce on current trials. For example, one may hypothesize that participants could tag past sets as being from an episodic context different from the current set, which could dampen the interfering ability of past items. However, our data suggest that the Recent-probes effect is not subject to executive control, making it unlikely that some of the participants in earlier experiments were engaged in strategic refreshing. Additionally, instructing participants to ignore past sets did not increase the RN – NRN effect (by potentially making RN items more salient), nor did it increase the variance of the effect compared to the no-instruction condition.

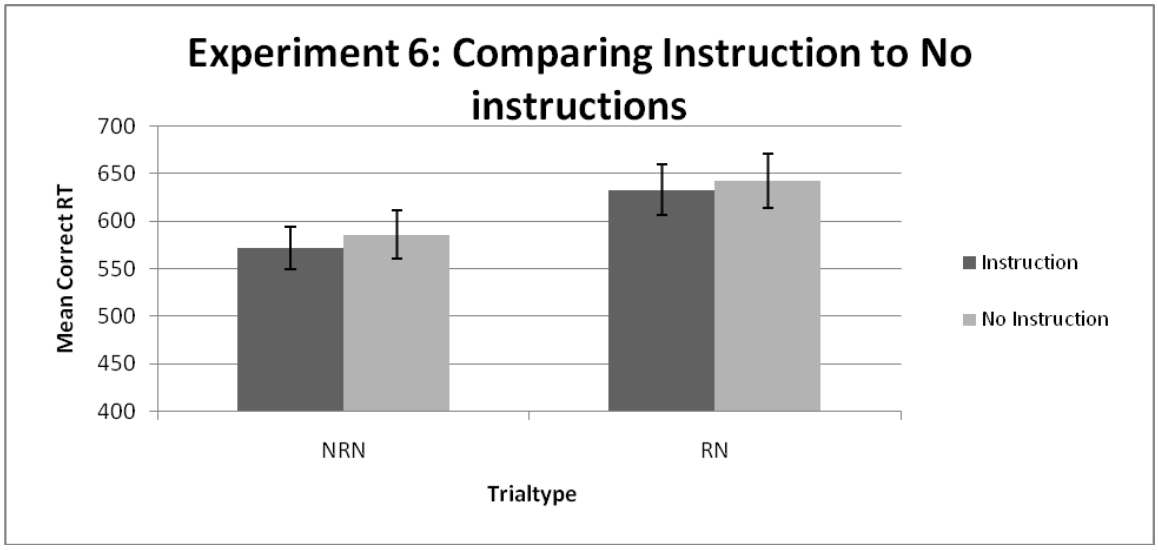

Figure 2-4: Mean correct response-time results for Experiment 6 where we either instructed participants to ignore past sets or did not provide any instructions.

Experiment 7: Direct Comparison of Decay and Interference

What we have in our first five experiments are null results, replicated over and over. It is these null results that have caused us to argue that decay plays little role in accounting for forgetting of the familiarity of information that underlies the Recent-probes effect. With that said, there were some unreliable trends that may have implicated some time-based decay. Of course, null results have to be taken with caution, but we have been cautious in various ways. We explored decay over various time intervals; we impeded rehearsal as a covert process; and we explored whether the effect could be

mitigated by instructing participants to ignore past sets. Even with this cautious attitude, we are left with a consistent finding: Variations in the delay interval in our task left the magnitude of the interference effect undiminished. This leads us to conclude that time-based decay has little effect on this short-term memory task.

With this in mind, we turned to interference as the key account of forgetting in this paradigm. To compare the effect of interference with the effect of the passage of time, we constructed an experiment that pitted interference against decay in short-term memory. Again, the Recent-probes task was used, with one major variation: There were 3 types of RN trials. One-third of the RN trials had probes that were taken from the 2-back set, and therefore had one intervening trial that separated the 2-back set from the current set. Another third of the RN trials were taken from the 1-back set, but had an ITI that was equated to the length of a single trial (10 sec). These two RN trials are shown in Figure 2-5. Finally, one-third of the RN trials had an ITI of 1 sec. (i.e., the canonical RN trial). With these RN trial-types we could directly compare interference versus decay by comparing response time and accuracy to the various RN trial-types. To test the effects of interference we could compare RN 2-back trials vs. RN 1-back trials with an ITI of 10 sec. To test the effects of time-based decay we could compare response time and accuracy of RN 1-back trials with an ITI of 10 sec vs. RN 1-back with an ITI of 1 sec. We predicted that 2-back RN trials would have faster response times compared to the other RN trials based on the idea that interference plays a stronger role in accounting for forgetting in this paradigm compared to decay[7].

[7] Of course, some of our previous experiments can be analyzed this way as well. Indeed, we analyzed Experiment 1 and another experiment that used the Recent-Probes task (Nee et al., 2007) where we looked

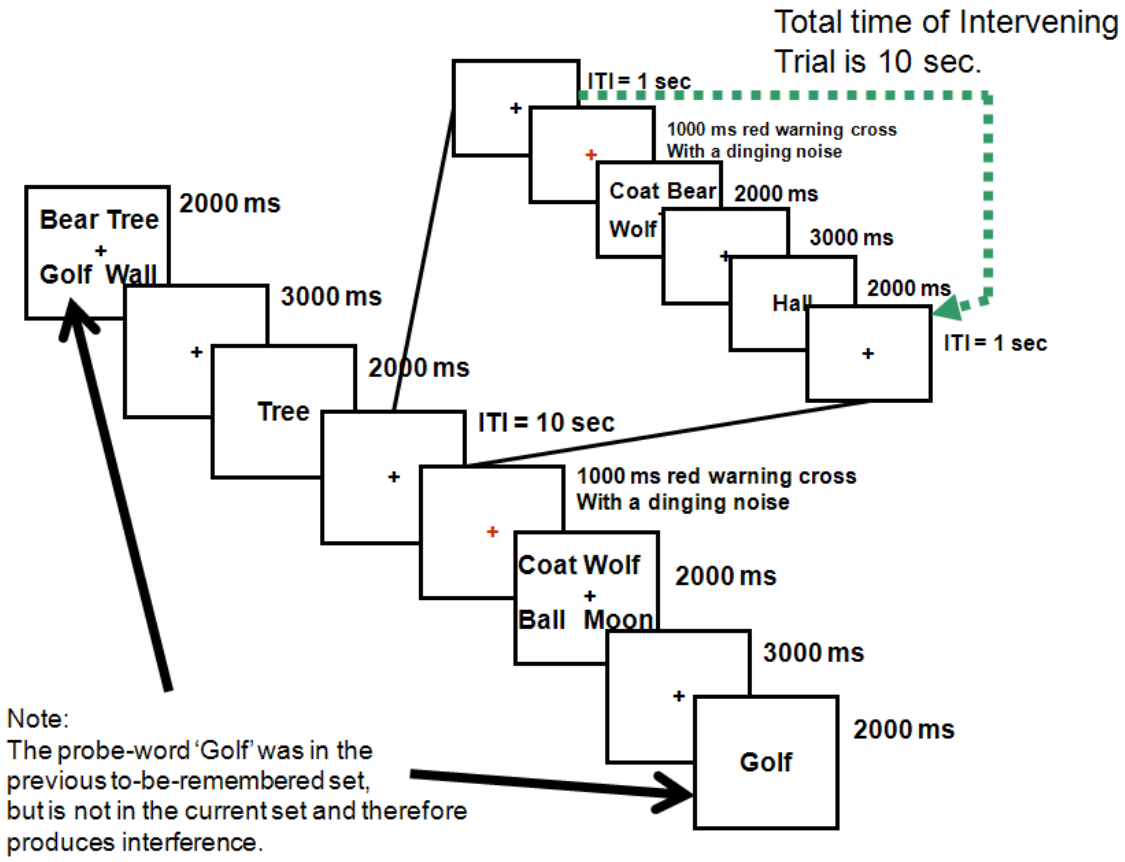

Figure 2-5: A schematic of two RN trials from Experiment 7. Notice that the ITI separating the two trials on the left can be a blank 10 sec. ITI or can be filled with another trial that lasts for 10 seconds. In that case, the word 'Golf' would be taken from the 2

Methods:

Twelve (7 females; mean age = 21.5) participants were recruited from the University of Michigan. All subject procedures were the same as in the previous experiments.

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at the impact of the number of intervening trials that separated the source trial that the negative probe-word was taken from. We found a decreasing linear relationship between response time and the number of intervening trials (i.e., the more intervening trials, the easier rejecting the recent-negative probe was).

Procedure: In this study there were 7 different trial-types: 2 types of positive trials[8] (one with an ITI of 1 sec and one with an ITI of 10 sec) and 2 types of non-recent negative trials (one with an ITI of 1 sec and one with an ITI of 10 sec) and 3 different types of recent-negative trials (one with an ITI of 1 sec, one with an ITI of 10 sec, and one where the probe-word was taken from the 2-back set with each of the two previous trials having an ITI of 1 sec). Therefore the total delay times from the past set were 7 seconds in the case of the 1 second ITI and 16 seconds in the case of the 10 second ITI. Half of the trials were negative and half of the trials were positive; there were 192 trials in total (48 of each positive trial-type, 24 of each RN trial-type, and 10 of each NRN trial-type). One additional change we made for this task was that stimulus sets had no overlapping words, so that each set was composed of a new set of words that had not been seen for at least three trials. This was done to eliminate recent positive trials to reduce the length of the experiment overall. The retention interval in this study was 3 seconds as it was for Experiments 1, 2, 5 and 6.

Design and Analysis: A repeated measures ANOVA with one predictor, interval type, was used in this design. The three intervals were a blank 1 sec interval, a filled interval with an intervening trial, and a blank 10 sec interval. In addition, there were 2 measures of interest, RN response time and the RN – NRN contrasts. In the response-time analysis only the means of correct trials were used. With this design we could explore how the

[8] For this study there were no recent positive trials because stimulus sets did not have any overlapping words

different intervals affected these 2 measures. Planned comparison t-tests were also performed on comparisons of interest.

Results and Discussion:

We found that interference played a large role in forgetting in short-term memory, and we found no evidence for decay, which replicated our previous findings. RN probes taken from 2-back stimulus sets were easier to reject than those taken from the 1-back set. In addition, longer delay times did not significantly alter performance, which confirmed that the mere passage of time does not cause forgetting in STM. The results from Experiment 7 are shown in Figure 2-6.

With our repeated measures ANOVA we found that interval-type was a significant predictor of RN response time ($F(2, 22) = 6.725$, $p < .01$) and the RN – NRN contrast ($F(2, 22) = 4.450$, $p < .05$). These reliable effects were driven by the 2-back condition, as RN probes taken from the 2-back stimulus set were easier to reject.

With planned paired t-tests, RN 2-back trials had significantly lower response times than 1-back RN probes at ITIs of 1 sec (mean diff = 61.21 ms, $t(11) = 5.15$, $p<.001$) and had significantly lower RT than 1-back RN probes at ITIs of 10 sec (mean diff = 70.51 ms, $t(11) = 2.97$, $p<.02$). However, there were no significant differences between 1-back RN probes at ITIs of 1 sec and 1-back RN probes at ITIs of 10 sec (mean diff = 9.3 ms, $t(11) = 0.37$, n.s.) showing that short-term memories do not decay with the passage of time. In addition, the RN – NRN difference was reliably smaller when RN probes were taken from the 2-back set compared to a blank 1 sec ITI and a blank 10 sec

ITI (2-back vs. blank 1 sec. interval, mean diff = 82 ms, $t(11) = 6.18$, $p < .001$; 2-back vs. blank 10 sec. interval, mean diff = 70.51 ms, $t(11) = 2.97$, $p<.02$[9]). However no differences were found between RN – NRN for long and short ITI's (mean diff = -11 ms, $t(11) = .46$, n.s.). These data provide strong evidence showing that forgetting in STM is due more to interference than to decay with time. There were no effects on accuracy as participants' accuracy for each trial-type was approximately 98%.

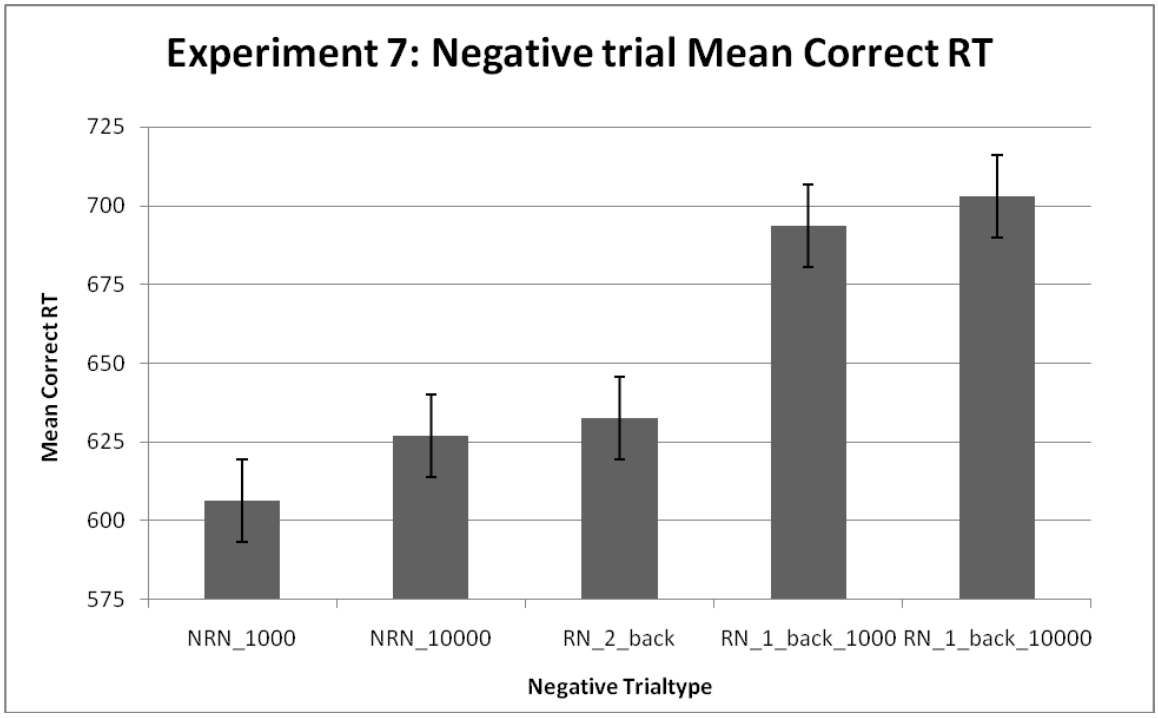

Figure 2-6: Results from Recent Probes task pitting decay against interference. Here we show the results from all of the negative trialtypes. The _1000 or _10000 suffix designates a blank ITI of that length in msec. The 2-back designation indicates that the probe word was taken from the 2-back set.

[9] Same values as comparing the RN conditions, because the same NRN baseline was used from the blank 10 sec. ITI.

Joint-Analysis

After completing these 7 experiments we thought it appropriate to aggregate the data from these studies together to explore decay further. We averaged the RN – NRN effects across the various time intervals from our experiment and calculated delay time as the time from the previous trial's probe word. Our time range was from 3.3 seconds to 19 seconds. We then regressed the RN – NRN effect against time, to see if time was a reliable predictor of the RN – NRN effect. In addition to this regression, we compared these aggregated data to those of Experiment 7 to compare the effect of decay to the effect of interference for RN trials and the RN – NRN contrast.

From this regression analysis we found a slight trend of decay with time, with the RN – NRN contrast decreasing by 1.225 ms per second of additional delay time. This regression was borderline reliable ($F(1,24) = 3.288$, $p = .082$). We then normalized the RN – NRN difference by dividing this effect by RN + NRN to remove some potential scaling effects from the different studies (i.e., Studies 3 and 4 had overall faster RT, and the articulatory suppression participants in Study 5 were slower overall). With this new regression we found that the time variable was more reliable in predicting the normalized effect ($F(1,24) = 9.127$, $p = .006$), where the beta for the regression was -0.001356 normalized effect units/sec. Doing a conversion utilizing the average RN + NRN effect of 1337ms, this slope converts to a decrease of 1.814 ms in the RN – NRN contrast with every additional second of delay time. Therefore we suspect that there is, in fact, a small but reliable decay effect when we aggregate our data across experiments. These results can be seen in Figure 2-7.

There are a few important points to make. First, what are we to make of the small decay effect that emerges after aggregating across experiments? Exploring our decay function in Figure 2-7, we see an initial increase in the RN – NRN effect with increasing time delay, followed by a drop in the effect with a long plateau. It seems that existing decay theories would have difficulty modeling these data with their existing smooth exponential functions. To make matters worse, what if there was steep decay from 0 seconds of delay to 3.3 seconds (intervals we could not test in our paradigm)? This would suggest a kind of step function, also inconsistent with current decay models. Second, in our experiments that explored decay at shorter time scales (Experiments 3 and 4), we found no evidence for decay with time, and in fact found a slight, but unreliable, increase. This suggests to us that at longer delays, participants might be engaged in some mental activity, such as mind-wandering, that would actually produce interference during these longer delays. Lastly, it is important to compare these effects of time with the known effects of interference. Figure 2-7 graphically shows the effect of time-based decay (the shallow sloped line) together with the effect of interference (the steep line). It is clear that the effect of interference swamps the small effect of decay. Based on the estimates from our simple regression analysis, it would take a delay of 78 seconds for time-based decay to reduce the RN – NRN effect to zero. For interference, this only required taking an RN probe from the 2-back trial. In sum, there appears to be a small, but reliable effect of time in our data. However, this effect may not be easily predicted by existing decay theories (a topic to which we return in more detail below), it is confounded with potentially increasing mental activity at longer delays, and most importantly, it was overshadowed by the effects of interference.

General Discussion

In this chapter we explored an important and prominent topic in short-term memory research: Does forgetting in short-term memory occur due to decay with time, interference from other material, or both? With 6 experiments we have shown that decay with time does not produce much if any forgetting in short-term memory (modulo the small effect found from the aggregate analysis), and that interference plays a much more prominent role. Recent research has also corroborated this finding (Lewandowsky, Duncan and Brown, 2004; Oberauer and Lewandowsky, 2008; Lewandowsky and Oberauer, 2008; Lewandowsky, Geiger, and Oberauer, 2008; Nairne, 2002). However, an advantage of our experimental task over past research is that we have taken a different approach to tackling the rehearsal problem, not by preventing it, but by rendering it counterproductive to participants' intentions. Therefore, we feel that our paradigm and results add important evidence to the growing consensus that time-based decay plays little role in causing forgetting in short-term memory.

There are still some remaining questions that need to be addressed. One concerns the sensitivity of the present experiments: Perhaps we did not find decay in the individual experiments because they lacked sufficient power. It is always possible, in principle, to construct a specific decay function with a quantitative form that is not detectable by any given experiment, so ruling out the entire class of decay theories is not possible (as evidenced by the small but reliable effect of time that was shown with our aggregated data). But we can also inquire about the ability of our data set to detect decay effects comparable to other empirical findings, and about its ability to provide

evidence against existing theoretical proposals for decay. We briefly consider these questions next, followed by a sketch of a candidate theory that we believe provides a promising account of the mechanisms underlying the phenomena surrounding the recent probes task.

Effect size and power relative to other empirical findings

One way to calculate an expected decay effect-size is to use the effect-size of McKone (1998). From 3-second to 7-second delays, McKone (1998) found roughly a 35 ms reduction in repetition priming, which can be used as an assay of decay. Our ability to detect such a reduction in the RN - NRN response time given our sample size and our observed variance is .52 and we found no such effect (our power here is smaller as we only had 12 subjects at the 3.3 second interval and needed to perform a between subjects analysis as the same subjects were not tested at the 3.3 second interval and the 7 second interval). In fact, from Figure 2-7, one can see an opposite trend from 3.3 to 7 seconds. In order to detect our small, but reliable effect of decay, we needed to aggregate 96 subjects worth of data. Additionally, such small decay effects are not clearly predicted by existing decay theories. In sum, we do not believe that our inability to find decay is due to a lack of power.

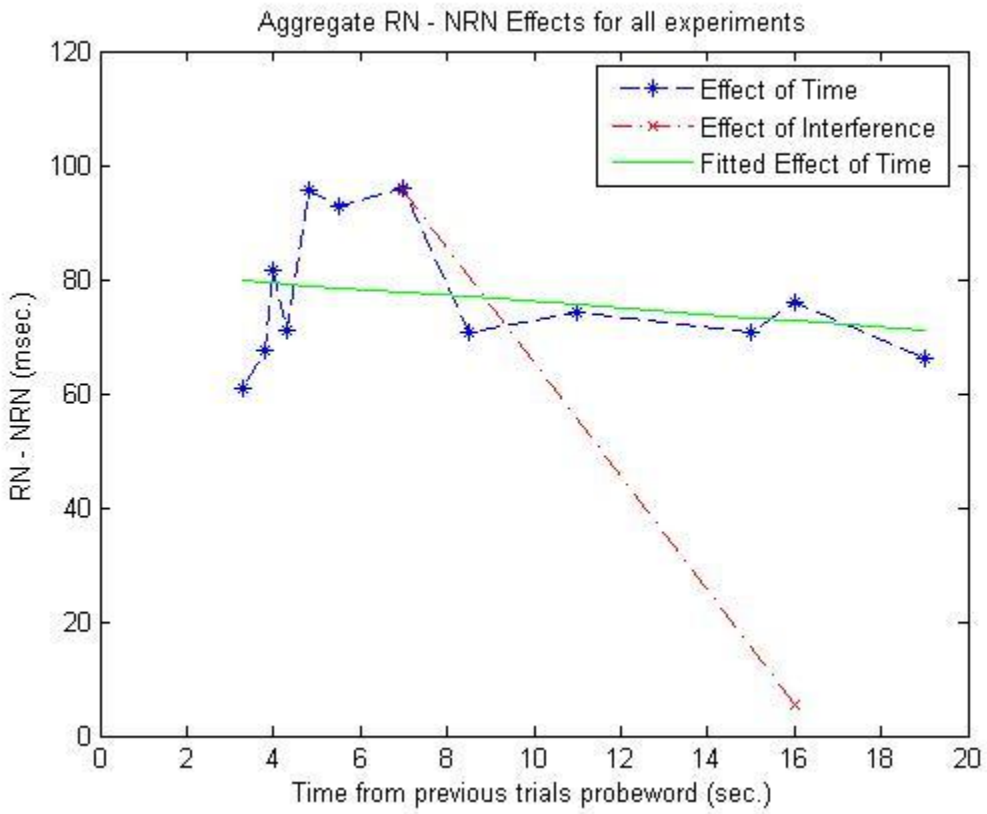

Figure 2-7: Aggregated data from all Experiments. The dashed blue line with asterisks represents the aggregated data based on delay time across all of our studies. The green line is the linear fit of the effect of delay time on the RN – NRN contrast. The red das dashed line with x's represents the effect of interference (i.e., taking the two back probe as the RN probe on the current trial). From the figure one can see the stronger effect of interference compared to time-based decay.

We must also consider whether we are exploring decay at the proper time scale. In our paradigm, the shortest time-scale with which we explored decay was that in Experiment 4. If we measure decay from the time when the probe from the last set was presented, when those items were reactivated by retrieval (and were last rehearsed), we explored decay between 3.3 and 5.1 seconds. At these intervals, McKone did find decay,

while we did not[10]. Therefore, we believe that we explored decay at sensible time intervals, ones that previous research had shown to be within the operating window of a decay mechanism. Lastly, if there is decay at very short intervals (less than 3.3 seconds), decay theories would need to be adjusted and may reflect more of a step function, of steep decay at short intervals followed by a paucity of decay at longer intervals. In summary, while our paradigm cannot examine decay at very short time-scales, our timing parameters are still sufficient to question what an overall decay function would look like (i.e., it may not be a smooth exponential).

Consistency with existing models of decay

A number of prominent existing models of memory include well-specified decay components that might be inconsistent with the data presented here. These include the Page and Norris (1998) *Primacy Model*, and its associated exponential decay equation. An examination of the form of this equation and the specific parameter values reported in Page and Norris (1998) suggests that it should predict a decline in response time with increasing delay times, assuming that the interference of a distractor is a function of its activation strength. But as we discuss now, the application of such theories may not be this straightforward.

Another prominent decay theory is the base-level activation equation of the ACT-R architecture (Anderson, 2007; Anderson et al., 2004), which posits that the activation levels of items in declarative memory follows a nonlinear, negatively accelerated form.

[10] McKone (1998) also explored decay at slightly shorter delay intervals of 2 seconds

This equation (with its associated fixed decay parameter of 0.5) is considered one of the most robust and successful components of ACT-R (Anderson, 2007). ACT-R's memory theory has a further advantage of being integrated with a more general theory of cognitive and motor control. We now consider briefly what is required to test that theory given our data set, not only because ACT-R is a prominent decay theory, but also because such consideration yields lessons for testing any decay theory.

It is tempting for present purposes to simply plug in appropriate time values into the decay and retrieval latency equations, and generate estimates of the effects of decay. But this approach skips a fundamental step in applying an architectural theory: specifying the task strategy. Effects of the basic architectural mechanisms are expressed through strategies that organize the mechanisms in service of task goals. These strategies can modulate—and sometimes even obscure—the effects of the underlying mechanisms, both quantitatively and qualitatively (the problem of strategic variation is a difficult one; e.g., see Newell, 1990 and Meyer & Kieras, 1997). In fact, in our initial attempts to develop detailed ACT-R models of the probe task using an existing published strategy (Anderson & Lebiere, 1998), we observed a surprising degree of this modulation. In general, directly testing the fixed memory mechanisms is a significant theoretical challenge—even in simple tasks. What is required is a combination of bringing the theory against multiple kinds of data sets (as advocated most persuasively by Newell, 1990), and adopting both modeling and empirical approaches (such as our rehearsal manipulations) that greatly constrain the choice of strategy as a theoretical degree of freedom (e.g., Howes, Lewis & Vera, submitted). We note that such methodological challenges are not restricted to applying general theories of cognitive architecture, such

as ACT-R. Any theory of some aspect of the fixed cognitive system—such as the nature of memory decay—faces these challenges, because any given posited fixed cognitive mechanism expresses itself only through selected task strategies.

Given these considerations, a more circumspect view of our results suggests that they represent a new set of quantitative regularities that should provide important constraints on any detailed theory of memory that makes precise assertions about decay mechanisms—but that this empirical constraint will be felt most sharply when joined with the broad set of other growing results, from other tasks, also showing flat effects of time (Lewandowsky, Duncan and Brown, 2004; Oberauer and Lewandowsky, 2008; Lewandowsky and Oberauer, 2008; Lewandowsky, Geiger, and Oberauer, 2008; Nairne, 2002). There is a major opportunity to use computational modeling to test extant theories of decay and interference, but we think such an exercise would be most profitable if it takes into account a wide range of empirical effects and uses modeling techniques that help control for effects of strategic variation.

With these caveats in mind, our results do seem to more straightforwardly align with more recent models of short-term memory that do not implicate decay, including models such as SIMPLE (Brown, Neath, and Chater, 2007), and SOB (Farrell and Lewandowsky, 2002). In SIMPLE, attention can (optionally) be directed away from time whereas SOB is necessarily completely free of any effect of time, and depends only on interference mechanisms. We now sketch our own approach to understanding the recent probes task that is consistent with such models that explain forgetting in terms of interference alone.

Possible Mechanisms of the Recent Probes Task

It is important to consider the mechanisms involved in the recent probes task and compare those mechanisms to processes involved in other tasks that found decay, such as McKone (1998). First let's consider different neural mechanisms that are involved in repetition priming compared to explicit item recognition (Berry, Henson and Shanks, 2006). Many authors have reported double dissociations both neurally and behaviorally between priming and recognition memory (Hamann and Squire, 1997a, 1997b; Gabrieli et al., 1995; Keane et al., 1995) with priming being dependent on the occipital lobe, suggesting a strong perceptual component (Fiebach, Gruber, and Supp, 2005). In contrast our task robustly activates the left ventrolateral prefrontal cortex[11] for the RN – NRN contrast (Nee, Jonides and Berman, 2007; Jonides et al., 1998; Nelson et al., 2003; Mecklinger et al., 2003; D'Esposito et al., 1999; Badre and Wagner, 2005; Bunge et al., 2001). In addition, McKone and Dennis (2000) found that phonological representations were less susceptible to time-based decay compared to orthographic representations in a similar repetition priming study. In sum, differences in task demands, underlying neural processes, and the nature of the encoding of the stimuli could explain why decay was found in the repetition priming task, but not in our Recent-probes task.

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[11] Nee, Jonides and Berman, 2007 report activation in Occipital cortex for the RN – NRN contrast, but the other 6 neuroimaging studies of our task that we cite do not report occipital cortex activation. In addition, we find increased activation in occipital cortex for the RN – NRN contrast, which is the reverse finding from repetition priming studies that find decreased activation for repeated items compared to non-repeated items. Therefore we do not believe that this task recruits the same visual perceptual processing that is found in priming studies and is less reliant on perceptual processing overall compared to repetition priming.

We must also consider what the Recent-probes task has allowed us to measure. Beyond the manipulation of inter-trial interval which allowed us to assess the effects of delay, we were also able to further investigate whether participants rehearse past items during the blank ITIs in this paradigm. As Experiments 5 and 6 showed, articulatory suppression did not modulate the effect, nor did instructing participants to ignore past sets. Therefore, we argue not only that there is no incentive for subjects to rehearse in the task; whether they had any incentive to rehearse, they did not.

To understand a bit better what causes the recent-probes effect that is at the heart of the paradigm we have used, we turn to a theoretical interpretation of the effect provided by Jonides and Nee (2006). In their review, the author's subscribe to the Biased-Competition model (Kan and Thompson-Schill, 2004; Desimone and Duncan, 1995) as a theoretical model to explain the Recent-probes effect. According to this model, when a RN probe is shown it activates attributes/features that are associated with the RN probe-word, such as its familiarity (which is high), context (seen on the previous trial), semantic representation, etc. The important features here are familiarity and item context. The high familiarity of the item will bias one to respond affirmatively when, in fact, the correct response is negative. At the same time the context of the RN probe does not match that of the current item's context, and this contextual mismatch will bias one to respond negatively, which is the correct response. Therefore, there are competing tendencies for RN items, and these competing tendencies slow participants compared to NRN items that have very low item familiarity, due to greater retroactive interference (Jonides and Nee, 2006). This model also correctly predicts that recent positive probes

will yield faster responses than non-recent positive probes (a facilitation effect), which is sometimes found in this paradigm.

In order for a decay theory to accommodate these data, it would need to hypothesize that the two opponent features (i.e., item-familiarity and item-context) decay at the same rate, thus hiding any effects of decay as these two attributes seem to counteract each other. Here we appeal to Occam's razor. An interference account need not rely on two opponent processes balancing each other out to explain our data; rather, an interference account can explain our data with one feature, namely the presence or absence of interference. Therefore we subscribe to an interference account based on its simplicity. In addition, the likelihood that two opponent processes would balance each other perfectly seems small; especially when considering the research done showing the dissociation between processes reliant on item-context vs. item-familiarity (Jacoby, 1991) and their different time-courses (Yonelinas and Jacoby, 1994).

Conclusion

In conclusion, although null results such as these cannot completely rule out the possibility of some effect of decay, the consistent pattern of results across these six experiments coupled with the extremely small effects observed, provide strong evidence against decay as a mechanism for forgetting in STM. We argue that the small effect of time detected in the aggregate analysis might be a result of interference playing a role at longer time delays, with participants performing some mental activity (e.g. mind wandering) that could be interfering. Furthermore, considerations of the sensitivity of the

paradigm with respect to the best existing empirical evidence for decay suggest that our experiments did have sufficient power to detect canonical decay effects at reasonable delay intervals where decay had been shown to exist (McKone, 1998). Our data show a persistence of short-term memory that may question the shape of existing decay functions, especially if there is rapid decay as shorter time delays. Finally, we found clear evidence for a major role of interference as a mechanism of forgetting, which overshadowed any effect of decay in our paradigm.

In the next chapter, interference in memory is explored in the context of Major Depressive Disorder (MDD) to determine whether MDD can be characterized by an inability to resolve interference from negatively valenced information in short-term memory.

Acknowledgments:

This research was supported in part by a grant from the National Science Foundation (NSF; #0520992), in part by a grant from the National Institute of Mental Health (NIMH; MH60655) and in part by a NSF Graduate Research Fellowship to the first author. We would also like to thank John Meixner, Katie Rattray and Courtney Behnke for help in data collection. Lastly, we thank our editor and our reviewers for their helpful revisions and suggestions. This work was conducted in collaboration with John Jonides and Richard L. Lewis.

Chapter 3

Neural and Behavioral Effects of Interference Resolution in Depression and Rumination

Abstract

Individuals diagnosed with Major Depressive Disorder (MDD) often ruminate about their depression and their life situations, impairing their concentration and performance on daily tasks. We examined whether rumination might be due to a deficit in the ability to expel negative information from short-term memory (STM); also, we examined the neural structures involved in this ability using fMRI. We tested MDD and healthy control (HC) participants using a directed-forgetting procedure in an item-recognition task. As predicted, MDD participants had more difficulty than did HCs in expelling negative, but not positive, words from STM. Overall, the neural networks involved in directed-forgetting were quite similar for both groups; but the MDDs exhibited more spatial variability in activation in the left inferior frontal gyrus (a region critical for inhibiting irrelevant information) which may mediate their relative inability to inhibit negative information.

Introduction

In the previous chapter it was shown that interference is a major cause of forgetting in short-term memory. In this chapter the role of interference is explored in relation to Major Depressive Disorder (MDD). MDD has been characterized by high levels of rumination -- uncontrollable negative thoughts about the depressed individual's symptoms and situation that interfere with his or her ability to concentrate and effectively carry out daily activities (Nolen-Hoeksema, 2000). Rumination is not merely a symptom of depression; it maintains and exacerbates depressive symptoms, and it predicts the likelihood of recurrence of depressive episodes (Nolen-Hoeksema, 2000; Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008). Therefore, identifying the cognitive and neural mechanisms of rumination may help us to gain a better understanding of the etiology and maintenance of depression.

Cognitive processes underlying rumination

It is likely that rumination involves difficulties in controlling the contents of short-term memory (STM; Joormann & Gotlib, 2008; Joormann et al., 2010); thus, we propose that depressed individuals have a specific deficit in removing negative self-relevant information from STM. The hypothesis is that this failure to expel negative information from STM leads to increased interference, which, in turn, results in difficulties in concentration and memory that have been associated with rumination and depression (Lyubomirsky, Kasri, & Zehm, 2003).

Considerable research has examined neural and cognitive mechanisms involved in resolving interference in STM (Berman, Jonides, & Lewis, 2009; D'Esposito et al., 1999; Jonides et al., 1998; Nee, Jonides, & Berman, 2007; Nelson et al., 2003; Otztekin and

McElree, 2007; Thompson-Schill et al., 1997). Although some investigators have demonstrated that depression is associated with an impaired ability to remove negative information from STM once it enters (Joormann & Gotlib, 2008; Joormann et al., 2010; Whitmer & Banich, 2007), little research has examined the neural underpinnings of the relationship between depression and the ability to control information in STM. In this study, therefore, a STM interference task was employed to elucidate both neural and behavioral mechanisms that may underlie rumination and depression.

Overview of Present Research

A directed-forgetting task was used to assess interference resolution of affectively valenced stimuli in STM (Nee et al., 2007; Zhang et al., 2003). The task required participants to attempt to forget previously encoded positive and negative words (see also Joormann & Gotlib, 2008; Joormann et al., 2010). We hypothesized that MDD and HC participants would differ with respect to both behavioral and neural functioning when trying to forget negative, but not when trying to forget positive information. Behaviorally, we hypothesized that MDD participants would exhibit longer reaction times and poorer accuracy than would HCs when trying to forget negative words. We also hypothesized that higher levels of rumination would be associated with greater difficulty in forgetting negative items.

Neurally, we expected to find differences between the two groups when forgetting negative items vs. positive items, specifically in the left inferior frontal gyrus (LiFG), a region that has been implicated in memory selection and inference resolution (D'Esposito et al., 1999; Jonides et al., 1998; Nee, Jonides, & Berman, 2007; Nelson et al., 2003). We hypothesized that neural differences could manifest themselves in any of three ways: 1)

there could be differences in the magnitude of activation in LiFG between the two groups (e.g., MDDs may activate LiFG to a lesser degree than HCs) 2) there could be differences in the temporal variance of activations in LiFG (e.g., MDDs may activate LiFG more variably over time than HCs) and 3) there could be differences in spatial variance of activations in LiFG (e.g., MDDs may activate LiFG more diffusely than HCs). While exploring variance in activations is relatively new when it comes to imaging data (researchers typically control for this variable, rather than measure it) variability has turned out to be an important measure in other subfields of psychology and behavioral science (Mischel & Shoda 1995,1998; Segerstrom & Nes, 2007; Riley & Turvey, 2002).

With that said, there has been some recent fMRI research exploring variance in the fMRI signal as a dependent measure. Garrett et al, (2010) found that variance in the BOLD signal during fixation periods differentiated older and younger adults with five times the predictive power of an amplitude-based analysis. Other research has shown that variance in the fMRI signal predicted psychotic symptoms for people with schizophrenia (Winterer et al., 2006a); it has been explored in other contexts as well (Musso et al., 2006; Winterer et al., 2006b). In addition, in Bush's (2010) recent review, he calls for more research examining variability in fMRI signals as they pertain to ADHD as such "noise" could be related to decreased dopamine levels and could help to evaluate hypoactivation in ADHD groups. Therefore, exploring both spatial and temporal variance for depressed and healthy participants seems apt here as well.

Methods

Participants and Measures

Thirty-two right-handed adults (21 females; mean age=24.4 years) participated in this study. Sixteen participants met criteria for MDD as assessed by the Structured Clinical Interview (SCID)[12] and 16 had no current or past Axis I pathology. All SCID diagnoses were confirmed by a second, independent interviewer. Participants also completed the Ruminative Response Styles (RRS) questionnaire (Nolen-Hoeksema & Morrow, 1991; Treynor, Gonzalez, & Nolen-Hoeksema, 2003) that assesses the degree to which participants engage in rumination with depressive content, and the Beck Depression Inventory II (BDI; Beck, Steer, & Brown, 1996), that assesses severity of depressive symptomatology. Three participants were excluded from all analyses (one for having poor fMRI normalization; one for dropping out of the experiment midway; and one for not performing the word-rating task at the end of the study), leaving 15 MDDs and 14 HCs for the final analyses[13].

Materials and Procedures

Participants saw a display of four words on a computer screen. Two words were presented in blue and two in red. Participants were instructed to encode and remember all four words. After a four-second delay, participants saw either a blue or red color patch indicating the color of the words they were now to remember; the words in the other color were to be forgotten. Following a jittered cue-to-stimulus interval (CSI) of 4, 6, 8, or 10 seconds (average CSI = 7 seconds), participants saw a single probe word and

[12] Six of the 16 MDDs had or were taking medication for depression.
[13] Three runs for one MDD were removed for chance accuracy, and one run was missing for one of the HCs.

pressed a “yes” key if that word was one of the two words they were to remember, and a “no” key if it was not one of the two words they were to remember. The Inter-trial-Interval (ITI) was jittered to be 4, 6, 8, or 10 seconds (average ITI = 7 seconds).

There were two types of “no” trials, the trials of main interest here: “control” probes were words not seen in over 100 trials on average, and “lure” probes were words drawn from the to-be-forgotten set of the current trial. Previous research has demonstrated that people are both delayed and less accurate in responding to lure trials than to control trials (Nee et al., 2007; Zhang et al., 2003). The difference in performance between lure and control trials indexes how well participants are able to control the contents of STM and to resolve interference. The task used in this study required participants to forget and remember both positively and negatively valenced items. Because of the high level of rumination by MDDs about negative material (Beck, 1967; Nolen-Hoeksema, 1991; Nolen-Hoeksema et al., 2009), we hypothesized that MDD participants (but not HC participants) would have more difficulty saying “no” to negatively valenced lures than they would to positively valenced lures, indexed by increased reaction time and decreased accuracy.

Participants first practiced 32 trials of the directed-forgetting task with words that they would not see again in the study. All words were selected from the Affective Norms of English Words (ANEW; Bradley and Lang, 1999). Words were specifically selected that were positively or negatively valenced according to ANEW norms to increase the likelihood that participants would perceive the words as differentially valenced. The mean ANEW valence was 3.15 for the negative words and 7.21 for the positive words. The positive and negative words were equated for arousal (negative: mean = 5.46, s.d. =

1.12; positive: mean = 5.48, s.d. = 1.12) and frequency (negative: mean = 24.9, s.d. = 36.1; positive: mean = 27.6, s.d. = 27.3). As described below, participants were asked to rate the valence of each word at the end of the experiment, and these idiosyncratic ratings were used in our behavioral and neural analyses so that the effect of affective valence as perceived by each subject individually could be examined. The experimental task contained 192 trials: 24 lure negative trials, 24 lure positive trials, 24 control negative trials, 24 control positive trials, 48 "yes" negative trials and 48 "yes" positive trials[14]. Participants completed 12 runs of the experiment (in 2 sessions of 6 runs each; see Figure 3-1).

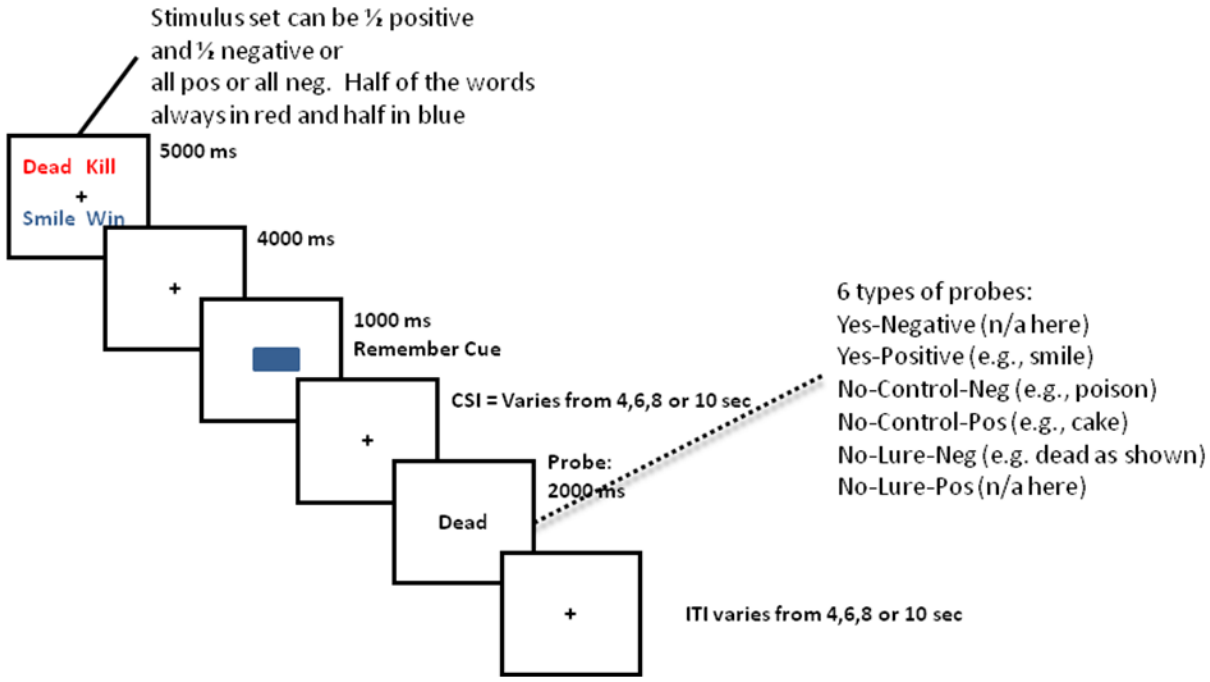

Figure 3-1: Schematic Diagram of the Valenced Directed Forgetting task. Each run consisted of 16 trials that were balanced for the different trial-type combinations, lasted 7 minutes and 38 seconds, and included 16 seconds of fixation at the beginning and end of each run.

[14] These trial numbers were based on the canonical ratings of valence from the ANEW list.

After completing session 1 (approximately 1.25 hours), participants filled out the BDI and the RRS questionnaires. They then performed a short automated operation span task in which they had to remember words while simultaneously solving math problems (Unsworth et al., 2005). Following these tasks, participants returned to the scanner to complete session 2 (also approximately 1.25 hours). The experiment was divided into two sessions to avoid the fatigue that would be caused by 2.5 hours of continuous scanning time[15]. After completing session 2, participants had three minutes to recall as many words as they could from the experiment. Following this, participants rated each word from the experiment on a scale from 1 to 7 indicating how negative or positive that word was to them (1 = this word is very negative to you to; 7 = this word is very positive to you)[16].

fMRI Methods

Images were acquired on a GE Signa 3-Tesla scanner equipped with a standard quadrature head coil. Functional T2* weighted images were acquired using a spiral sequence with 40 contiguous slices with 3.44×3.44×3 mm voxels (repetition time (TR)=2000 ms; echo time (TE)=30 ms; flip angle=90°; field of view (FOV)=22 cm). A T1-weighted gradient echo anatomical overlay was acquired using the same FOV and slices (TR=250 ms, TE=5.7 ms, flip angle=90°). Additionally, a 124-slice high-resolution T1-weighted anatomical image was collected using spoiled-gradient-recalled acquisition

[15] We realigned all of our functional images together from session 1 & 2 and coregistered and normalized them all to the same high resolution anatomical image separately for each subject.
[16] Due to a programming error, 27 participants did not rate 12 of the 444 words, which led, on average, to 5 trial-types not being rated in the directed-forgetting task.

(SPGR) in steady-state imaging (TR=9 ms, TE=1.8 ms, flip angle=15°, FOV=25–26 cm, slice thickness=1.2 mm).

Each SPGR anatomical image was corrected for signal in-homogeneity and skull-stripped using FSL's Brain Extraction Tool (Smith et al., 2004). These images were then normalized with SPM5 (Wellcome Department of Cognitive Neurology, London); the normalization parameters for warping to the standard MNI template were recorded. These normalization parameters were applied to the functional images maintaining their original 3.44×3.44×3mm resolution, and they were spatially smoothed with a Gaussian kernel of 8mm. Functional images were corrected for differences in slice timing using 4-point sinc-interpolation (Oppenheim et al., 1999) and were corrected for head movement using MCFLIRT (Jenkinson et al., 2002). To reduce noise from spike artifacts, we implemented AFNI's de-spiking algorithms. Voxel time series were temporally high-pass filtered at .0078Hz.

fMRI analysis parameters

Our functional images were entered into a general linear model in which fixation (at the beginning and end of each run), the stimulus display (all negative items, all positive items, and half negative and half positive items separately), the remember cue and the probe were modeled. There were 3 types of probes: Lure, Control, and Yes trial probe words which were modeled separately based on participant ratings. Words with ratings of 1 or 2 were categorized as negative, of 3-5 as neutral, and of 6 or 7 as positive. MDD and HC participants did not differ significantly in the number of words they rated as positive and negative, but both groups rated more words as negative than as positive,

$t(28) = 7.8$, $p < .001$**.** This fMRI analysis matched many of our behavioral analyses in which similar valence trials were aggregated. Incorrect trials were modeled separately, as well as probe words that had missing word ratings. Furthermore, 24 motion regressors were added into our model that included the linear, squared, derivative, and squared derivative of the six rigid-body movement parameters (Lund et al., 2005) resulting in a total of 40 regressors (some participants did not have incorrect trials or un-rated words resulting in 38 regressors for those participants).

For all fMRI analyses a threshold of $p < .005$ (uncorrected) at the voxel-level was used, which was then corrected using a cluster-size threshold of 20 contiguous voxels producing a $p < .05$ (corrected) threshold (Forman et al., 1995).

Behavioral Analysis

Our analyses focused on the 'no' response trials because examining participants' ability to expel information from STM was of interest. To correct for outliers, trials for which reaction times (RTs) were either greater than 3 standard deviations from each participant's mean (calculated separately for each trial type) or less than 400 msec were excluded (a standard procedure used to trim reaction time data). On average this trimming procedure removed only 1.35% of trials. The resulting means for the correct trials were used in our analyses. We hypothesized that, compared with HCs, MDDs would show a larger Lure – Control difference for negative words than for positive words (i.e., slower RTs, more errors). To test for this, two 2 (Group: MDD vs. HC) x 2 (Trial Type: Lure vs. Control) x 2 (Valence: Positive vs. Negative) repeated measures analyses

of variance (ANOVAs) were conducted (one on RTs and one on accuracy), with group as a between-subjects factor and trial type and valence as within-subject factors.

Results

Behavioral Results

MDDs had more difficulty removing negative information from short-term memory than controls, but no differences were found between groups when removing positively valenced information from short-term memory. A 2 (Group: MDD vs. HC) X 2 (Trial Type: Lure vs. Control) X 2 (Valence: Positive vs. Negative) ANOVA was performed on our behavioral data. There was a highly reliable main effect of trial type as responses to Lure trials were less accurate, $F(1,28) = 11.352$, $p < .005$, and slower, RT $F(1,28) = 81.85$, $p < .001$. There was not, however, a reliable Group X Trial Type interaction for RT, $F(1,28) = 1.473$, n.s. or accuracy, $F(1,28) = 1.759$, n.s., nor was there a reliable Trial Type X valence interaction for RT, $F(1,28) = 2.275$, n.s. or accuracy, $F(1,28) = 1.611$, n.s. Critically, for RT, there was a reliable 3-way interaction of Group X Trial Type X Valence as MDDs and HCs differed in the Lure – Control contrast by valence, $F(1,28) = 5.12$, $p < .05$. These results show that MDDs have more difficulty than HCs in resolving interference from negatively valenced items. These results also seem not to be driven by a more generic effect of Group or Valence as evidenced by the two null 2-way interactions. These effects were explored in greater detail with planned comparison t-tests on RT, and MDDs had a greater Lure – Control difference than HCs for negatively valenced words, $t(27) = 2.05$, $p < .05$; this was not so for positively

valenced words, t(27) = .04, n.s. Also, MDDs had a reliably larger Lure – Control difference for negatively valenced words than to positively valenced words, t(14) = 2.23, p < .05. These results can be seen in Figure 3-2 and Table 3-1. There were no differences by valence for HCs. None of these valence effects was reliable with accuracy as the dependent variable.

	Individual Ratings of Valence			
	Lure Neg	Lure Pos	Control Neg	Control Pos
MDD				
RT	1095.31 (76)	1027.07 (74)	876.03 (63)	882.11 (52)
Acc	0.89 (.04)	0.92 (.04)	0.99 (.01)	0.99 (.01)
HC				
RT	882.92 (39)	895.64 (42)	751.31 (34)	749.17 (30)
Acc	0.95 (.02)	0.97 (.02)	0.99 (.01)	1.00 (0.0)

Table 3-1: Mean RTs and accuracies for word valence as determined individual participants' ratings of the words. Standard errors are in parenthesis.

In sum, these results show that MDDs, in contrast to HCs, are slower to remove negatively valenced information from STM than positive. In a separate analysis using all the word ratings, not just the extremes, we confirmed this finding. The slope of the function relating the Lure – Control contrast to ratings of valence was reliably different for the two groups, t(27) = 2.40, p < .05. For MDDs, as the valence of the words became more positive, the Lure – Control difference became smaller. In contrast, HCs displayed a mild trend in the opposite direction. These data suggest that while the majority of the

effect lies in the extremes of valence, the effect also exists at intermediate levels of valence. These plots can be seen in Figure 3-3.

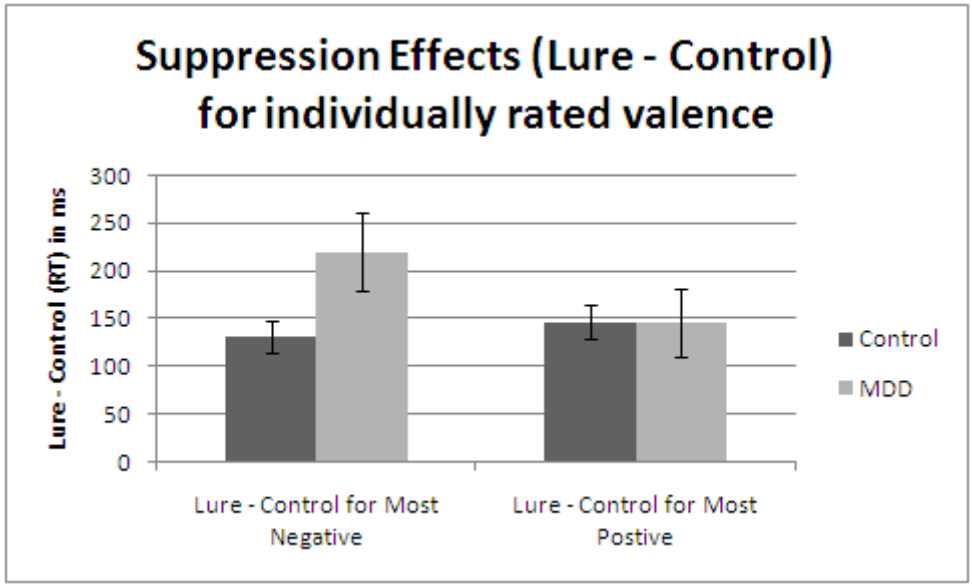

Figure 3-2: Mean Correct RT for the Lure – Control contrast for the most negatively (ratings of 1 and 2) and positively (ratings of 6 and 7) rated words for both MDDs and HCs. Here valence was determined by each individual participant. MDDs exhibit more difficulty MDDs exhibit more difficulty in removing negative information from STM than positive. HCs do not show this pattern.

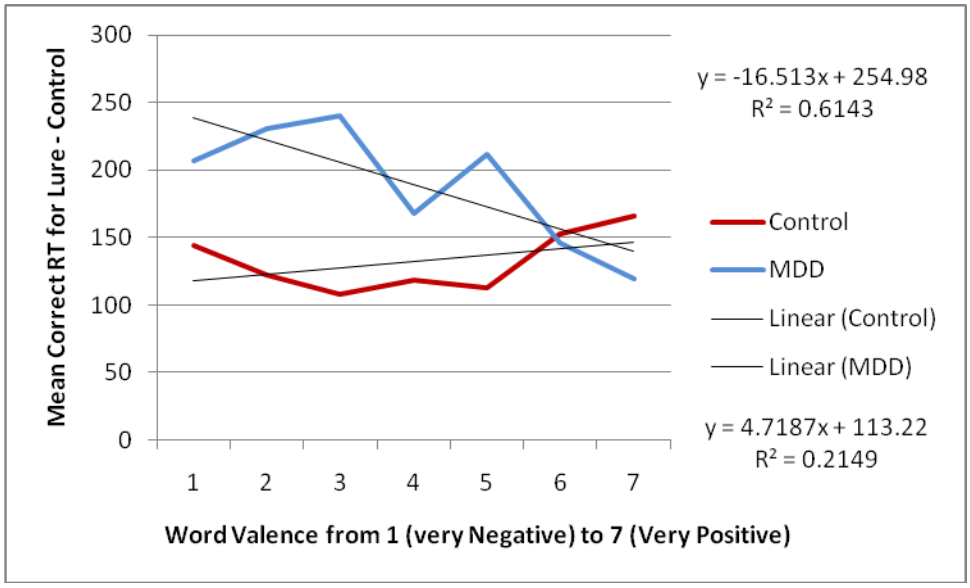

Figure 3-3 Mean Correct RT for the Lure – Control contrast for each valence rating. Valence was determined by each individual participant. MDDs exhibit more difficulty in removing negative information from STM compared to positive. HCs show the opposite pattern. T The top linear equation explains the pattern for MDDs, while the bottom linear equation explains the pattern for HCs.

Additional Behavioral Effects

Rumination Response Styles inventory scores (RRS, Nolen-Hoeksema and Morrow, 1991; Treynor, Gonzalez, and Nolen-Hoeksema, 2003) were correlated with the difference in RT for the Lure - Control contrast for negative valence minus positive valence. As seen in Figure 3-4, the more participants ruminated, the more difficulty they had removing negatively valenced information from STM versus positively valenced information, $r = .43$, $t(29) = 2.5$, $p < .05$. This result was nearly identical when Lure Neg – Lure Pos RTs were correlated with RRS, yielding a reliable value, $r = .42$, $t(29) = 2.43$, $p < .05$. This shows that it was the Lure trials that were driving these results. These same correlations were explored substituting the full-RRS scores with the brooding and reflection subscales. There was a trend for brooding scores to correlate positively with

RT differences for Lure – Control Negative vs. Lure – Control Positive, $r = .31$, $t(29) = 1.73$, $p < .1$, but no trend existed for reflection scores, $r = .16$, $t(29) = .85$, n.s. These results further corroborate that the difficulty in expelling negative relative to positive information is related to negative forms of rumination (e.g., brooding) and not to general pondering (e.g., reflection). Operation span scores[17] were also reliably lower for MDDs than HCs, $t(27) = 2.23$ $p < .05$[18] , and there was a trend for spans to be negatively correlated with rumination scores ($r = -.31$, $p = .10$), which all suggest that depressive rumination may consume cognitive resources.

To check whether our directed forgetting effects may be driven by these differences in operation span scores, we performed two stepwise regressions. For the first, RTs for the Lure – Control contrast for negatively valenced words were used as the dependent measure, with depression status (MDD vs. HC) and operation span scores as potential regressors. Our criterion for inclusion was having a p-value for the regressor < .05, and our criterion for exclusion was having a p-value > .10. For this stepwise regression, only depression status was entered, and operation span scores were excluded. We performed a second stepwise regression with the same regressors, but changed the dependent variable to the difference in RT for the Lure - Control contrast for negatively valenced words vs. the Lure – Control contrast for positively valenced words. Again, only depression status was included and operation span scores were excluded. Based on these analyses, it seems that the differences in the directed-forgetting task were not driven by differences in operation span scores.

[17] We used the total score as the operation measure where any correct trial was counted as correct. Participants did not need to get 2/3 of trials correct at each load level to be counted as correct.
[18] One HC was removed for having a deviant operation span score of 0.

At the conclusion of the experiment, participants were asked to recall as many words as as possible regardless of whether the words were to-be-remembered or to-be-forgotten (since words were repeated 4 times throughout the course of the experiment, a word could appear as a to-be-remembered item on one trial, and a to-be –forgotten item on a later trial, or vice versa). MDD's recalled more negatively valenced words (8.2 negative vs. 5.7 positive), and HC's recalled more positively valenced words (8.1 positive vs. 5.7 negative), producing a reliable group x valence interaction, $F(1,28) = 7.8$ $p < .01$. Lastly, these effects were explored separately for our non-medicated MDDs (9 participants) vs. HCs. All of these behavioral effects were found reliable, but the directed-forgetting 3-way interaction was reduced to a trend. This may be because the medicated MDDs had more severe forms of depression or because we had reduced power for this contrast due to the smaller sample size.

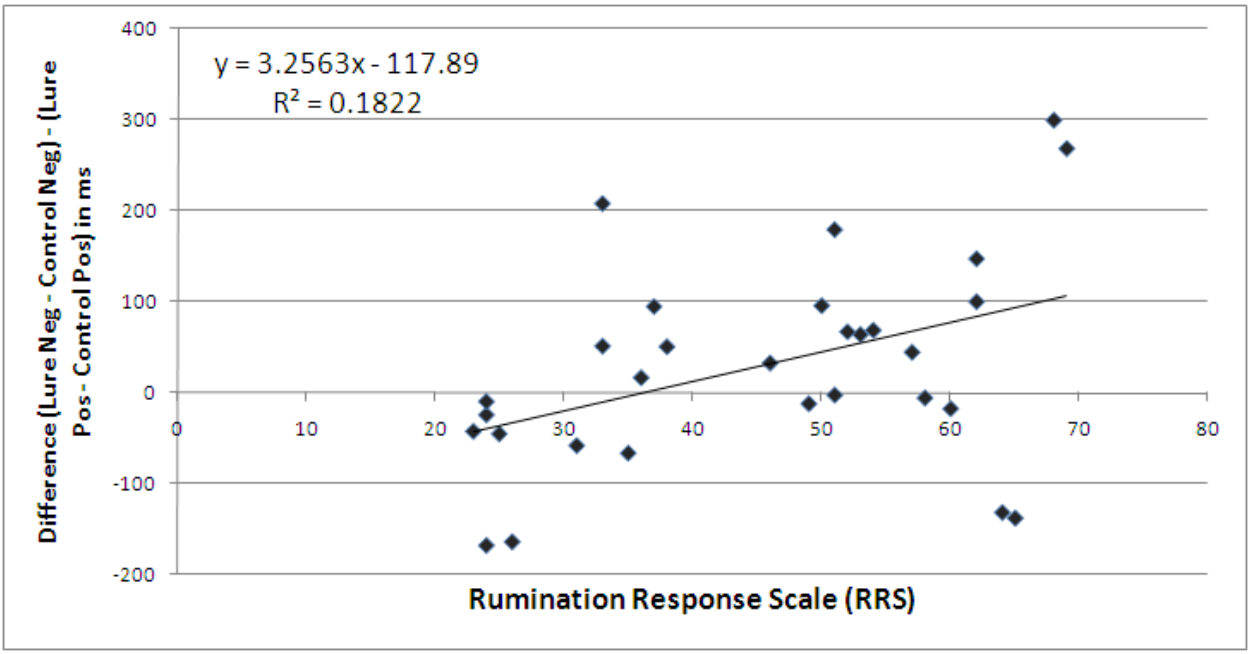

Figure 3-4: The difference in the Lure – Control contrast for the most negatively and positively valenced words as rated by individual participants plotted against Rumination

scores (RRS) of each participant. The linear equation is shown in the upper left of the figure

fMRI Results

These behavioral results show differences between MDDs and HCs in removing negatively valenced information from STM: MDDs had more difficulty doing so. The fMRI results were analyzed to uncover the neural mechanisms that may support these differences, to better understand why MDDs are deficient in removing negatively valenced information from mind.

Similarities in Magnitude of Activation

For the Lure – Control contrast at the onset of the probe, both groups robustly activated a network that has been repeatedly implicated in interference resolution for verbal material, including left inferior frontal gyrus (LiFG), dorsal anterior cingulate cortex (ACC), and left and right parietal cortex (Nee, Jonides and Berman, 2007; Zhang et al., 2003). In order to quantify this overlap, the group-averaged t-statistical maps for the Lure – Control contrast were separately calculated for MDDs[19] and HCs. These two statistical maps (Lure – Control group contrast for MDDs and HCs) were then correlated to obtain a single Pearson correlation coefficient across all brain voxels. A correlation of .50 was found indicating substantial similarity in the networks supporting the two groups. Furthermore, when we focused on the activation only in the LiFG (defined anatomically from the WFU PickAtlas), the correlation increased to .60.

[19] One MDD was not included in probe results because that participant had only 50% accuracy on Lure trials and therefore had low power for that contrast.

Of course, the behavioral data show that valence matters. Therefore, the Lure Neg – Control Neg contrast was examined in the anatomically defined LiFG region of interest (ROI). There was no difference when comparing the magnitude of activation for the two groups. We also performed whole brain analyses comparing the two groups for the Lure Neg – Control Neg and Lure Pos – Control Pos contrasts, but found few differences between the groups at conservative statistical thresholds. All of these results suggest that the two groups activate similar networks to the same magnitude when suppressing positive and negative information.

While few differences were found between groups for these contrasts, some differences were found with a multiple regression using RRS scores as a predictor. This analysis is similar to the analysis that was performed on the behavioral data when we correlated RRS scores with the difference in RT for the Lure – Control contrast for negatively valenced items vs. RT for the Lure – Control contrast for positively valenced items and when we performed this correlation on the Lure trials only (Lure Neg – Lure Pos). For this analysis we used RRS as a predictor for differences in activation for Lure Neg – Lure Pos (we focused on the Lure trials, because those trials seemed to be driving the behavioral correlation). This regression produced a significant result in the right inferior parietal lobe (BA 40) centered at x = 62, y = -41, z = 45 and contained 39 contiguous voxels. This region is commonly activated for the Lure – Control contrast and activates for sensory and attentional processing (Corbetta & Shulman, 2002). Focusing on this region alone may not be entirely correct though. If the threshold was decreased to admittedly low thresholds such as $p < .05$ uncorrected for 20 contiguous voxels, many more regions were found, including LiFG and some other regions of the

fronto-parietal network. This analysis shows that the greater the rumination score, the more participants need to engage this frontal-parietal network to resolve interference from negatively valenced Lures compared to positively valenced Lures, thereby complimenting our behavioral analyses.

Differences in Spatial Variance

Few differences were found between the two groups when exploring activation magnitude, though there were some effects when RRS scores were used as a predictor. However, as we indicated above, what may be telling in differentiating the groups might be differences in the variance of activations, not in the overall magnitude. Therefore, we examined spatial variance, for which we differences between the groups, specifically in LiFG. When spatial variance of activations was examined within this ROI for each participant for the Lure Neg – Control Neg contrast, MDDs showed more spatial variance than HCs, $t(27) = 2.8$, $p < .01$ (This spatial variance difference was still reliable when we excluded our medicated MDD participants.). This variance difference can be seen in Figure 3-4, which displays a 3-dimensional rendering of the LiFG for both groups with activations superimposed in a wiremesh plot. We used the marching cubes algorithm (Lorensen & Cline, 1987) to compute these three dimensional wireframe representations of the contour curves as implemented in the misc3d package in the statistical program R.

Exploring Figure 3-5, one can see that HCs activate more focally in LiFG and MDDs activate more diffusely. Spatial variance in the ROI also correlated impressively with the behavioral difference for Lure_Neg – Control_Neg in RT ($r = .60$, $p < .001$)[20];

[20] When two participants were removed from this analysis because they may have been outliers, this correlation was reduced to a trend ($r = .32$, $p = .10$).

because we were concerned that the correlation might be driven by two outlier points, we ran a robust regression in MATLAB (The Mathworks Inc., MATLAB version R2008b) with the robustfit function using the Huber weight function and still obtained a significant correlation ($r = .35$, $p < .01$). In addition, there was a trend for the spatial variance for the Lure Neg – Control Neg contrast to correlate positively with RRS scores, $r = .34$, $t(29) = 1.9$, $p < .1$.

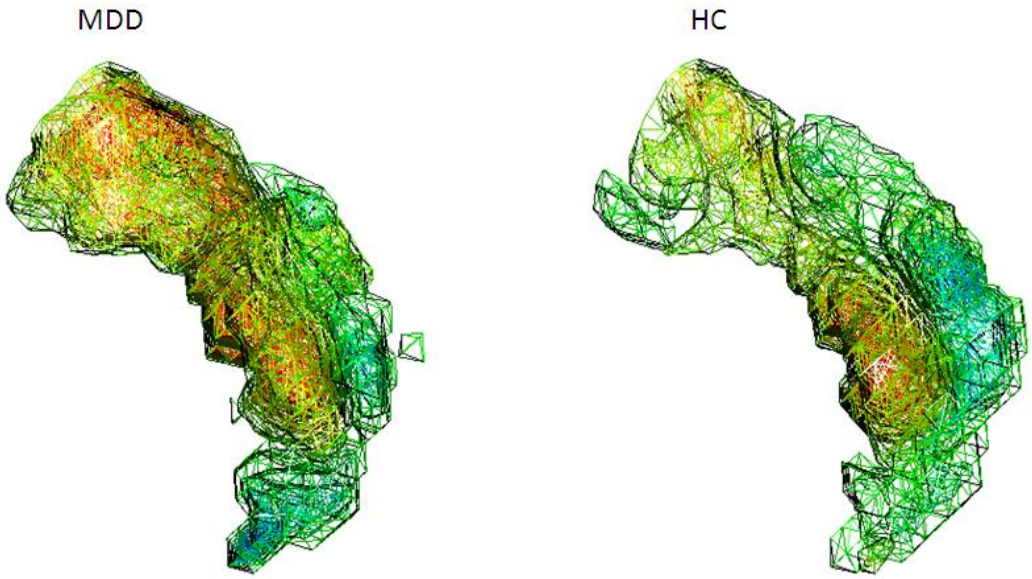

Figure 3-5: Three-dimensional renderings of LiFG for MDDs on the left and HCs on the right for the Lure_Neg – Control_Neg contrast. Deactivations are in blue, and activations are in yellow/red. From the figure one can see that MDDs activate LiFG more diffusely, while HCs activate this region more focally, with activation clusters centering in lower to middle portions of the LiFG. Contrast values range from -1.5 (blue) to +1.5 (red).

The spatial variance difference was not seen everywhere in the brain; for example, the Anterior Cingulate Cortex (ACC; defined anatomically from the WFU

PickAtlas) did not show spatial variance differences between the two groups, t(27) = 1.8, n.s. In addition, the spatial variance effect does not appear for all contrasts: For the Lure Pos – Control Pos contrast, no differences were found in spatial variance in LiFG between the two groups, t(27) = 1.5, n.s. Therefore, it appears that there is some selectivity to the spatial variance difference between the two groups as it was seen more for the negatively valenced contrasts in LiFG, which is critical for this and other interference-resolution tasks.

To explore more how these variance differences in LiFG manifest themselves for the Lure Neg – Control Neg contrasts, a clustering analysis was performed on the activation contrast values in LiFG. An unsupervised clustering algorithm[21] (Kaufman & Rousseeuw, 1990; Mathematica v 7.0 Wolfram Research Inc., 2008) was run on the group activation maps in LiFG, and more clusters were found for MDDs (7 clusters) than for HCs (3 clusters). This analysis supports the claim of a wider distribution of activation for the MDDs, as Figure 4 suggests visually. This analysis, in conjunction with the visual display of LiFG from Figure 4, suggests that MDDs are activating this region more diffusely than HCs, and that the degree of diffuseness or variance may affect the ability of MDDs to remove negative information from short-term memory.

There is, however, an alternative explanation for the variance result, which is that MDDs are not uniformly more spatially varied than HCs, but rather are activating a separate region(s) within LiFG that HCs are not activating. For example, exploring Figure 4, it appears that MDDs may be activating a superior portion of the LiFG that HCs

[21] This method is based on the minimization of the silhouette statistic (Kaufman & Rousseeuw, 1990), which incorporates both cohesion and separation of data.

may not be activating. To test this idea, two separate functional ROIs were built based on the group data for the Lure – Control contrast across all subjects, one centered in the inferior portion of LiFG (x = -31, y = 31, z = 0) and one centered on the superior portion (x = -41, y = 6, z = 33). Differences in spatial variance were tested in these two regions as well as differences in mean activation, and no reliable differences were found for either ROI. This analysis suggests that MDDs are not activating a separate sub-area within the LiFG. Figure 3-6 provides an alternative representation of the data, which shows a more uniform spatial variance difference across the ROI. This chromosome-style plot shows activation for both groups for the Lure Neg – Control Neg contrast at each slice through Z across the x-axis (from 1 -22). Activation is shown for every x,y pair at each z-slice level. Each subject is represented by a different color and alphanumeric symbol. From Figure 5 it is apparent that the spatial variance effect seems to be present continuously through nearly all slices of Z.

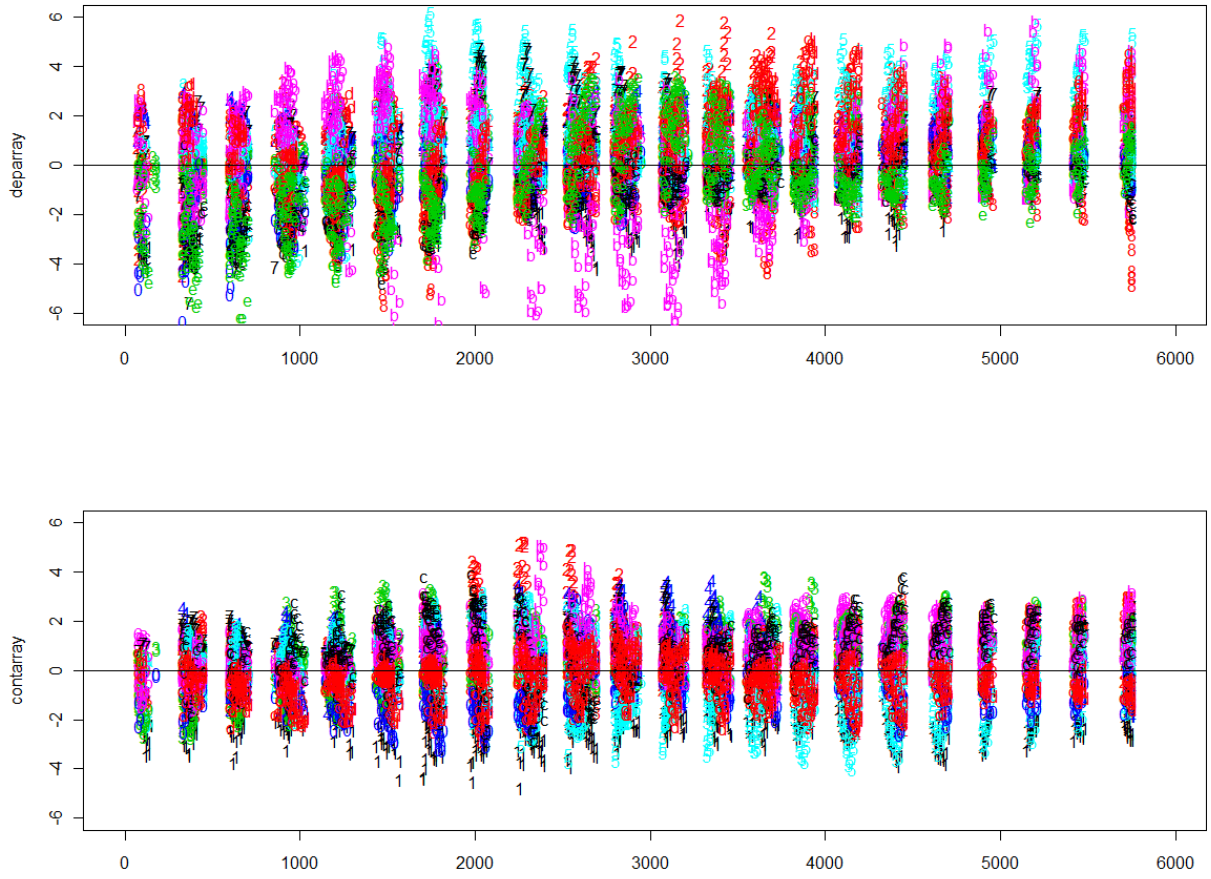

Figure 3-6: Chromosome style plot of LiFG for the Lure Neg – Control Neg contrast. The y-axis shows the contrast score for each voxel in LiFG for each participant. The X-axis is showing the different slices through Z, from 1 to 22. MDDs are displayed in the top panel and HCs are displayed in the bottom panel. We have vectorized the data over x and y, but each x and y pair is represented separately, and each subject is represented by a different color and alphanumeric symbol. From the figure it is apparent that MDDs show greater spatial variance at each slice through Z, indicating that the variance effect appears continuous throughout the ROI.

These differences in neural spatial variance inspired the exploration of variance differences between groups behaviorally. We ran a 2 (Group: MDD vs. HC) X 2 (Trial

Type: Lure vs. Control) X 2 (Valence: Positive and Negative) ANOVA with variance in RT as the dependent measure. Variance for each of the four trial types was calculated separately for each individual participant. We found a reliable 3-way interaction, in which variance differed by Group, Trial type, and Valence, $F(1,28) = 5.082$, $p < .05$. Exploring this interaction more directly with post-hoc t-tests, we found a significant difference between MDDs and HCs for Lure Neg variance, $t(28) = 2.80$, $p < .01$, but not for the other trial types, so it appears to be the Lure Neg trials that drive the variance differences between groups in RT. In addition, a reliable positive relationship was found between variance for the Lure Neg – Control Neg contrast in RT, with the amount of spatial variance for the Lure Neg – Control Neg contrast, $t(27) = .389$, $p < .05$. This analysis suggests that more noise in the fMRI signal, the more noise there is behaviorally, indicating a tight coupling between neural and behavioral variance.

Temporal Variance

Differences in temporal variance between MDDs and HCs were also explored. It could be that MDDs may be more varied in their activations over time, which may lead to some inabilities to resolve interference for negatively valenced items. This analysis was restricted to the Lure Neg condition and whole brain data for the scans corresponding to the trials when the Lure Negative probe word was shown. Two TRs from each trial type were taken. In addition, motion-related activity from the functional data was covaried out. These TR data were then concatenated and the variance in activation for each voxel across time was calculated. Since LiFG was of most interest, the temporal variance of all voxels in LiFG was averaged and entered into a two-sample t-test comparing the two

groups. When doing so, no differences were found in temporal variance $t(27) = .66$, n.s. in LiFG.

Summary

It appears that there are no differences in the magnitude of activation between the two groups even when the analysis was restricted to the LiFG. However, MDDs activated this region more diffusely than HCs, which was related to worse abilities to remove negative information from STM and was associated with greater behavioral variance in RT. Finally, no differences in temporal variance (i.e., more varied activations over time) were found between these two groups.

Discussion

In this study, MDDs experienced more difficulty removing negative information from STM but not positive information, extending the results of Joormann and Gotlib (2008) and Joormann et al., (2010) by relating behavioral findings directly to rumination and by uncovering the neural mediators of the directed-forgetting effects.

MDDs also had lower operation span scores, which corroborate hypotheses that depressive rumination may consume cognitive resources. Other research has shown that lower memory span scores are related to more task-unrelated thoughts (Kane et al., 2007) and less ability to suppress unwanted thoughts (Brewin and Smart, 2005). These results could indicate a harsh self-sustaining cycle for MDDs, in which ruminative thoughts could lower STM spans by increasing the amount of negative task-unrelated thoughts, which would subsequently diminish the ability to suppress such thoughts. While

differences in operation span scores were found between groups, these differences did not drive our directed-forgetting results.

Importantly, both MDD and HC participants activated similar neural networks to resolve interference. MDDs, however, had greater spatial variance in activations in LiFG than did HCs, even though both groups activated this region to a similar magnitude. These differences in spatial variance may indicate that MDD's are not as effective at using the mechanisms of this region to resolve the interference that is caused by negatively valenced conflicting probes, leading to their larger behavioral interference effect for this valence. In support of this noisy interference resolution process is the correlation that was found between spatial variance and behavioral variance for the Lure Neg – Control Neg contrast in RT. Elucidating the direction of this relationship, however, will require further research.

The physiological significance of spatial variance result may be related to dopamine. As Bush (2010) mentions, increased 'noise' in the fMRI signal may be attributable to decreased dopamine levels, which serve to dampen background neural firing noise. In fact, Winterer, et al. (2006b) found that Val polymorphic carriers of the COMT gene (who have less available synaptic dopamine) show less mean activation (i.e., smaller magnitude) and more varied activation in pre-frontal areas in a visual odd-ball task. These results suggest that dopamine may help to sharpen fMRI signals and suppress surrounding noise (Winterer et al., 2006b). A similar argument could be made and applied to depression. It is thought that people suffering from major depression have reduced dopamine neurotransmission levels relative to healthy controls (Hasler et al., 2008). Therefore, the increased noise or variance that was found for MDDs relative to

HCs, may be a reflection of decreased dopamine levels, which may hinder MDDs' ability to dampen background neural noise. Our effects were selective to negatively valenced stimuli, which may indicate that there is more noise for MDDs to suppress when negative information has entered short-term memory, but MDDs may not be able to suppress such noise due to a lack of dopamine. While admittedly speculative, rumination may be the culprit for increased noise/background neural firing for negatively valenced trials.

We would like to caution, however, that we are not claiming that spatial variance is "the" variable that distinguishes MDDs from HCs. Different tasks and designs may produce differences between groups in activation magnitude as well, as many authors have shown (Sheline et al., 2001; Siegle et al., 2002; Elliott et al., 2002; Engels et al., 2010). However, adding spatial variance as a potential dependent measure may have probative value.

There has been some controversy surrounding the directed-forgetting procedure and more generally whether memories can be suppressed (Anderson and Green, 2001). The most common directed-forgetting paradigms are usually implemented with a list-method procedure in which participants are instructed to remember a list of words and then given some instruction to forget that list and learn a new list. Then participants are usually tested by trying to recall as many words as they can from either list. Some controversy has surrounded this task, and whether directed-forgetting affects recall (Bjork, LaBerge & Legrand, 1968) and not recognition (Block, 1971; Elmes, Adams & Roediger, 1970), or whether it affects both (Benjamin, 2006). More specifically, the debate centers on whether the processes of directed forgetting involve retrieval inhibition or simply selective rehearsal (Benjamin, 2006). While the time scales of these effects are

outside the realm of our paradigm, one could still ask whether our effects are due to impaired inhibitory mechanisms or impaired selective rehearsal. Unfortunately, our present data cannot speak to this issue directly, and future research will be needed to answer this question. Whether the impaired process involves insufficient inhibition, rehearsal or both, the impairment seems to be selective to negatively valenced stimuli for MDDs.

In sum, although MDDs have the ability to resolve interference in STM, they have more difficulty in resolving interference for negative than for positive stimuli, and this difficulty is related to the propensity to ruminate. As such, the inability to remove negative information from STM may be a mechanism of rumination. Moreover, MDDs do not activate LiFG as efficiently/focally as do HCs in resolving interference for negative stimuli, which is related to their behavioral difficulties and increased behavioral variance for negative material. In turn, depression may be perpetuated by the difficulty demonstrated by MDDs in suppressing negative stimuli leading to continued depressive rumination.

Acknowledgments

This work was supported in part by NIMH grant MH 60655 to JJ, and NSF graduate fellowships to DEN and MGB. We thank Courtney Behnke for extraordinary help with data collection. This work was conducted in collaboration with Derek Evan Nee, Melynda Casement, Hyang Sook Kim, Patricia Deldin, Ethan Kross, Richard Gonzalez, Emre Demiralp, Ian H. Gotlib, Paul Hamilton, Jutta Joormann, Christian Waugh and John Jonides.

Chapter 4

Depression, Rumination, and the Default Network

Abstract

Major Depressive Disorder (MDD) has been characterized by excessive default-network activation and connectivity with the subgenual cingulate. These hyper-connectivities are often interpreted as reflecting rumination, where MDDs perseverate on negative, self-referential thoughts. However, the relationship between connectivity and rumination has not been established. Furthermore, previous research has not examined how connectivity with the subgenual cingulate differs when individuals are engaged in a task or not. The purpose of the present study was to examine connectivity of the default network specifically in the subgenual cingulate both on- and off-task, and to examine the relationship of connectivity to rumination. Analysis using a seed-based connectivity approach revealed that MDDs show more neural functional connectivity between the posterior-cingulate cortex and the subgenual-cingulate cortex than healthy individuals during rest periods, but not during task engagement. Importantly, these rest-period connectivities correlated with behavioral measures of rumination and brooding, but not reflection.

Introduction

Rumination is defined as "a mode of responding to distress that involves repetitively and passively focusing on symptoms of distress and on the possible causes and consequences of these symptoms" (Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008). This tendency to ruminate characterizes depression (Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008), and it has been ascribed to deficient control processes that cannot rid memory of negative information (Joormann, 2005). As such, a growing literature has examined the relationship between depressive rumination and cognitive control during demanding cognitive tasks.

However, it is likely that the most prominent display of rumination is not when people are engaged in a task, but when they are at rest. Examining how MDDs and healthy controls (HCs) compare during such rest periods is important because interleaved with the ongoing tasks of life are significant periods in which people do not engage in structured tasks, and instead are left to mind-wander or ruminate. Interestingly, recent research has shown the high propensity of people to mind-wander, which has been estimated to be around 10-15% of their wakeful hours[22] (Sayette, Reichle, & Schooler, 2009). Neurally, mind-wandering appears to engage regions of a "default network" (Christoff, et al., 2009, Mason et al., 2007). The default network has been defined as a set of neural regions that activate in unison during off-task or "rest" periods, which include the posterior-cingulate, portions of lateral parietal cortex, as well as portions of the medial temporal lobe and medial prefrontal cortex (Fox et al., 2005; Raichle, 2010; Shulman et al., 1997; Raichle et al., 2001).

[22] Participants in this study were engaged in a reading task.

Recent research examining the default network has revealed striking differences between MDDs and HCs. MDDs show increased default-network connectivity (compared with HCs) with the subgenual-cingulate cortex (a region located in the medial prefrontal cortex), which is positively correlated with the length of MDDs' current depressive episodes (Greicius et al., 2007). Other researchers have shown abnormalities in the subgenual cingulate for MDDs (Sheline et al., 2009 see Drevets, Price, and Furey, 2008 for a review), and this brain region has also been linked to poor emotional regulation (Abler, Hofer, and Viviani, 2008) and is activated more when healthy young adults were induced to ruminate (Kross et al., 2009). Moreover, stimulation of white matter tracts leading to the subgenual cingulate in MDDs has been associated with remission of depression concomitant with a decrease in hyperactivity of the subgenual-cingulate itself (Mayberg et al., 2005). It should not be surprising then to find differences between MDDs and HCs in the subgenual cingulate.

Even with all of this research, it is not clear what cognitive processes are reflected by these differences in default network connectivity (indeed, if they reflect them at all; Raichle, 2010) and more specifically with hyper-connectivity in the subgenual cingulate. Although some researchers have speculated that this hyper-connectivity reflects rumination (Greicius et al., 2007), no research has directly tested this hypothesis; so, the first goal of the present research was to test whether default-network connectivity, especially in the subgenual cingulate, is related to rumination.

A second goal of this research was to examine how differences between MDDs and HCs in default-network connectivity changed when participants were on-task versus off-task. In everyday life, people's attention wavers between tasks and unfocused thought

(Sayette, Reichle, & Schooler, 2009; Christoff et al., 2009). For example, the accountant at work may focus intensely on a balance sheet, but divert attention intermittently to thoughts unrelated to this task. In the present research, the relationship between default-state connectivity and rumination was examined using a situation that approximates such real-world conditions. The relationship between rumination and default-network connectivity was explored when participants performed a demanding short-term memory task interleaved with periods of rest. Alternating between rest and task epochs in this manner allowed us to explore whether default-network connectivity for MDDs and HCs varied between off-task and on-task periods. In addition, the relationships between self-report measures of rumination and default-network connectivity could then be compared for rest and task epochs separately.

In sum, this work was designed to examine whether measures of rumination predicted connectivity of the default state especially in the subgenual cingulate for depressed and healthy individuals, whether connectivity differences at rest persisted for on-task epochs, and whether the relationship between rumination and default-network connectivity varied for on-task and off-task periods.

Methods and Materials

Participants and Behavioral Measures

Default-network connectivity in 15 MDDs (10 female, 5 male, mean age = 25.7) and 15 HCs (10 female, 5 male, mean age = 23), was explored during non-task fixation periods at the beginning and end of each run of a short-term memory experiment

conducted in a functional magnetic resonance imaging environment. The short-term memory task was a variant of a directed forgetting task (Nee, Jonides, and Berman, 2007), in which participants were initially instructed to remember 4 words, and after a delay were instructed to forget half of the words and remember the other half. After another delay interval, participants saw a single word and responded yes or no if that word was one of the words in the to-be-remembered set. Sometimes the single words were words from the to-be-forgotten set, and the ability of MDDs and HCs to forget positively valenced vs. negatively valenced words was examined. A more detailed explanation of the task can be found in Chapter 3.

The Diagnosis of MDD was determined with a Structured Clinical Interview for the DSM-IV (SCID) by an advanced clinical psychology graduate student and was confirmed by a second independent rater. Behavioral rumination scores were measured with the Rumination Response Styles (RRS) inventory (Treynor, Gonzalez, & Nolen-Hoeksema, 2003), and depressive severity was also assessed with the Beck Depression Inventory II (BDI; Beck, Steer, & Brown, 1996). The RRS measured rumination subjectively with questions such as: "[How often do you] think 'What am I doing to deserve this?'" or "[How often do you] think 'Why do I always react this way?'" Participants responded with a 4-point scale ranging from 1-almost never, to 4-almost always. There were 22 items in total. The RRS can further be subdivided into 3 components: brooding, reflection and depression related items (Treynor, Gonzalez, and Nolen-Hoeksema, 2003). MDDs and HCs differed significantly on brooding, the full RRS, and the BDI, but no differences were found between the two groups on reflection

scores. These scores can be seen in Table 4-1. Six MDDs were medicated, and two MDDs had co-morbid anxiety[23].

[23] We did not find any differences between medicated and non-medicated MDDs in any rumination scores, BDI or neural connectivity.

Descriptive Statistics MDD = 1.00 HC = 0.00

		N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
						Lower Bound	Upper Bound		
Brooding	.00	15	7.4000	2.52982	.65320	5.9990	8.8010	5.00	14.00
	1.00	15	13.8000	3.85820	.99618	11.6634	15.9366	6.00	20.00
	Total	30	10.6000	4.56826	.83405	8.8942	12.3058	5.00	20.00
Reflection	.00	15	9.0667	3.57505	.92307	7.0869	11.0465	5.00	15.00
	1.00	15	11.2667	2.60403	.67236	9.8246	12.7087	8.00	17.00
	Total	30	10.1667	3.27038	.59709	8.9455	11.3878	5.00	17.00
Depression	.00	15	17.6667	5.12231	1.32258	14.8300	20.5033	13.00	28.00
	1.00	15	32.5333	7.07982	1.82800	28.6127	36.4540	18.00	42.00
	Total	30	25.1000	9.69660	1.77035	21.4792	28.7208	13.00	42.00
Full RRS	.00	15	34.1333	9.96327	2.57250	28.6159	39.6508	23.00	53.00
	1.00	15	57.6000	10.01285	2.58531	52.0551	63.1449	33.00	72.00
	Total	30	45.8667	15.45122	2.82099	40.0971	51.6362	23.00	72.00
BDI	.00	15	.8667	1.50555	.38873	.0329	1.7004	.00	4.00
	1.00	15	30.0000	8.81557	2.27617	25.1181	34.8819	8.00	40.00
	Total	30	15.4333	16.06599	2.93324	9.4342	21.4325	.00	40.00

Table 4-1: Descriptive Statistics for MDDs (1.00) and HCs (.00) for the different subjective measures including the Brooding, Reflection and Depressive Symptoms subscales of the RRS.

fMRI Parameters

Images were acquired on a GE Signa 3-T scanner equipped with a standard quadrature head coil. Functional T2* weighted images were acquired using a spiral sequence with 40 contiguous slices with 3.44×3.44×3 mm voxels (TR=2000 ms; TE=30 ms; flip angle=90°; FOV=22 mm^2). A T1-weighted gradient echo anatomical overlay was acquired using the same FOV and slices (TR=250 ms, TE=5.7 ms, flip angle=90°). Additionally, a 124-slice high-resolution T1-weighted anatomical image was collected using spoiled-gradient-recalled acquisition (SPGR) in steady-state imaging (TR=9 ms, TE=1.8 ms, flip angle=15°, FOV=25–26 mm, slice thickness=1.2 mm).

Each SPGR image was corrected for signal in-homogeneity and skull-stripped using FSL's Brain Extraction Tool (Smith et al., 2004). These images were then normalized with SPM5 (Wellcome Department of Cognitive Neurology, London), and normalization parameters were calculated from the standard MNI template. These parameters were then applied to the functional images maintaining their original 3.44×3.44×3mm resolution, and were spatially smoothed with a Gaussian kernel of 8×8×8mm. Functional images were slice-time corrected using a 4-point sinc-interpolation (Oppenheim, Schafer, & Buck, 1999) and were corrected for head movement using MCFLIRT (Jenkison et al., 2002). To reduce the impact of spike artifacts, AFNI's de-spiking algorithm was implemented. There were 16 TRs of Fixation, 8 at the beginning and end of each run, and 168 TRs of task (where participants performed a short-term memory task). There were 12 runs in the experiment.

Seed Analysis

Default-network connectivity was revealed by selecting a seed voxel in the Posterior- Cingulate Cortex (PCC), x = -7, y = -45, z = 24, and that voxel's time-course was correlated within-subjects for all voxels in the brain. This seed was selected anatomically and is similar in location to regions that other authors have used to define the default network (Greicius et al., 2003; Fox et al. 2005; Monk et al., 2009; Raichle, 2010). The posterior cingulate has been found to reveal connectivity in the default network most effectively (Monk et al., 2009) and is an area of greatest deactivation during off-task behavior (Shulman et al., 1997).

Default-network connectivity was calculated separately for fixation and task blocks in which participants performed a short-term memory task. Task and fixation epochs were low-pass filtered, de-trended to remove within-run drift in the fMRI signal (de-trending was performed separately for the beginning and end fixations and acts as a high-pass filter), and processed to have a mean of '0' and a standard deviation of '1' separately for each TR, which was done to control for global activation changes that may have occurred over time. These runs were then concatenated together, which may have biased the correlations positively, but this potential bias did not interact with group. Thus, there were 192 TRs of fixation/rest (6.4 minutes) and 2,016 TRs of task (Inter-Trial-Intervals were removed). While this may not be an ideal design due to the imbalance in number of TRs, the difference in the number of TRs for task and rest should not interact with group, which is of main interest in this study (i.e., comparing MDDs vs. HCs during rest, during task, and the difference between rest and task epochs). Correlation coefficients were converted to z-scores and entered into our two-sample t-

tests in SPM 5. Results were thresholded at $p < 0.001$ (uncorrected) at the voxel-level and corrected by using a cluster-size threshold of 26 voxels to produce a $p < 0.05$ (corrected) threshold (Forman et al., 1995).

Results

As depicted in Figure 4-1A, both groups showed high connectivity in the default network during fixation periods. A two-sample t-test comparing the default networks for MDDs vs. HCs revealed that MDDs had stronger connectivity with the subgenual cingulate than HCs (Figure 1B) at standard statistical thresholds. At more liberal thresholds, MDDs show more connectivity in other areas as well, which can be seen visually in Figure 4-1A. To explore how rumination scores may relate to connectivity between the subgenual cingulate and the posterior cingulate, a functional ROI of the subgenual cingulate was created based on the two-sample t-test. Rumination scores (from the RRS) were then correlated with connectivity in this functionally defined region of interest (ROI) across all participants, which revealed a very high positive relationship ($r = .68$; $p < .001$) that can be seen in Figure 4-2A. This relationship also held for both MDDs and HCs separately as exhibited in Figure 4-2B, though the correlations were, of course, smaller due to the lower sample sizes and the reduced range of the RRS measure ($r = .30$ for MDDs, $r = .23$ for HCs).

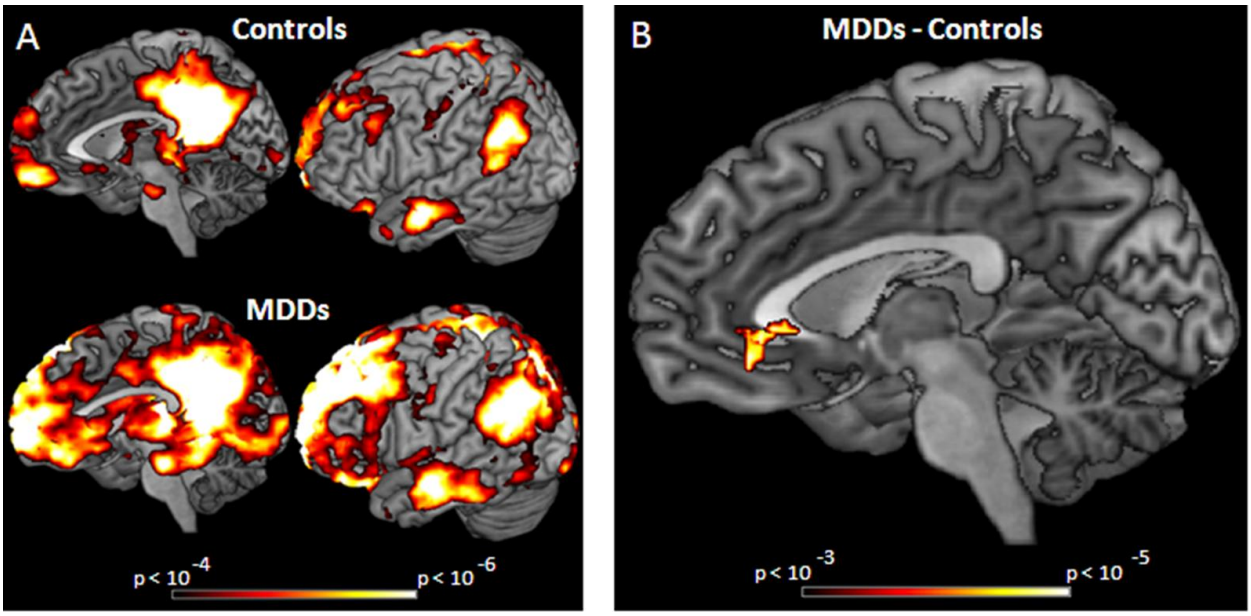

Figure 4-1: Default-Network connectivity for MDDs and HCs during fixation periods defined by connectivity with posterior-cingulate cortex , x = -7, y = -45, z = 24. Correlations above .25 ($p < .001$) are displayed (A). Results of a two-sample t-test comparing MDDs' and HCs' default-network connectivity during fixation periods. MDDs show more connectivity in the subgenual-cingulate compared to HCs ($p < 0.05$ corrected; peak at x = 0, y = 38, z = -9; 46 voxels) (B).

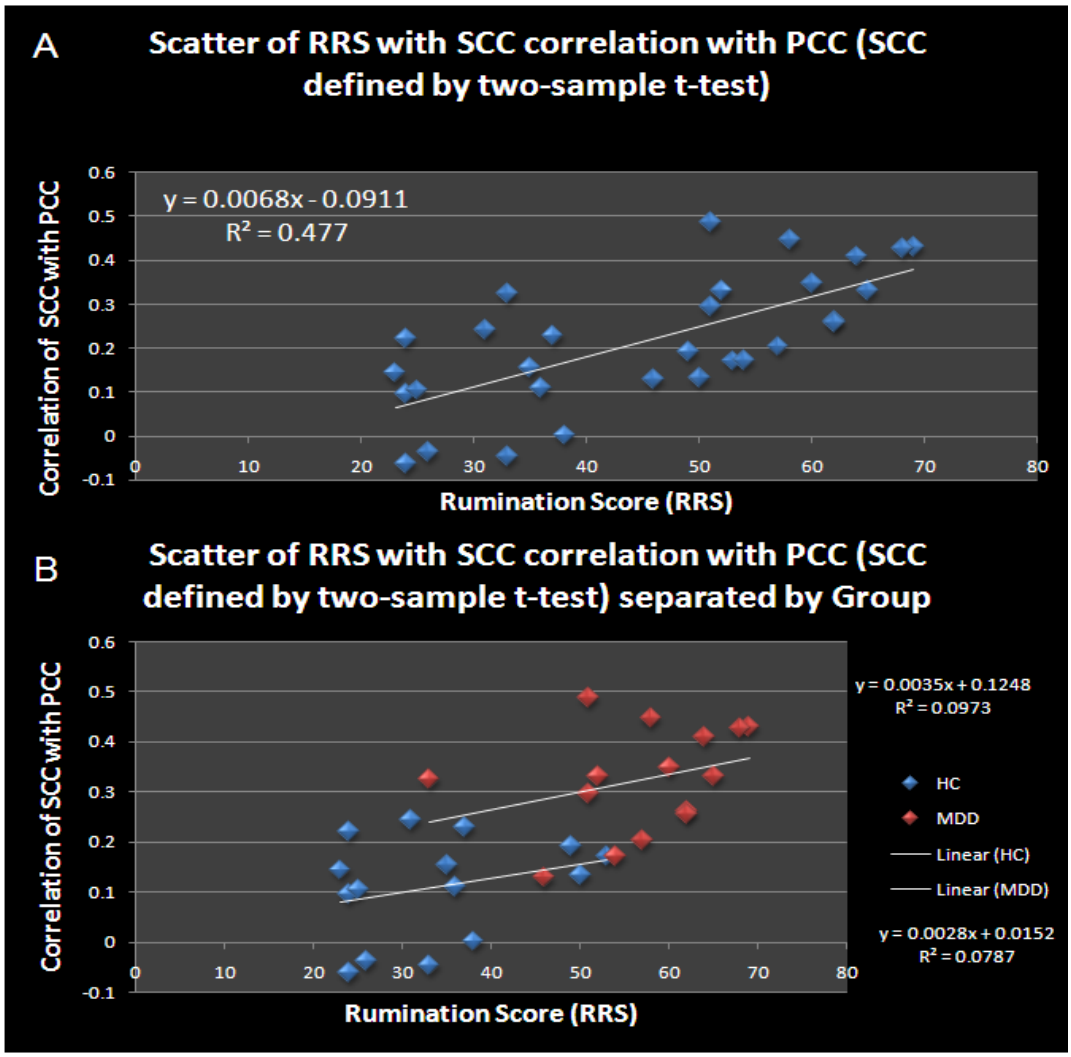

Figure 4-2: Correlations drawn from the resulting subgenual-cingulate ROI from the two-sample t-test comparing the groups at rest. Subgenual-cingulate (SCC)/posterior-cingulate (PCC) connectivity correlates positively with subjective rumination scores across groups (r = .68, 95% C.I. r = .44 - .85) (A). Correlations drawn from the resulting subgenual-cingulate ROI from the two-sample t-test comparing the groups at rest. SCC/PCC connectivity correlates positively with subjective rumination scores for both MDDs and HCs. The linear relationship equation is shown in the upper right for MDDs, and lower right for HCs (B).

The functionally defined ROI that was used may be biased in that it was based on connectivity that was greater for MDDs, which may inflate the relationship between

rumination scores and connectivity in that MDDs have reliably higher RRS scores. Therefore, a 10 mm sphere centered on subgenual-cingulate coordinates (x = 6, y = 36, z = -4) was constructed from an independent study (Zahn, et al., 2009) and connectivity scores were extracted within this ROI. These connectivity scores were then correlated with RRS scores across all participants. Again, a reliable correlation ($r = .53$, $p < .005$; Table 1) was found suggesting that default network connectivity with the subgenual cingulate is related to ruminative tendencies. The correlation between RRS scores and connectivity was not driven by a main effect of group (i.e., the relationship between RRS and PCC-SCC correlations seems to be a continuous positive trend as it was for the functionally defined ROI from the two-sample t-test). In addition, the relationship between rumination and connectivity did not reliably differ between groups, $Z(30) = 1.46$, n.s. This may not be too surprising in that HCs also ruminate; they just do so to a lesser extent, so the relationship between connectivity and rumination should be the same for MDDs and HCs. In sum, the relationship between rumination and connectivity appears to be a continuous effect and is not driven by a main effect of group.

Correlations for All Participants								
		Connectivity Rest	Brooding	Reflection	Depression	Full RRS	BDI	Connectivity Task
Connectivity Rest	Pearson R	1	.437*	.194	.554**	.518**	.557**	.562**
	Sig. (2-tail)		.016	.304	.002	.003	.001	.001
Brooding	Pearson R	.437*	1	.628**	.758**	.904**	.636**	.294
	Sig. (2-tail)	.016		.000	.000	.000	.000	.115
Reflection	Pearson R	.194	.628**	1	.429*	.666**	.302	.158
	Sig. (2-tail)	.304	.000		.018	.000	.105	.404
Depression	Pearson R	.554**	.758**	.429*	1	.943**	.864**	.362*
	Sig. (2-tail)	.002	.000	.018		.000	.000	.050
Full RRS	Pearson R	.518**	.904**	.666**	.943**	1	.794**	.347
	Sig. (2-tail)	.003	.000	.000	.000		.000	.060
BDI	Pearson R	.557**	.636**	.302	.864**	.794**	1	.391*
	Sig. (2-tail)	.001	.000	.105	.000	.000		.033
Connectivity Task	Pearson R	.562**	.294	.158	.362*	.347	.391*	1
	Sig. (2-tail)	.001	.115	.404	.050	.060	.033	
*. Correlation is significant at the 0.05 level (2-tailed).								
**. Correlation is significant at the 0.01 level (2-tailed).								

Table 4-2: Bivariate correlations for all participants for the subjective measures of rumination and depression and the brain connectivity scores during rest and task periods extracted using the ROI from (Zahn et al., 2009). Depression is the sub-scale of the RRS with the depression related items.

One problem with using the full RRS is that it contains items that assess depressive severity, therefore our rumination results may be driven by depression severity and not rumination. To control for this, connectivity scores from the ROI drawn from (Zahn et al., 2009) were correlated with the brooding component of the RRS, which does not contain items related to depression, yielding a significant positive correlation ($r = .44$, $p < .05$; Table 4-2). Unlike brooding, the reflection sub-component of the RRS did not correlate with connectivity scores ($r = .19$, n.s.; Table 4-2). Furthermore, when reflection scores were partialed out from the correlation between brooding and connectivity, the relation was unchanged, ($r = .41$, $p < .05$). By contrast, when brooding scores were partialed out from the correlation between reflection and connectivity, this relationship became mildly although not reliably negative ($r = -.12$, n.s.). These two partial correlations were also found to be reliably different from one another ($Z(30) = 2.04$, $p < .05$), which suggests that the correlation between PCC and SCC during rest periods is more related to negative forms of rumination than to other forms of continuous thinking or pondering.

These patterns of connectivity in the default network, however, were markedly different when participants were engaged in the memory task. A two-way ANOVA conducted on the subgenual-cingulate ROI from Zahn et al., (2009) was used to explore rest vs. task-related connectivity and revealed a significant task (rest vs. task) by group (MDD vs. HC) interaction ($F(1,28) = 4.27$, $p < .05$; Figure 3). Compared with rest, MDDs demonstrated significantly reduced connectivity while engaged in a task ($t(14) = 2.87$, $p < .05$). By contrast, HCs showed no reliable changes in connectivity for task

versus rest. Finally, during task epochs, MDDs and HCs did not differ in subgenual-cingulate connectivity, $t(28) = 1.47$, n.s., but did differ reliably for rest epochs as expected, $t(28) = 3.15$, $p < .005$. In addition, the correlation between rumination scores and connectivity between the PCC and SCC during task epochs was not reliable ($r = .347$, n.s.; Table 1) nor was task connectivity reliably correlated with brooding ($r = .294$, n.s.; Table 1), which suggests that being engaged in a task may disrupt the ability to ruminate by distracting participants and thereby interrupting the neural circuit that may mediate rumination.

The correlation of resting-state connectivity and task-related connectivity in the sub-genual cingulate was found to be reliably correlated for HCs ($r = .63$, $p < .05$), but was not reliably correlated for MDDs ($r = .38$, n.s.). While this interaction was not reliable (potentially due to a lack of power), these results suggest that the ruminative connectivity pattern is more dissimilar for task and rest for MDDs (they may be ruminating at rest, but may not be able to during task engagement) than HCs (they may be maintaining a similar degree of rumination or mind-wandering throughout) whose connectivity patterns remain similar for both task and rest epochs.

Anand et al. (2007) found some differences in connectivity between the anterior cingulate cortex (ACC) and limbic areas after MDDs had been on medication for 6 weeks. Six of our MDDs were medicated, thus posterior-cingulate to subgenual-cingulate connectivities were compared for our medicated and un-medicated groups for both task, fixation, and the interaction between the two for both the independent Zahn et al. (2009) ROI and the ROI that resulted from our two-sample t-test. No differences in

connectivity between the medicated and non-medicated participants were found, which mitigates some concerns that our results may vary based on medication status.

Another analysis was performed to interrogate whether our results may be specific to the posterior cingulate cortex as the seed to define connectivity. The other common seed region that is used to define default mode networks is the medial Pre-Frontal Cortex (mPFC; Fox et al., 2005, Greicius et al., 2003). Utilizing mPFC coordinates from Fox et al.,(2005) for the mPFC (x = -1, y = 47, z = -4), default network connectivity during fixation was calculated with this mPFC seed utilizing the same procedure that was implemented with the posterior cingulate seed. When the two groups' connectivity maps were compared at standard whole brain thresholds, no differences were found. However, when an ROI analysis was performed within the posterior cingulate cortex, two clusters were discovered in which MDDs showed more connectivity in this area at corrected thresholds FWE < .05 ($p < .05$ for 8 contiguous voxels; 22 voxels centered at -10, -45, 24 and 11 voxels at 17, -58,3; there were 455 voxels total in this ROI). This analysis shows that a similar pattern of results is found using the mPFC as the seed, however, it is not clear whether the same result should be expected with the mPFC as the seed vs. the posterior cingulate.

In addition, Bar (2009) proposes that rumination may be due to the mPFC exhibiting hyper-inhibition of the medial temporal lobe (MTL), which would constrain thinking and therefore produce rumination. A second ROI analysis was performed within the MTL (consisting of the hippocampus, para-hippocampus and the amygdala). Again, MDDs showed more connectivity in this area at corrected thresholds FWE < .05 ($p < .05$ for 8 contiguous voxels; 20 voxels in the left amygdala centered at -24, 7, -18; 29 voxels

in the left para-hippocampal gyrus centered at -14, -41, 0; 17 voxels in the right amygdala centered at 14, -3, -21; and 18 voxels in the right hippocampus/parahippocampal gyrus centered at 31, -24, -18; there were 978 voxels total in this ROI). This analysis seems consistent with the Bar (2009) hypothesis that hyper-connectivity (that may be due to hyper-inhibition) between the mPFC and MTL may lead to increased rumination.

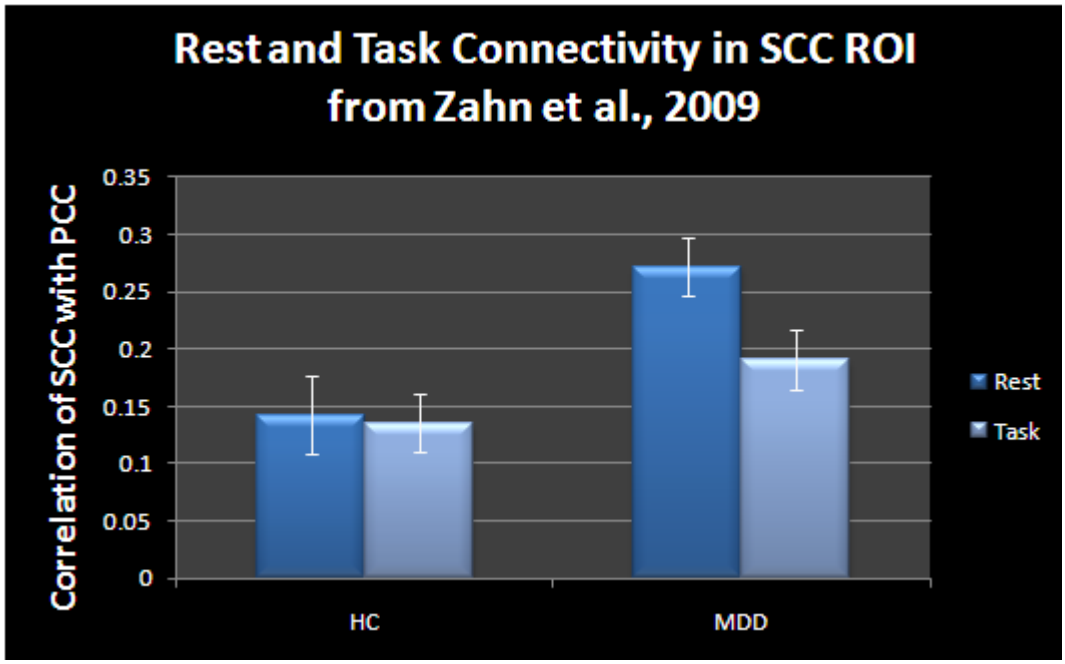

Figure 4-3: The subgenual-cingulate ROI as defined from (Zahn et al., 2009) demonstrates a task (rest, task) x group (MDD, HC) interaction highlighting a selective difference during periods of quiescence. No differences were found between groups for task epochs.

In summary, these data show that the degree of correlation between the posterior cingulate and the subgenual cingulate is related to rumination and may distinguish MDDs from HCs, but *only* during off-task periods. Furthermore, the relationship between rumination and connectivity exists *only* during off-task periods. Lastly, brooding scores

correlated with off-task connectivity, but reflection scores did not, which suggests that the thought contents during these off-task periods were negative and not entirely driven by depression severity. Therefore, it seems important to explore the relationship between rest and task connectivity when comparing MDDs and HCs.

Discussion

Neural hyper-connectivity with the subgenual-cingulate seems to exist only during off-task periods for MDDs, and the connectivity of this area with the posterior cingulate is highly related to behavioral assays of depressive rumination. These results build on connectivity differences found in the subgenual cingulate by relating connectivity in that area to psychological processes such as rumination and brooding. These results also showed that hyper-connectivity at rest existed when rest periods were joined with task periods, a finding that may have implications for depression in the wild. Lastly, these results showed the selectivity of these neural differences (between MDDs and HCs) to off-task periods and that the relationship between ruminative psychological processes and connectivity is mitigated by engaging in a task.

The fact that hyper-connectivity in the subgenual cingulate for MDDs was found only during rest or off-task periods supports behavioral research suggesting that "distraction"(in our case, responsibility for completing a task) can be effective at temporarily relieving rumination and improving mood (Kross and Ayduk, 2008, for a review see Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008). When MDDs engaged in the memory task, they displayed attenuated levels of connectivity in rumination-related

regions. However, when left to their own thoughts, ruminative processes were engaged. This finding has important implications for future neuroimaging research and theory-building about the cognitive neuroscience of depression.

Additionally, when the mPFC was used as a seed, some similar results were found. It is noteworthy that differences in the MTL were found, where MDDs showed greater connectivity, which could reflect constrained thinking, which Bar outlines as a mechanism of rumination. More work will be needed to flesh out the relationship between rumination and constrained thought processing and their relation to the neural connectivity, but it seems to be a promising enterprise that could lead to some important therapies.

Some researchers may try to parcel out depression status from rumination, but this can be quite challenging considering that depression and rumination are highly overlapping constructs. This is evidenced by the high correlation found between rumination scores and BDI scores $r = .79$. As such, an alternative explanation of our findings is that the connectivity between the posterior cingulate and the subgenual cingulate reflects depression severity more than rumination. While separating depression from rumination is not easily done, brooding scores (which do not contain depression-related items) correlated positively and reliably with connectivity, which suggests that this relationship is not driven by depression severity alone. Furthermore, reflection scores did not relate to connectivity scores, which indicate that this network does not signal positive thought patterns in our sample. In sum, depression severity does relate strongly to the connectivity between the subgenual cingulate and the posterior cingulate,

but it may do so because of the tight coupling between rumination and depression as they are highly overlapping constructs.

The measure of rumination that was used in our study was a trait measure, namely how much people ruminate in their daily lives. However, it seems reasonable that this trait level measure would predict state rumination. First, as stated above, our correlations between brooding and connectivity scores during rest are greater than the correlations between reflection scores and connectivity during rest, thus providing some evidence that the thinking going on during these rest periods is probably not constructive. Second, partialing out reflection scores did not affect the correlation between brooding and connectivity during rest, indicating that other forms of thinking seem not to be explaining these data. It would have been difficult for us to ask participants what they were doing during these rest breaks post-hoc, because it would have been difficult for participants to remember the thoughts they were having after the fact. Participants could have been prompted with rumination questions throughout the rest periods, but then the rest periods would not be as unguided. Since our rest periods were unguided (i.e., participants were not induced to ruminate) and interspersed with task epochs, some ecological validity may have been gained, since participants in the real world are not prompted to ruminate, but do so spontaneously.

As a more general point, our data suggest that studying on-task behavior may mitigate some differences between MDDs and HCs in that engaging in a task may disrupt rumination. Our data showed that the hyper-connectivities that were found at rest disappeared during the task, and the relationship between trait rumination and connectivity was also eliminated when performing a task. If rumination is a critical

component of depression, then studying it may require moving to more unguided types of paradigms. This idea is consistent with Raichle's (2010) suggestion of studying the resting state in both health and disease rather than focus solely on reflexive or "on-task" performance.

Importantly, our results build on the results of Greicius et al., (2007) as MDDs demonstrate increased default network connectivity with the subgenual cingulate that can be linked to rumination, but only during unguided rest-periods. Based on these results, ruminative behavioral and psychological processes can be ascribed to these neural differences linking brain and behavior. In sum, subgenual-cingulate hyper-connectivity in MDDs was restricted to periods of quiescence and may provide a neural mechanism of rumination/brooding, a destructive form of mind-wandering.

Acknowledgments

This work was supported in part by grant MH 60655 grant to J.J., and an NSF graduate fellowship to M.G.B. We thank Courtney Behnke, Melynda Casement, and Hyang Sook Kim for help with data collection. This work was conducted in collaboration with Scott Peltier, Derek Evan Nee, Ethan Kross, Patricia Deldin and John Jonides.

Chapter 5

Conclusion

"*Man can alter his life by altering his thinking*." William James

This dissertation has explored the role of interference in short-term memory and its relationship to major depressive disorder. In Chapter 2 it was shown that interference is a major cause of forgetting in short-term memory as stimuli from one trial back seemingly overwrote memory traces from stimuli two trials back. This retroactive interference (which mitigated proactive interference from the 2-back memory set) swamped the effect of decay with the mere passage of time. This series of experiments reinforced the powerful role that interference plays in short-term memory, specifically in forgetting.

In Chapter 3 basic paradigms aimed to explore interference resolution in short-term memory were applied to depression. Utilizing a variant of the directed-forgetting task with valenced materials, it was found that people suffering from major depression had more difficulty resolving interference from negatively valenced material and that this inability was related to the propensity that one has to ruminate about negative life events. These results show that the inability to remove negative information from short-term memory (i.e., the inability to resolve interference from negative information in short-term

memory) may underlie ruminative processing. While the neural networks supporting interference resolution for both groups were quite similar, MDDs showed more spatial variance in LiFG, a region critical for interference resolution, and the amount of variance was related to the amount of difficulty in suppressing negative information in short-term memory. What is not clear at this point is whether such increased noise levels reflect a noisy interference resolution system, or more task-unrelated thoughts associated with having negative information in mind. Future research will be required to parse out this important distinction.

Chapter 4 presented a very different approach to studying depression. Most researchers focus on reflexive and task oriented behavior to understand psychological processing, but as Raichle (2010) pointed out in his recent review, much of what the brain does may be more intrinsic and not necessarily affected by engaging in cognitive tasks. This intrinsic activity has been termed the default mode network (Raichle, 2010). Others have found differences between MDDs and HCs in the default mode network (Greicius et al., 2007), however, it has not been shown how these neural differences relate to psychological variables. The results presented in Chapter 4 show that more default network connectivity, specifically in the subgenual cingulate, is related to more rumination, a psychological variable. In addition, this rumination was negative in valence as more positive forms of thinking, such as reflection, did not correlate with these off-task connectivities. Interestingly, these differences between MDDs and HCs disappeared when participants were engaged in a task, just like the relationship between rumination and default network connectivity. Taken together these results suggest that studying depression may require researchers to explore off-task or unguided behavior, in

addition to on-task behavior, because one's task of interest may distract MDDs from the very activity that may underlie their depression, namely rumination.

The relationship between Chapter 4 and Chapters 2 and 3 becomes stronger when one conceptualizes rumination as an internally generated form of interference. For example, if one has just been rejected in a romantic relationship, thinking about that relationship creates a form of interference that makes it difficult to work and concentrate. As was shown in Chapter 4 engaging in a task seemed to distract MDD participants and prevent the default network from being as engaged. However, we know that such distraction only temporarily alleviates negative moods (Kross & Ayduk, 2008) and therefore is not a long-term solution.

This, however, relates to the James quote above that "man can alter his life by altering his thinking." What Kross & Ayduk (2008) found to be effective in alleviating negative moods that were induced by recalling negative life events was not to distract oneself, but to think about such events from a distanced or third party perspective. Such an approach is not escapist in nature, but rather confronts problems, but in a way that removes a lot of the distortions that may accompany rumination when one attributes negative life events to one's intrinsic character. In some sense, this is the basic approach of Cognitive Behavioral Therapy (CBT) where psychologists help clients restructure their thoughts and their thought patterns, thus changing their lives by changing their thinking. While, James is correct in thinking that altering thinking can alter lives, it is a process that is easier said than done. How might we inspire people to change their thinking?

It has been found that interacting with nature can have profound impacts on cognitive functioning and self-regulation performance (Kaplan & Berman, 2010). Interacting with nature has been shown to increase attention and short-term memory capacity (Berman, Jonides & Kaplan, 2008), reduce the incidence of aggression and crime (Kuo & Sullivan 2001a&b), improve health outcomes for breast cancer patients (Cimprich & Ronis, 2003) and reduce attentional problems in children (Taylor & Kuo, 2009). It seems that interacting with nature has a broad and diverse impact on a wide range of problems. Therefore, in future research we hope to explore how interacting with nature might aid people suffering from depression, under the hypothesis that interacting with nature may promote distanced strategies when thinking about negative life events. Such an intervention may provide people the resources and strategies to resolve internally generated forms of interference created by rumination that time alone may not heal.

While there may be some ways to reduce the effects of rumination and the interference that results from such rumination, there is another question that is worth exploring and that is the nature of the mechanism of interference. Namely, what is causing interference? This is an important question to answer in order to understand more mechanistically how interference works. While there are many potential mechanisms of interference, only a few will be focused upon here. For example, might interference be the result of a faulty inhibitory system, where neural activation that represents interfering thoughts in mind cannot be dampened down by inhibitory control. In this case lateral inhibition or maybe even more forms of global inhibition are not operating strong enough to dampen neural activity that represents interfering thoughts or memories. Another mechanism of interference may have to do with resource

competition. While our brains contain a seemingly infinite number of neurons, we know that the number is actually around 10-100 billion. Therefore, we have a limited number of neural resources to represent our current thoughts and actions. If superfluous information is in mind, that information will be represented by some set of neurons, which may limit the number of neural resources that are available to focus on the things that are task relevant. There is yet another way to frame resource competition and that is with respect to broader attentional mechanisms. As Kaplan & Berman (2010) discussed directed attention may be a resource common to many cognitive and self-regulatory behaviors. If some attentional resources are devoted to interfering information, than there will be less directed attention resources available to help maintain current items in the focus of attention. Whether interference is the result of inefficient inhibition, resource limitations or both, is certainly an important area of future research, which would help in the design of systems and interventions aimed to mitigate the negative impacts of interference on current task performance.

Lastly, all of the work presented in this dissertation, along with the work we have done looking at the impact of nature on cognitive functioning have implications for broader environmental and system design. In showing how powerful interference is to causing forgetting in short-term memory, it seems important to consider how we might design work and school environments that would limit interference. One problem is that many school and work environments are actually incorporating more interference into the environment rather than trying to mitigate it. For example, many school and work settings have TV or video displays that may actually produce interference in memory. In addition, in designing school or work curriculums more emphasis is placed on

incorporating more information into daily practices, which may actually have counterproductive effects, but producing more interference rather than increasing knowledge. It could be that for many of these situations, less is more. It seems that providing environmental supports to help limit or mitigate interference would provide individuals with more cognitive resources. In addition, while it was shown that MDDs ruminate more than HCs, thereby creating more internal interference, HCs ruminate as well. If we could design workplace settings and schools that helped to mitigate rumination, we may be able to improve overall health and productivity for many individuals. Natural environments may be one such design possibility.

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