The role of the dorsolateral prefrontal cortex in self-initiating elaborative episodic encoding: Evidence from fMRI and TMS

Colin S. Hawco

Integrated Program in Neuroscience

McGill University, Montreal

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Dedication

I'd like to dedicate this Thesis to my wife Alexia, who has made more sacrifices for my career than I ever did. Thanks Sweetie!

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Abstract

Several clinical populations (e.g. Schizophrenia, Alzheimer's disease, frontal lobe damage, and healthy aging with memory decline) display memory deficits which may be related to a failure to engage efficient memory encoding strategies. However, these groups often show improved memory performance when cued towards the use of efficient encoding strategies, suggesting the deficits are related to self-initiating elaborative encoding processes. At present, little is know about the neural correlates of self-initiating elaborative encoding strategies in episodic memory. The purpose of this thesis was to better understand the process of initiating elaborative encoding strategies. We hypothesized that the left dorsolateral prefrontal cortex (DLPFC) was involved in self-initiating elaborative encoding strategies. Experiment 1 was an fMRI study in which we presented conditions in which participants were either cued to use an efficient encoding strategy (semantic analysis) or were not cued to do so (a self-initiated condition), while presenting stimuli with variable semantic relatedness. We observed activity in the left DLPFC and bilateral supramarginal gyrus in response to semantic relatedness in the non-semantic (self-initiated) encoding condition. In experiment 2, we attempted to confirm the role of the left DLPFC in self-initiating elaborative encoding using transcranial magnetic stimulation (TMS), a method in which we can transiently disrupt neural activity in a limited cortical area. We performed stimulation of the left DLPFC and a control site (the vertex) during a memory encoding task. We observed a significant correlation in a subsequent cued recall task (a measure of encoding success) between the effects of TMS during encoding and participant's use of memory strategies during encoding only in the condition in which self-initiated elaborative encoding was beneficial to memory performance. This suggests a causative role for the DLPFC in self-initiating elaborative encoding. Experiment 3 was a concurrent TMS-fMRI study.

Participants performed an encoding task (similar to the self-initiated condition in experiment 1) while we measured brain activity using fMRI. TMS stimulation was presented for 300ms on ¾ of trials. The onset of stimulation was varied, starting at 200ms, 600ms, or 1000ms after stimulus onset. We observed time-specific changes in neural activity in response to TMS stimulation, suggesting that concurrent TMS-fMRI can be used to measure time-varying interactions between the DLPFC and distal brain regions These three experiment provide evidence o f the role of the left DLPFC in self-initiating elaborative encoding strategies, and the utility of TMS and fMRI (separately or combined) as research techniques to address these techniques. These studies also demonstrate the utility of our selected paradigms to directly address the issue of self-initiating elaborative encoding (rather than correlating activity to specific encoding strategies).

Résumé

Plusieurs populations cliniques (ex. schizophrénie, maladie d'Alzheimer, lésions du lobe frontal, vieillissement normal avec déclin de mémoire) démontrent des déficits de mémoire qui peuvent être reliés à une incapacité d'initier des stratégies efficaces d'encodage de mémoire. Cependant, ces groupes démontrent souvent une amélioration de leur performance lorsqu'on les aide à choisir une stratégie d'encodage efficace, suggérant que les déficits seraient reliés à l'utilisation spontanée de stratégies d'encodage élaborées. A ce jour, nous savons très peu de choses à propos des corrélats neuronaux de l'utilisation spontanée de stratégies d'encodage élaborées. Le but de cette thèse est de mieux comprendre les processus de l'initiation de stratégies d'encodage élaborées. Nous émettons l'hypothèse que le cortex préfrontal dorsolatéral (DLPFC) est impliqué dans l'utilisation spontanée de stratégies d'encodage élaborées. L'expérience 1 consiste en une étude d'IRMf dans laquelle nous avons présenté des conditions dans lesquelles les participants étaient guidés à utiliser une stratégie d'encodage efficace (analyse sémantique) ou non guidés d'utiliser cette stratégie (condition auto-initiée), en présentant des stimuli de relations sémantiques variées. Nous avons observé une activité dans le DLPFC gauche et le gyrus supramarginal bilatéral en réponse à la relation sémantique dans la condition d'encodage non-sémantique (auto-initiée). Dans l'expérience 2, nous avons tenté de confirmer le rôle du DLPFC gauche dans l'utilisation spontanée de stratégies d'encodage élaborées en utilisant la stimulation magnétique transcrânienne (SMT), une méthode avec laquelle nous pouvons perturber l'activité neuronale de façon transitoire dans une aire corticale limitée. Nous avons performé une stimulation du DLPFC gauche et d'un site contrôle (le vertex) durant une tâche d'encodage de mémoire. Nous avons observé une corrélation significative dans la tâche de reconnaissance subséquente (une mesure de la réussite de l'encodage) entre les effets de la SMT

durant l’encodage et l’utilisation de stratégies de mémoire du participant pendant l’encodage seulement dans la condition où l’utilisation spontanée de stratégies d'encodage élaborées était bénéfique pour la performance de mémoire. Ceci suggère un rôle causal du DLPFC dans l’utilisation spontanée de stratégies d'encodage élaborées. L’expérience 3 était une étude simultanée de SMT-IRMf. Les participants devaient faire une tâche d’encodage (similaire à la condition auto-initiée de l’expérience 1) pendant que l’on mesurait l’activité du cerveau avec l’IRMf. Une SMT était faite pendant 300ms sur les trois-quarts des essais. Le début de la stimulation était varié, commençant à 200ms, 600ms ou 1000ms après le début du stimulus. Nous avons observé des changements spécifiques au temps dans l’activité neuronale en réponse à la stimulation SMT, indiquant que l’utilisation simultanée de SMT-IRMf peut être utilisée pour mesurer l’interaction en fonction du temps entre le DLPFC et les régions distales du cerveau. Ces trois expériences apportent des évidences du rôle du DLPFC gauche dans l’utilisation spontanée de stratégies d'encodage élaborées et l’utilité de la SMT et de l’IRMf (séparément ou combinées) comme techniques de recherche pour étudier ces processus. Ces études démontrent aussi l’utilité de nos paradigmes pour étudier directement l’utilisation spontanée de stratégies d'encodage élaborées (au lieu de corréler l’activité à des stratégies d’encodage spécifique).

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Chapter 1: Introduction

1.1 Early Research on Memory

Research on memory has gone through a number of phases over the last century or more, with theories of memory becoming ever more complex as our knowledge and understanding of memory processes evolves. In early conceptions of memory, it was often thought of as a unified, singular process of 'remembering', without a necessarily clear definition of what was meant by memory or remembering. Alternately, when distinctions between memory sub-types were considered, it was often a simple dichotomy between two types of memory. It wasn't until after examination of the severely amnesiac patient HM (Scoville & Milner, 1957) that researchers really began to understand memory as not a unified process, but instead as a series of distinct cognitive and neural processes.

A model separating memory into multiple sub-systems was proposed by Squire (1987). In this taxonomy, memory was divided into two main types, declarative and non-declarative. Non-declarative memory referred to unconscious, automatic memory systems, such as procedural memory, priming, and classical conditioning. Declarative memory referred to the more colloquial idea of memory as conscious recollection of fact and events. Declarative memory was sub-divided into two distinct sub-systems according to the proposals of Tulving (1983). Semantic memory refers to memory for facts, without the necessity of actual recollection of the context in which those facts were learned. Episodic memory, in contrast, was thought of as the recollection of events from our past, and the ability to 're-experience' those events through remembering.

Significant gains in the research of memory processes have occurred over the past 20 years, especially with regards to the neurological processes underlying episodic memory. Specifically, the advent of functional neuroimaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) has resulted in a revolution in memory research. Early studies noted that in addition to the well established role of the medial temporal lobes in memory processes, activation was consistently found in the frontal lobes. This lead to the proposal of the hemispheric encoding-retrieval asymmetry (HERA) model (Tulving, Kapur, Craik, Moscovitch, & Houle, 1994) which proposed that encoding was lateralized to the left prefrontal cortex (PFC) while memory retrieval was related to the right PFC. While the role of medial temporal lobe structures in memory has been reasonably well established, the role of areas in the prefrontal cortex, particularly the dorsolateral prefrontal cortex (DLPFC) and the ventrolateral prefrontal cortex (VLPFC), is less well understood. The role of areas within the PFC has become an active and interesting area of debate within long-term memory research.

1.2 DLPFC and VLPFC in Item and Associative Memory during Encoding

One commonly used contrast in neuroimaging studies of episodic long-term memory is the subsequent memory effect (SME; Paller & Wagner, 2002). In an SME study, participants engage in a scanned encoding task, followed by a recognition task typically performed outside the scanner. Trials in which participants perform correctly on the recognition test (i.e. trials which are remembered) are contrasted with trials which were forgotten (as judged by the participant's response on the recognition test). This allows an examination of neural activity that is related to successfully encoded trials compared to trials which were not successfully encoded.

Neuroimaging studies of item memory have often found a subsequent memory effect in

the VLPFC for remembered items (Blumenfeld & Ranganath, 2007; Paller & Wagner, 2002). In contrast, DLPFC activity has not been consistently shown in neuroimaging studies of subsequent item memory, and a few studies have even suggested that DLPFC activity may be increased in items that are forgotten (Daselaar, Prince, & Cabeza, 2004; Otten & Rugg, 2001; Wagner & Davachi, 2001). The VLPFC has been suggested to be involved in the selection of goal-related detailed information in working memory, therefore promoting LTM for this information.

Studies examining associative memory haven painted a different picture of DLPFC activity. Many early neuroimaging studies examining associative and item memory have compared trials with single items (for item encoding) to trials with pairs of items (for associative encoding). To more directly compare associative and item memory with equivalent experimental conditions, Achim & Lepage (2005) presented pairs of images, along with either an item or associational encoding task. They found increased activity in both the DLPFC and VLPFC during encoding of associations over items (though note that this was not an SME analysis).

Blumenfeld & Ranganath (2006) had participants perform a working memory task, in which triplets of words were either reorganized (promoting encoding of the relationships for those words), or rehearsed. In a subsequent test of LTM, DLPFC activity was only associated with subsequent memory for triplets in the associational task. To test the hypothesis that the DLPFC was important for forming inter-item associations, Murray & Ranganath (2007) compared item and associative memory in an SME paradigm. Participants were shown sequentially paired words, with the second word involving either an item or associative memory task (related to the first word). When examining activity to the second word in the pair, they found greater DLPFC activity for confidently remembered associations between the first and second word. Activity in the VLPFC was observed both for remembered associations between

items and memory for the items themselves. Of note, the DLPFC was still active for associations (and items) which were forgotten or remembered with low confidence, suggesting the DLPFC is still active even during poor encoding.

In a test comparing free recall to recognition memory, Staresina & Davachi (2006) had participants make plausibility judgments about concrete words, and a color (such as the color yellow, and the word elephant). They found free-recall specific effects in the DLPFC, which were not related to associative memory. They suggest higher level working memory processing in the DLPFC during encoding may embed the items within a richer associative network, facilitating later recall.

Activity in the PFC during associative encoding is often observed along with MTL activations. To further examine the roles and relationship in PFC and MTL activity, Hales, Israel, Swann, & Brewer (2009) examined associative binding of sequentially images. Participants were presented a sequence of image, which in some cases was followed by a plus sign. This indicated they should associate that image with the following images. They found greater activity in the DLPC and VLPFC, as well as the parahippocampal cortex, for second items that were associated with the previous items as opposed to second items that were not. Interestingly, when they examined the delay between images, prolonged activity was observed in the DLPFC, but not the VLPFC or MTL, when the associative instruction was given. This suggests that the DLPFC plays a specific role in maintaining items and/or instructions in memory for later associative binding.

When considering activity in the VLPFC and DLPFC during item and associative encoding, it is important to consider that associative tasks tend to require higher levels of executive control or elaborative encoding relative to item encoding tasks. Thus, increased activity in the DLPFC during associative memory could be attributed to more elaborative

encoding, as opposed to forming associations. Blumenfeld, Parks, Yonelinas, & Ranganath (2011) examined this issue with a task comparing relational item-specific information, using tasks that required effortful, elaborative encoding. Activity in the DLPFC was only correlated with successful associative encoding (and not item encoding), while the VLPFC was more active for both successful item and successful associative encoding. This further strengthens the argument that the DLPFC plays a specific role in forming relationships between items.

1.3 Frontal Lobe Functions in Memory: Evidence from Neuropsychology

Patients with frontal lobe lesions have long been observed to show subtle memory deficits, but do not show the profound amnesia observed after bilateral hippocampal lesions. Patients with frontal lobe lesions have been observed to show deficits on tests of free recall (Dimitrov et al., 1999; Jetter, Poser, Freeman, & Markowitsch, 1986; McAndrews & Milner, 1991; Moscovitch & Winocur, 1995a; Stuss et al., 1994) , while recognition memory has been reported to be relatively preserved (Janowsky, Shimamura, Kritchevsky, & Squire, 1989; Jetter et al., 1986). Patients with PFC damage have also been shown to have impairments in source memory (Janowsky, Shimamura, & Squire, 1989), memory for the temporal order of events (Milner, Petrides, & Smith, 1985; Shimamura, Janowsky, & Squire, 1990), and associative learning (Dimitrov et al., 1999).

Perhaps more striking than the presence of memory deficits in patients with prefrontal damage is the behavioral pattern observed when these patients are given memory tasks. Healthy controls will, when possible, categorize items to be remembered by semantic relationships. Patients with PFC lesions tend to not do this, even though it is an effective memory organizational strategy (Gershberg & Shimamura, 1995; Hirst & Volpe, 1988; Incisa della Rocchetta & Milner, 1993; Stuss et al., 1994). However, patients are capable of categorizing lists

when instructed to do so (Hirst & Volpe, 1988), and show an improvement in memory performance (Gershberg & Shimamura, 1995; Incisa della Rocchetta & Milner, 1993). Healthy controls, in contrast, do not show a memory improvement when specifically instructed to use categorization cues, as they by default will use such cues automatically.

Evidence indicates that this lack of spontaneous use of categorization among patients is not reflective of a deficit within the process of categorization, or forming semantic relationships, but instead reflects an inability to self-initiate the use of this effective cognitive strategy. For example, Hirst & Volpe (1988) presented patients and controls with 20 index cards on a table, with each card belonging to one of four categories. Patients were told that they could rearrange the cards to help them remember them (without any suggestions as to how to rearrange them), or specifically told to rearrange the words into semantic categories. Healthy controls rearranged the words into categories regardless of instruction, while patients only rearranged the cards into categories when explicitly instructed to do so. More interestingly, patients showed improved memory performance when specifically instructed to rearrange the cards into semantic categories (while controls showed no difference across these conditions), demonstrating that patients could both perform the semantic categorization, and benefited from doing so. The results of this study, and others (Gershberg & Shimamura, 1995; Incisa della Rocchetta & Milner, 1993) suggest that much of the memory deficit in patients with frontal lobe damage is due to a deficit in the spontaneous use of effective memory strategies, even though these patients are able to use these strategies if explicitly instructed to, and perform the cognitive operations required by such mnemonic operations (such as semantic clustering).

A few caveats are worth mentioning when considering the literature reviewed above. The first is that many of the deficits reported were greater in patients with lesions lateralized to the

left hemisphere. It is not clear if this is because the left PFC plays a particular important role in organizational memory strategies and control, or if it is because most studies examining this issue have used verbal materials (e.g. word lists). Also, there has been very little specification of what specific regions within the PFC may be involved in the memory impairments seen after frontal lobe damage, as many studies have used heterogeneous patients with lesions to various areas of the frontal lobes. However, Alexander, Stuss, & Fansabedian (2003) have suggested the most severe memory impairments are seen following damage to BA 46 and 9 (the DLPFC) and BA 44 (part of the VLPFC).

1.4 Effects of Different Memory Strategies during Encoding

In addition to different types of memory (and the neural systems underlying them), there may also be a tremendous impact on varying self-initiated cognitive strategies used during memory tasks. In most neuroimaging experiments, groups of participants are pooled together, and the 'average' activation is considered (as defined, for example, by significant BOLD activity observed in the group analysis). A random effects analysis is a very powerful tool in that it enables researchers to generalize the observed patterns of activity to the general population being studied, but it does not provide any information about the variations in activity among individuals. Indeed, it is questionable how valuable a statistically significant group response is if only a subset of that group actually shows such a pattern of activation.

This issue may be particularly salient to memory research, as studies have shown that individuals can vary quite a bit in their use of different cognitive strategies (which should show different patterns of brain activation) when performing memory tasks (McDaniel & Kearney, 1984). For example, when examining verbal stimuli, some possible memory strategies include rote-repetition, binding the word into a semantic context (including categorization of words

within lists), building a sentence from the words, or mental imagery. Some strategies, such as sentence generation, are more effective than rote repetition (Dunlosky & Hertzog, 2001; Sibylle Heinze et al., 2006). Generally, the use of more elaborate and efficient encoding strategies has been linked to better memory performance (Camp & Maxwell, 1983; Hertzog, Dunlosky, & Brian, 2004).

Within neuroimaging, some studies have examined the effects of individual differences in brain activity during encoding and retrieval. Total volume of activated cortex has been found to be correlated with individuals subsequent memory performance during scene encoding (Machielsen, Rombouts, Barkhof, Scheltens, & Witter, 2000), and activity in specific brain areas (including the medial temporal lobes and the PFC) and have been correlated with individual's subsequent memory performance (Cahill et al., 1996; Canli, Zhao, Desmond, Glover, & Gabrieli, 1999; Casasanto et al., 2002). More recently, studies have begun examining differences in encoding strategies on brain activity. Savage et al. (2001) reported that regional cerebral blood flow within the right orbitofrontal cortex was positively correlated with semantic clustering scores. Frings et al. (2006) reported differences in left or right lateralized hippocampal activation according to whether participants used visual or verbal encoding strategies. Kirchhoff & Buckner (2006) presented pairs of objects interacting in some way (such as a banana in the back of a dump-truck), and instructed participants to memorize the images. They then conducted a memory test, as well as asking participants to rate their use of various methods of encoding. They found that verbal elaboration and visual imagery were related to subsequent memory performance, and found distinct patterns of brain activation for each type of encoding. In particular, they found that regions within the VLPFC (BA 45 and 47) were related to the use of

verbal elaboration, but not visual imagery. Areas within the DLPFC (BA 9) were also implicated in the use of verbal elaboration, though not necessarily with memory performance.

Overall, there is good evidence that individual differences in the use of encoding strategies may result in significant differences in brain activity. In addition to differences in activity within groups, it is possible that brain activity can be modulated between groups (such as healthy controls and patients) depending on the ability of each group to initiate the use of encoding strategies. For example, individuals with schizophrenia have been demonstrated to have noticeable impairments in memory. These patients have been shown to be less likely than healthy controls to use personal-relevance or mental imagery during encoding (Bacon, Izaute, & Danion, 2007). Patients with schizophrenia have also been reported to be less likely than healthy controls to indicate using semantic clustering or semantic association strategies during intentional word encoding (Chan et al., 2000; Ragland et al., 2004). This suggests that these patients may have a deficit in self-initiated encoding use, which may explain some of the differences in fMRI activity observed in these patients (especially within the frontal lobes).

Other studies (Bonner-Jackson, Haut, Csernansky, & Barch, 2005; Bonner-Jackson, Yodkovik, Csernansky, & Barch, 2008) have attempted to examine the use of encoding strategies during item encoding in schizophrenia, and how this affects brain activity between controls and schizophrenia. They have used a levels of processing approach, providing instructions during encoding that encouraged wither ‘deep’ (e.g. semantic) or ‘shallow’ (e.g. perceptual) encoding. It has been well demonstrated that deep encoding results in better memory performance (Craik & Lockhart, 1972; Craik & Tulving, 1975), and that patients with schizophrenia show improved performance when oriented to use deep encoding strategies such as semantic encoding (Bonner-Jackson et al., 2005; Ragland et al., 2005). Bonner-Jackson et al. (2005) found increased activity

in several areas, for both patients and controls, for deep over shallow processing. Interestingly, patients recruited more areas in the PFC to perform deep encoding than controls, but that higher performing patients showed a more normalized pattern of activity. This extra pre-frontal activity may reflect compensation for dysfunctional PFC activity in poor performing patients. Bonner-Jackson et al. (2008) compared intentional encoding (instructing participants to remember items) to incidental encoding (abstract/concrete judgments, without explicit instructions to encode the items) in patients with schizophrenia and controls. They found fewer differences between patients and controls for incidental encoding as opposed to intentional encoding. This suggests that brain activity within patients can be somewhat normalized when they are explicitly instructed to use specific encoding strategies, though some abnormalities remain. However, there are some difficulties with interpreting the results from Bonner-Jackson et al. (2005, 2008). Because there are levels of processing differences across the conditions in their design, it is possible that their data does not reflect the use of memory strategy so much as an effect of depth of processing. While engaging in deeper processing can somewhat be equated with the use of memory strategies (a deep vs. shallow memory strategy), there are well-documented neurological effects of levels of processing which make it difficult to separate memory strategy from the levels of processing effects.

1.5 Hypothesis and Goals of Thesis

Many previous neuroimaging studies have found activity in the DLPFC during associative memory tasks (Blumenfeld & Ranganath, 2007), leading to the suggestion that the DLPFC plays a role in binding items together during association. However, the literature on frontal lobe damage suggests that memory deficits following frontal lobe damage may be mainly attributable to a deficit in self-initiating elaborative encoding. Such elaborative encoding is

beneficial for later remembering, and is generally performed automatically by healthy young individuals. We have formed the hypothesis that the DLPFC may play a role in self-initiating elaborative encoding strategies.

Previous studies examining memory strategies using brain imaging techniques have typically relied on self-report of the use of different memory strategies (e.g. Frings et al., 2006; Kirchhoff & Buckner, 2006). One limitation of these sorts of studies is that memory strategy is not a controlled factor, as that they rely on self-report from the participants who are not instructed to use specific strategies. While such studies have been informative with regards to the neural correlates of specific types of memory strategies, such designs may not well capture regions involved in actually initiating the use of encoding strategies. This is a critical issue, as a deficit in initiating encoding strategies may play a role in memory deficits in a larger number of groups, including frontal lobe damage (Alexander et al., 2003; Gershberg & Shimamura, 1995; Incisa della Rocchetta et al., 1995; Incisa della Rocchetta & Milner, 1993; Stuss et al., 1994), schizophrenia (Bacon et al., 2007; Brebion, Amador, Smith, & Gorman, 1997; Brebion, David, Jones, & Pilowsky, 2004; Chan et al., 2000), healthy aging with memory decline (Hertzog, McGuire, Horhota, & Jopp, 2010; Hertzog, Sinclair, & Dunlosky, 2010; Rowe & Schnore, 1971), and Alzheimer's Disease (Uttner et al., 2010). Bonner-Jackson et al. (2005, 2008) tried to overcome this issue by directing memory strategies using either deep or shallow encoding. But, as discussed above, it may be difficult to parse the effects of levels of processing from mnemonic strategy (and the frontal lobe activity associated with activating those strategies), and such a design once again does not specifically examine the self-initiation process of utilizing elaborative encoding strategies.

When designing our experimental tasks, we sought to find an experimental design which would allow an objective examination of brain regions involved in self-initiating elaborative encoding. We also desired a task which could be used on clinical populations to examine differences in this self-initiation process. We concluded that such a design required two components. Firstly, we required conditions in which elaborative encoding was likely to be utilized vs. a condition where elaborative encoding was not likely to be used. For this component of task design, we chose to utilize semantic relatedness. Binding semantically related items together during encoding is an effective memory strategy which facilities later remembering (Addis & McAndrews, 2006). However, comparing related and unrelated stimuli was not sufficient, as there is extensive neural activity related to performing semantic analysis which is not related to self-initiating elaborative encoding. We therefore added the second component to the design, which was encoding instructions which either cued participants to evaluate semantic relationships, or did not cue participants to evaluate such relationships (a self-initiated condition). When participants encounter a trial with semantically related items during the self-initiated condition, any semantic analysis which is performed is by definition self-initiated, as we did not cue participants to consider how the items are related. In this way, we can examine brain regions involved in self-initiating elaborative semantic encoding. This design philosophy was carried through the experiment performed as part of this Thesis.

During the course of this Thesis, we conducted three experiments. The first experiment was an fMRI study designed to discover which regions were involved in self-initiating elaborative semantic encoding. Experiment two used transcranial magnetic stimulation to examine the brain region identified in experiment 1, and find causative evidence for the role of that region in self-initiating elaborative semantic encoding. Experiment 3 then used a combined

TMS-fMRI design to examine the neural networks involved in these processes. Each experiment will be presented in the form of a manuscript, with an intermediate chapter linking the studies together, and providing a more detailed background relevant to that particular study.

Chapter 2: Experiment 1: Neural Activity Related to Self-Initiating Elaborative Semantic Encoding in Associative Memory

Colin Hawco, Jorge L. Armony, and Martin Lepage

Contributions: Colin Hawco was the lead author of the study, designed and implemented the paradigm (in discussion with other authors), collected and analyzed the data, and was the primary author of the manuscript. Jorge Armony assisted with aspects of design, and particularly data analysis, and contributed to the written manuscript. Martin Lepage assisted with aspects of the study, particularly at the design phase, and contributed to the written manuscript.

Abstract

During episodic memory encoding, elaborative encoding strategies have been related to greater performance on later memory tests. However, many clinical populations display a deficit in self-initiating encoding strategies. We designed an fMRI study to examine the neural correlates of self-initiating elaborative encoding which may promote successful memory formation. Twenty-three healthy participants were presented triads of objects in which either neither, one or both objects in the bottom of the triad were related to the top object, and given two encoding instructions that required them to indicate the number of semantic ('related?') or physical ('smaller?') relationships in the triad. Reaction time decreased with more semantic relationships for both encoding instructions, indicating that semantic analysis was performed during the non-semantic encoding task. Recognition memory was better for the semantic encoding condition ('related?'), but there was no modulation of the number of semantic links on memory performance for either encoding condition. We performed a conjunction analysis on the fMRI data to find areas with greater activity for the non-semantic > semantic encoding tasks that were modulated by increasing semantic relationships during non-semantic encoding. Activity was

found in the left dorsolateral prefrontal cortex (DLPFC) and bilaterally in the supramarginal gyrus. We suggest that the DLPFC is the most likely candidate region for the self-initiation of elaborative encoding while the supramarginal activity is likely related to attentional effects. This fMRI study explicitly focused on regions which may be involved in the self-initiation of elaborative encoding during episodic memory formation.

2.1. Introduction

The proper encoding of information is critical for successful recollection of that information at a later time. One issue that can have a strong impact on encoding success is the use of efficient or elaborate encoding strategies (Camp & Maxwell, 1983; Christopher Hertzog et al., 2004; Shaughnessy, 1981). There has recently been a growing interest in the impact of encoding strategies on functional neuroimaging data (see Kirchhoff, 2009, for review), as it has been shown that individuals can vary quite substantially in their use of encoding strategies while performing a given task (McDaniel & Kearney, 1984). To further examine this issue, we conducted an fMRI study designed to identify regions involved with the self-initiation of elaborative strategy use (as opposed to areas activated only when strategy use is externally-cued).

Studies of individuals suffering brain lesions have suggested that the prefrontal cortex (PFC) plays an important role in the self-initiation of encoding strategies. While patients with PFC damage demonstrate subtle deficits in memory performance, the behavioral pattern observed in these patients is quite striking. When given a task in which semantic categorization is an effective memory strategy, healthy controls will group items into categories while PFC lesioned patients typically do not (Gershberg & Shimamura, 1995; Hirst & Volpe, 1988; Incisa della Rocchetta & Milner, 1993; Stuss et al., 1994). However, these patients are capable of categorizing lists when instructed to do so, and can actually show an improvement in memory performance when they are explicitly instructed to use semantic categorization strategies (Gershberg & Shimamura, 1995; Hirst & Volpe, 1988; Incisa della Rocchetta & Milner, 1993; Stuss et al., 1994). In contrast, healthy controls tend to engage in spontaneous categorization, and

as such, do not benefit from explicit instructions to use such strategies (as they are already utilizing semantic categorization without the need for an external prompt). Thus, patients with frontal lobe damage show a deficit in the self-initiation of strategy use but are capable of benefiting from such strategies when specifically instructed to use them.

While studies of individuals with brain lesions have yielded important insights, it is difficult to identify a specific region of the PFC associated with a particular memory processes. It is also hard to separate effects related to encoding deficits from retrieval/recognition memory deficits, as patients with frontal lesions may have difficulties with both processes. Due to the difficulty in recruiting patients with frontal lobe lesions, most studies group patients with a wide variety of lesions which often encompass several areas of the prefrontal cortex, making specific localization of function difficult. However, Alexander et al. (2003) have suggested that the most severe impairments on memory performance are observed following damage to BA 46 and BA 9 (the dorsolateral prefrontal cortex, DLPFC) and BA 44 (part of the ventrolateral prefrontal cortex, VLPFC).

Recently, issues related to encoding strategy have begun to be studied using neuroimaging techniques. Savage et al. (2001) used PET to examine semantic clustering scores on a variation of the California Verbal Learning Task. Participants were presented with a list of unrelated words, followed by a list which could be sorted into semantic categories, and lastly with a list that they were specifically instructed to categorize. They found activity in the left DLPFC (BA 9) and VLPFC (BA44) when they examined directed clustering > spontaneous clustering > unrelated lists. They suggest that the DLPFC activity represented increased demands on executive control related to the increased use of semantic clustering. Using a similar paradigm, Strangman et al. (2009) observed greater left DLPFC activity for healthy controls than

individuals with traumatic brain injury (who displayed a deficit in semantic clustering), while another study demonstrated increased bilateral DLPFC and VLPFC activity after participants were trained to utilize semantic clustering (Miotto et al., 2006). Kirchhoff & Buckner (2006) presented pairs of objects interacting in some way (such as a banana in the back of a dump-truck), and instructed participants to memorize the images. They then conducted a memory test and asked participants to rate their use of various methods of encoding. They found that verbal elaboration and visual imagery were related to subsequent memory performance, and found distinct patterns of brain activation for each type of encoding. In particular, they found that regions within the VLPFC (BA 45 and 47) were related to the use of verbal elaboration, but not visual imagery. Areas within the DLPFC (BA 9) were also implicated in the use of verbal elaboration, though not necessarily related with memory performance.

Many studies examining encoding strategies with neuroimaging use self-report measures to retrospectively draw inferences about neural activity related to encoding strategies (Frings et al., 2006; Kirchhoff & Buckner, 2006), or utilized a blocked design of progressive clustering across word lists (Miotto et al., 2006; Savage et al., 2001; Strangman et al., 2009). Our goal was to design an event-related fMRI study which could examine differences in memory strategy using a controlled study design, with a particular emphasis on the self-initiation process during elaborative semantic encoding (as opposed to elaborative encoding which is externally cued by the experimental task). By self-initiated elaborative semantic encoding, we mean a process in which participants evaluate semantic relationships between objects (considering how the objects are related) when this evaluation is not prompted or directly required for the task at hand. Such a paradigm requires several features. Firstly, there must be conditions which are likely to elicit self-initiated elaborative processing which might help with memory encoding. Secondly, there

must be a control condition which would not strongly evoke self-initiated elaborative processing (although it is likely impossible to completely remove any self-initiated elaborative processing from any task). There must also be a means to demonstrate that the self-initiated elaborative processing actually occurred. That is, behavior or brain activity must be modulated in some way to demonstrate that additional processing, not required by the task, was performed. This modulation should not take the form of an improvement in memory, as many factors outside elaborative encoding can improve memory performance.

We chose to examine semantic processing as our elaborative encoding process. We chose semantic processing because it has been shown to be a memory strategy which improves subsequent performance, and semantically related objects are often processed faster than unrelated objects. We can therefore expect a behavioral modulation of reaction time and subsequent memory performance with semantic relatedness even on trials in which participants are not explicitly evaluating those relationships. We adopted and expanded a semantic-relatedness task (Mathews, 1977), similar to the paradigm of Addis & McAndrews (2006) and Lepage, Habib, Cormier, Houle, & McIntosh (2000). They presented triads of words in which the top word was a category word and the other (bottom) words could be exemplars of this category. Neither, one, or both of the bottom objects could be category exemplars. We expanded upon this paradigm by introducing two separate encoding conditions; an associative semantic encoding condition in which participants were explicitly instructed to judge the number of relationships (similar to Addis & McAndrews, 2006, and Lepage et al., 2000), and an encoding condition in which the number of relationships between the objects was not relevant to the encoding task (the "non-semantic" encoding task). By examining activity related to processing semantic relationships in the non-semantic encoding conditions, our intention was to identify

regions involved with the self-initiation of elaborative encoding strategies (semantic analysis when not instructed to do so). The use of object triads rather than pairs was intended to increase task complexity, to ensure any semantic analysis in the non-semantic encoding condition was less likely to be driven by simple, automatic yes/no relatedness judgments. Participants were made aware that there would be a later memory test, to ensure that explicit (as opposed to only implicit) encoding occurred during the experiment.

An area involved in the self-initiation of associative semantic processing during non-semantic encoding trials (elaborative processing) should show increased activity for the non-semantic as opposed to semantic encoding task. However, several areas can be expected to show greater activity that is not related to elaborative semantic processing (i.e. regions involved in the non-semantic encoding task, but not the semantic encoding task). We will therefore focus on regions in which activity is also modulated by the number of semantic relationships. In the case where none of the objects are related, participants are unlikely to utilize extensive elaborative encoding evaluating semantic relationships (because there are no obvious semantic relationships) when it is not necessary for task performance. By examining areas with activity that is both greater for non-semantic than semantic encoding, but still influenced by the number of semantic links, we can provide good candidate regions for the self-initiation of elaborative semantic encoding. We hypothesized we would observe significant clusters in the prefrontal cortex, particularly the DLPFC, with possible additional areas (the parietal or medial temporal lobes) involved in a network for self initiation of elaborative semantic encoding.

2.2. Methods

2.2.1 Participants: Twenty-three participants were recruited for this study. All participants were between the ages of 18-35, had no self-reported history of psychiatric or neurological illness, and were able to safely undergo an MRI experiment. All participants signed an informed consent and filled out a screening questionnaire prior to the experiment. This experiment was conducted in accordance with ethical guidelines at the Montreal Neurological institute, and consistent with the declaration of Helsinki.

2.2.2 Stimuli: Many previous studies on associative memory, and most studies on memory strategies, have used verbal materials. One of the goals of our study was to utilize a design with a higher level of ecological validity in that we might be assessing processes which are used in day-to-day life. We chose to use high quality color photographs of common objects in order to expand our understanding of these issues outside the purely verbal domain, and also because many associations formed in real-world situations involve objects rather than purely verbal material. All stimuli were high quality color photographs of common objects taken from the Bank of Standardized Stimuli (BOSS; Brodeur, Dionne-Dostie, Montreuil, & Lepage) . We used these pictures as stimuli as the high quality color photographs may represent stimuli with a higher ecological validity than the line-drawing or clip-art pictures used in many studies, and the objects in the BOSS represent real world common object that participants could expect to encounter during the normal course of their lives (such as might be found around a house or office). In order to select pairs of objects which were semantically related, 8 participants (who were not included in the fMRI study) completed a stimulus norming procedure, in which pairs of objects were rated for semantic relatedness on a 7-point scale (1- totally unrelated , e.g. hammer and apple, to 7- extremely related, e.g. hammer and nail). Any two objects with a relatedness score of greater than 4, and a standard deviation less than 2 were considered to be semantically

related. Object triads were presented with one object on top and two below (see Figure 1). Three types of triads were created; zero-link, one-link, and two-link. For two-link triads, both bottom objects were related to the top object. For one-link triads, one of the bottom objects was related to the top object, while the second bottom object was one in which there was no relationship between either the top object or other bottom object. In zero-link triads, there was no semantic relationship between any of the objects. The objects were all common household objects which were photographed. Thus, the size range of objects was limited (the smallest object was the paper clip, while the largest was an axe). As the non-semantic encoding task involved judging sizes of object (see below), care was taken that unrelated objects did not systematically differ in size more so than the related objects.

2.2.3 Experimental Task: Prior to the experiment, both the encoding and recognition tasks were explained to all participants. It was emphasized that this was a memory task, and there would be a memory test for the associations between objects presented during the encoding phase of the experiment. For the encoding session, participants were asked one of two possible encoding questions: ‘related?’ or ‘smaller?’. In the case that the question was related, participants were instructed to look at the object triad, and judge how many of the bottom objects were semantically related to the top object (zero, one, or two). It was explained to participants that by semantically related, we mean that one object would be associated with the other; that when they think of one object, they might think of the other as well, or the objects were both members of the same category. In the case where the encoding question was ‘smaller?’, participants were instructed to judge how many of the bottom objects would be smaller than the top object in the real world (as opposed to based on the size of the images). Objects of similar size were defined as not smaller in the task instructions. While both of these task instructions can

be said to involve semantic encoding (as the 'smaller?' condition still requires participants to access semantic features of the presented objects), the related condition includes an explicit instruction to perform associative semantic encoding between the objects. While we use the labels semantic encoding (for the 'related?' condition) and non-semantic encoding (for the 'smaller?' condition), we are referring in this case to associative semantic encoding rather than accessing the specific semantic features of individual objects. Both of these encoding conditions should also involve deep, elaborative encoding of the items, insuring any differences between encoding conditions is not related to depth of processing.

There were six separate conditions in the experiment (semantic encoding, two-link; semantic encoding, one-link; semantic encoding, zero-link; non-semantic encoding, two-link; non-semantic-encoding, one link; and non-semantic encoding, zero-link), each with 16 unique triads, for a total of 96 unique object triads in total. During encoding, each object triad was presented twice to promote effective memory formation, resulting in the presentation of 192 trials. Repeated presentation of trials during encoding has been previously used in several studies on memory encoding (Bonner-Jackson & Barch, 2011; Rand-Giovannetti et al., 2006; Sergerie, Lepage, & Armony, 2006). Encoding trials were divided into 4 runs of 48 trials. Each trial consisted of a fixation cross presented for 1000 to 5000 ms in 100 ms increments, followed by presentation of the encoding question for 2000 ms, followed by presentation of the object triad with the encoding question still on the screen for 7000 ms. The average trial length was 12 seconds. In order to avoid task-switching effects, each encoding question was presented for six consecutive trials. In this way, the task was predictable, which should help minimize carry over effects of the semantic encoding task prompting participants to perform associative semantic

analysis during the non-semantic encoding trials. Details of the trial design are presented in Figure 1.

Following the scanned encoding task, an anatomical MRI was performed during which no tasks were performed, allowing a consolidation period. Participants were then presented with a recognition task in the scanner. The recognition task followed the same format and timing as the encoding task, save that the task instruction presented was always ‘rearranged?’. Participants were instructed to judge if the objects presented in the triad where presented together in the encoding phase (intact) or if this was a novel configuration of objects (rearranged). Half of the unique triads from the encoding phase were rearranged into new configurations, resulting in 48 intact and 48 rearranged triads respectively. The top object of each triad was re-presented with the same number of semantic links (zero, one, of both bottom objects) as in the encoding phase. No new objects were introduced during the recognition test.

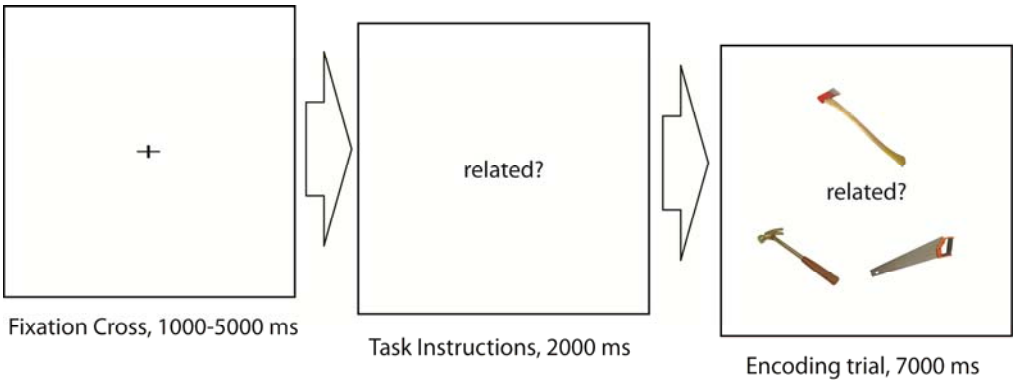

Figure 1: Encoding task experimental design. Participants saw the fixation cross for 1000 to 5000 ms (mean 3000 ms), flowed by the encoding instruction for 2 seconds, and finally the triad of objects, along with the encoding instruction, for 7000 ms. Participants responded to the encoding task while the triad was on the screen.

2.2.4 Behavioral analysis: For the encoding trials, accuracy was examined for the semantic encoding trials (for which we had norms to define a correct response) with a repeated measures ANOVA. For reaction time data, we performed a repeated measures ANOVA on all

trials with a 2 X 3 design (encoding condition and number of semantic links) using Greenhouse-Geisser correction. We also evaluated the consistency of responses between the first and second presentation of each triad for the semantic and non-semantic encoding conditions by calculating the number of triads for which participants gave the same response on the first and second presentation.

Recognition accuracy data was evaluated using discrimination index, which provides an unbiased estimate of memory accuracy by factoring in the rate of false alarms. Discrimination index is defined as hit minus false alarms. For determining false alarms for each condition, rearranged trials were separated into the encoding conditions based on the top object (to which the encoding question specifically referred).

2.2.5 fMRI Scanning Parameters: Echo-planar images were collected on a Siemens 3T Tim trio MRI (TR = 2000 ms, TE = 30 ms, flip angle = 90, 36 slices of 4 mm thick, 64 x 64 voxel plane with an FOV of 256 mm, giving 4 mm x 4 mm x 4 mm voxels). Each BOLD run was preceded by 4 volumes that were later discarded to allow a magnetic steady state, and included 312 whole brain volumes and 48 experimental trials. The anatomical scan was an MPRAGE (TR = 2300 ms, TE = 2.98 ms, FOV 256 mm, 1mm x 1mm x 1 mm voxels, flip angle = 9). The anatomical scan lasted for 5.21 minutes.

2.2.6.1 Functional MRI Data Analysis: Data analysis was performed using SPM 8 (Wellcome Department of Cognitive Neurology, London, UK). Images from all encoding runs were realigned to the first scan from the first encoding run. Realigned images were then normalized using the ICBM template and then smoothed with an 8mm FWHM isotropic Gaussian kernel to account for differences in individual anatomy across participants. Statistical

analysis was implemented in customized Matlab scripts which automated the standard voxel-wise least squares general linear model, using the standard canonical HRF plus the derivative and dispersion. Low frequency drifts were removed by applying a high-pass filter with a cut-off of 128 seconds. Statistical contrasts were created comparing the two encoding conditions (semantic > non-semantic encoding, and vice-versa), and separate contrasts comparing the number of semantic links (relatedness contrast, either increasing or decreasing relatedness). Once the fixed effects model for each participant was completed, the data was subjected to a random effects analysis across participants to produce a group t-map using the Beta value for the HRF. Statistical significance was defined at the cluster level, using a t-value of 3.5, which corresponds to an uncorrected p-value of 0.001 at the single voxel level. Results of a monte-carlo simulation (Slotnick, Moo, Segal, & Hart, 2003) of 1000 iterations indicated a cluster of 48 contiguous voxels in the normalized image (384 mm^3) corresponded to a cluster significance of $p < 0.05$, corrected for multiple comparisons.

2.2.6.2 Conjunction Analysis: We performed a conjunction analysis, using inclusive masking (Prince, Daselaar, & Cabeza, 2005), between the non-semantic > semantic encoding and the relatedness contrast by creating a mask of active voxels in the encoding contrast and applying that mask to the relatedness contrast. This analysis indicates areas in which we have more activity for non-semantic encoding, but activity that is nonetheless modulated by the number of semantic relationships. For activity specific to semantic relatedness, there were two possible explanations for any modulation of neural activity by semantic relationships: explicit analysis of semantic relationships and automatic semantic priming. Semantic priming typically results in a decrease in activity (Schacter & Buckner, 1998), meaning more semantic relationships should result in a smaller hemodynamic response. Therefore, we only considered activation in the

direction of increasing relatedness for the conjunction analysis, as such activity is unlikely to reflect automatic priming.

To clarify if neural activity in clusters identified by the conjunction analysis was related to semantic analysis during the non-semantic encoding questions (as opposed to a large effect for the semantic encoding question and no effect of non-semantic encoding), we performed a post-hoc repeated measures ANOVA on the HRF beta values comparing number of links in the non-semantic encoding condition (two-link, one-link, and zero-link trials for non-semantic encoding).

2.2.6.3 Effects of Trial Repetition: All trials were presented twice during encoding. In order to ensure the effects of our conjunction analysis were not related to repeating trials (e.g. repetition suppression effect, Buckner & Koutstaal, 1998), we performed a supplementary analysis including the effects of trial repetition by separating events into first or second presentation. Because there were few or no events of some type in some runs (as the majority of run 1 was first presentation of triads, and the majority of run 4 was second presentation), we concatenated runs (treating all four runs as a single time series) by adding a linear regressor and a linear drift term for each run. We then reran the original masked conjunction analysis, then repeated the conjunction analysis separately for the first presentation and second presentation of trials.

2.3. Results

2.3.1 Behavioral Data: Accuracy and reaction time data for the encoding trials were not available for the first two participants due to technical problems. There were no significant differences in accuracy between the number of semantic links for semantic encoding trials, $F(2,40) = 1.6$, $p = 0.215$. Reaction time data for the encoding task and discrimination index for

the recognition task are shown in Figure 2. Repeated measure ANOVA on encoding reaction time revealed a significant main effect of encoding task, $F(1,20) = 112.3$, $p < 0.001$ (semantic < non-semantic encoding), and a main effect of the number of semantic links, $F(2,40) = 9.182$, $p = 0.004$, and no significant interaction, $F(2,40) = 1.568$, $p = 0.23$. Post-hoc contrasts indicated a significant linear trend for number of semantic links, $F(1,22) = 6.945$, $p = 0.005$, as participants had a shorter RT when there were more semantic links in the triad. When we examined the consistency of responses across repeated triads, participants gave the same response for an average of 89% of triads for the semantic encoding condition and 79% of triads for the non-semantic encoding condition. The difference in response consistency was statistically significant (paired-sample t-test, $p < 0.05$).

For the recognition data, results from one participant were excluded due to problems with their responses (likely caused by the participant pressing the wrong keys on the response pad). A significant main effect of encoding condition was observed, $F(1,21) = 8.93$, $p = 0.007$, with semantic encoding resulting in greater recognition than non-semantic encoding, but no significant main effect of relatedness, $F(2,42) = 0.420$, $p = 0.66$, and no significant interaction, $F(2,42) = 0.29$, $p = 0.74$.

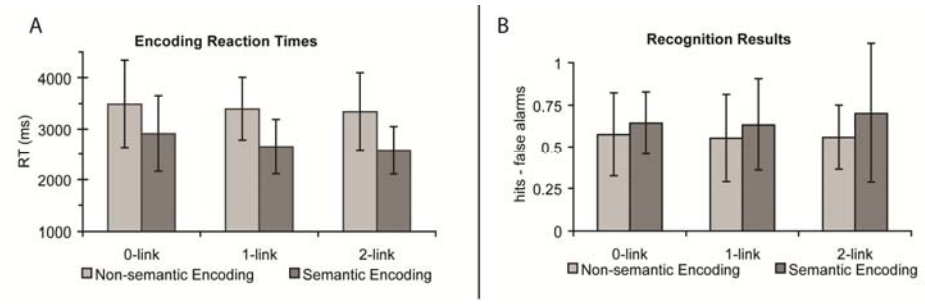

Figure 2: Behavioral Results. A: Results for reaction time analysis of the encoding trials (mean and standard deviation). B: Discrimination index (% hits - % false alarms) for the recognition task (mean and standard deviation).

2.3.2 fMRI Results

2.3.2.1 Encoding Questions: Results of the encoding contrasts (semantic > non-semantic encoding, and non-semantic > semantic encoding) are shown in Figure 3. When we examined activity in the semantic > non-semantic encoding contrast, we observed widespread and often bilateral activity across a wide range of brain areas. Activated areas include the supramarginal

Table 1: Results of encoding contrasts (multiple regions shown for large activations)

Peak t Value	*Voxels*	*x*	*y*	*z*	*Hemishpere*	*Region*	*BA*
Semantic > Non-semantic Encoding							
9.81	7363	-55	-24	-12	Left	Mid Temporal Gyrus	21
					Left	Angular Gyrus	39
					Left	Supramarginal gyrus	40
					Left	Posterior Insula	13
					Left	Putamen/Globus Pallidus	
					Left	Anterior Hippocampus	
					Left	Amygdala	
					Left	Parahippocampal Gyrus	36
					Left	Anterior Inferior Frontal Gyrus	47
8.55	5255	65	-39	35	Right	Supramarginal gyrus	40
					Right	Superior Temporal Gyrus	22
					Right	Mid Temporal Gyrus	21
					Right	Inferior Frontal Gyrus	6
					Right	Insula	13
					Right	Putamen	
					Right	Amygdala	
					Right	Mid-Temporal Pole	38
6.94	3324	-6	-14	34	Left/Bilateral	Anterior Cingulate	24
					Left/Bilateral	Posterior Cingulate	23
					Left	Superior Parietal	5
6.02	1398	-8	54	30	Left/Bilateral	Superior Frontal Gyrus	9
					Left	Mid Frontal Gyrus	10
4.62	330	28	-34	62	Right	Superior Parietal Lobe	2/5
4.39	149	-18	-5	19	Left	Body of the Caudate Nucleus	
4.62	112	61	-2	37	Right	Superior Frontal Gyrus	6
3.94	68	51	33	-7	Right	Inferior Frontal Gyrus	47
Non-semantic > Semantic Encoding							
5.99	441	50	38	24	Right	Mid Frontal Gyrus	9/46
5.38	291	44	-37	44	Right	Supramarginal gyrus	40
6.04	153	26	8	51	Right	Superior Frontal Gyrus	6
5.08	148	-46	-81	11	Left	Mid Occipital Gyrus	19
4.35	114	-6	18	45	Left	Medial Frontal Gyrus	8
4.64	100	-38	-43	41	Left	Supramarginal gyrus	40
5.33	94	-50	29	32	Left	Mid Frontal Gyrus	9/46
5.27	65	-26	1	50	Left	Mid Frontal Gyrus	6
4.27	64	44	-81	13	Left	Mid Occipital Gyrus	19
4.69	57	16	-65	60	Right	Superior Parietal Lobe	7

gyrus, extending forward along separate branches through the mid temporal gyrus or into the frontal lobes (bilaterally), the superior parietal lobe (around BA 5, bilaterally), the insula, basal ganglia, and amygdala (bilaterally) and the anterior hippocampus on the left, midline activity in the cingulate gyrus and anterior medial frontal lobes, and bilateral activity in the inferior frontal gyrus (in the VLPFC), which was much more extensive on the left. A full list of activations is presented in Table 1.

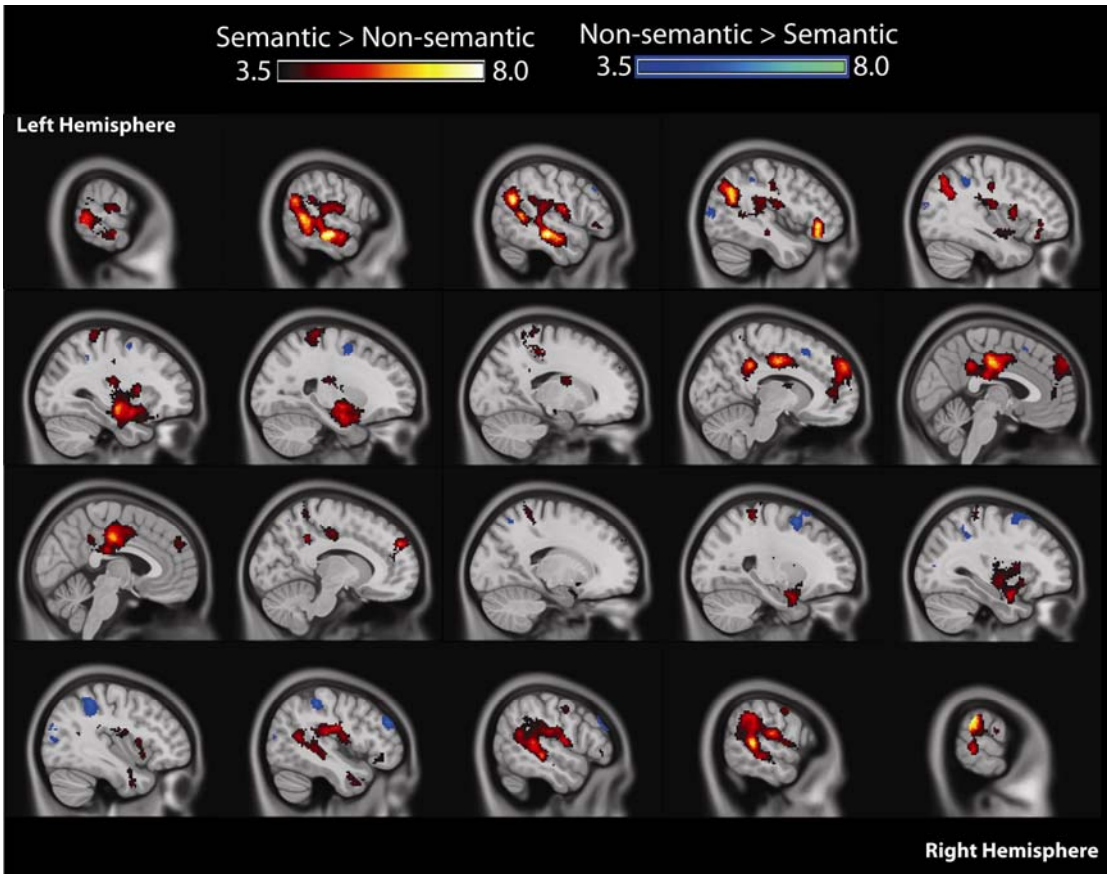

Figure 3: Results of the encoding condition contrasts (semantic > non-semantic encoding, in red-yellow, and non-semantic > semantic encoding, in blue-green). Only significant clusters (48 contiguous voxels with t > 3.5) are shown.

The non-semantic > semantic contrast showed less widespread activity, largely consisting of sets of bilateral clusters of activity. Activated areas include the supramarginal gyrus (bilaterally, superior and medial compared the area involved in the semantic > non-semantic

encoding contrast), bilateral activity in the superior frontal gyrus (BA6) and mid frontal gyrus (the DLPC, BA 9/46), bilateral activity in the superior occipital gyrus (BA 19), and unilateral activity in the right superior parietal lobe (BA 7) and left medial frontal gyrus (BA 8). A full list of activations are presented in bottom of Table 1.

Table 2: Results of Semantic Relatedness Contrasts (multiple regions shown for large activations)

Peak t Value	*Voxels*	*x*	*y*	*z*	*Hemishpere*	*Region*	*BA*
Increasing Relatedness							
7.67	4928	-46	-38	55	Left	Supramarginal gyrus	40
					Left	Angular Gyrus	39
					Left	Mid Temporal Gyrus	21
5.57	2299	14	45	46	Bilateral/Right	Superior Frontal Gyrus (Medial)	8
					Bilateral	Superior Frontal Gyrus	6
					Left	Superior Frontal Gyrus	9
6.4	1850	44	-31	40	Right	Supramarginal gyrus	40
4.71	298	-12	-47	32	Left	Dorsal Posterior Cingulate Cortex	31
					Left	Medial Parietal	7
5.97	254	-53	12	12	Left	Inferior Frontal Gyrus	44
5.8	189	-36	50	-9	Left	Mid Frontal Gyrus	10
5.08	88	61	-47	-4	Right	Posterior Mid Temporal Gyrus	21
5.65	78	48	51	1	Right	Mid Frontal Gyrus	10
Decreasing Relatedness							
13.86	6131	30	-84	-4	Right	Inferior Occipital Gyrus	18
					Right	Mid Occipital Gyrus	19
					Right	Fusiform Gyrus	37
					Right	Parahippocampal Gyrus	36
13.33	5369	-16	-101	7	Left	Inferior Occipital Gyrus	18
					Left	Mid Occipital Gyrus	19
					Left	Fusiform Gyrus	37
					Left	Parahippocampal Gyrus	36
4.69	125	38	24	14	Right	Anterior Insula	13
5.34	75	32	-34	15	Right	Posterior Insula	13

2.3.2.2 Number of semantic links:

The complete results of the semantic relatedness contrasts are presented in Figure 4 and Table 2. For increasing relatedness, we observed activity in the left inferior parietal lobe (supramarginal gyrus and angular gyrus), extending into the mid temporal gyrus, and activity in the right supramarginal gyrus. There was also a cluster in the medial superior frontal gyrus (BA 8, larger on the right) extending laterally into the superior frontal gyrus (BA6) and mid frontal

gyrus (BA 9/46). The opposite contrast (decreasing relatedness) resulted in two large clusters which activated the medial occipital lobe and extended into the posterior medial temporal lobe, through the fusiform gyrus into the parahippocampal gyrus bilaterally. There was also smaller clusters activity in the right insula.

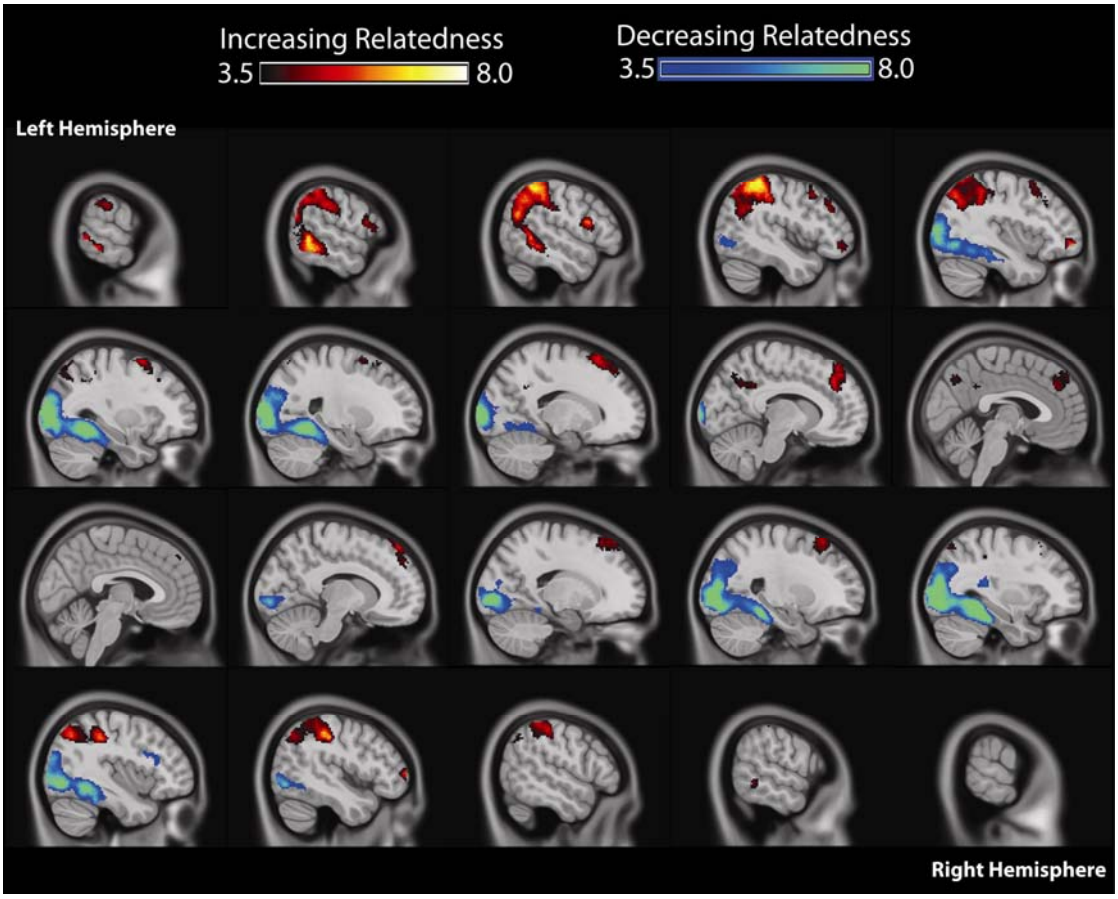

Figure 4: Results of the relatedness contrasts (increasing relatedness in red-yellow, and decreasing relatedness, in blue-green). Only significant clusters (48 contiguous voxels with $t > 3.5$) are shown.

2.3.2.3 Conjunction Analysis: The masked conjunction analysis revealed areas which were active in both the non-semantic > semantic contrast, and the increasing relatedness contrast. Six distinct clusters were observed, in the left and right supplementary motor area (SMA; BA 6), the left and right inferior parietal lobe in the supramarginal gyrus (SMG, BA 40, with more

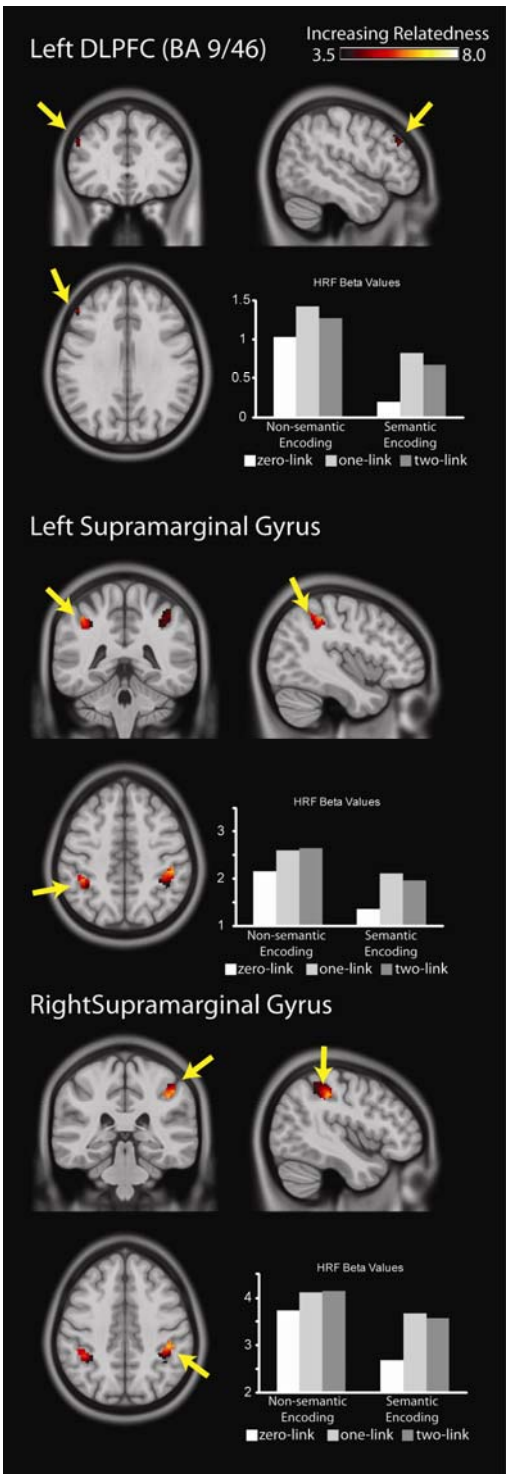

Figure 5: Results of the masked conjunction analysis. HRF beta values were extracted from a cluster of 39 voxels centered on the peak t-value.

voxels active on the right), and the left DLPFC (BA 9/46 on the mid frontal gyrus). The clusters in the SMA were not further considered due to their exteremely small size (2 resampled voxels on the right and 5 on the left). Results of the conjunction analysis are shown in Figure 5. The post-hoc ANOVAs revealed a significant effect for number of links during non-semantic encoding in the left DLPFC, $F(2,44) = 3.97$, $p = 0.0027$, and both left parietal, $F(2,44) = 4.91$, $p = 0.014$, and right parietal, $F(2,44) = 8.36$, $p = 0.001$, but not the right DLPFC, $F(2,44) = 0.55$, $p = 0.55$.

3.2.4 Repetition Effects: The conjunction analysis with events separated by first and second presentation of triads and runs concatenated produced results very similar to the original analysis. Separating events into first and second presentation resulted in reduced t-values, as we were dividing our number of trials into two. To compensate for this, we performed the supplementary conjunction analyses for first or second presentation of a triad using a reduced single voxel threshold ($t > 2.8$, corresponding to $p < 0.005$ uncorrected). Results are presented in Figure 6. For

both the first and second presentation of the triads, we observed activity in the conjunction analysis in the left DLPFC and left and right SMG, overlapping the results of the original analysis. No additional clusters were observed. This indicates that our results were not influenced by the effects of repeating triads during encoding.

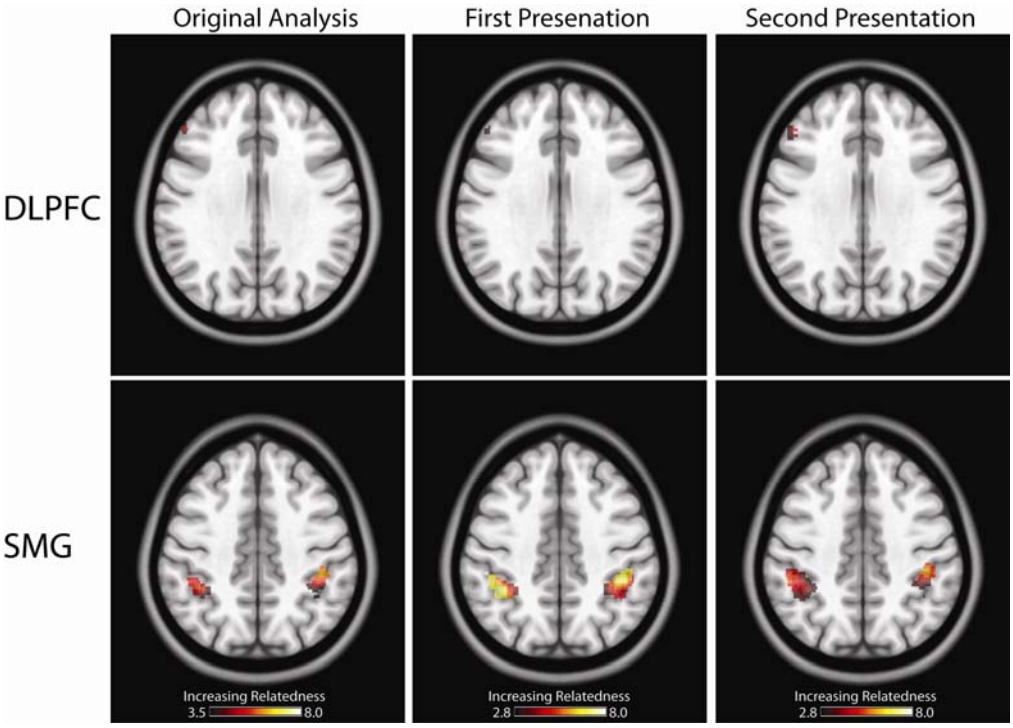

Figure 6: Results of the masked conjunction when trials are separated into first or second presentation of the triads. Note that for the analysis separating into first or second presentation, we used a reduced voxel threshold of $t > 2.8$ (rather than 3.5 as in the original) to compensate for reductions in t-value from reduced power when diving trials into sub-types.

2.4. Discussion

We conducted an fMRI study of memory formation in which we attempted to control encoding strategy with the use of orienting instructions. Rather than focus on specific encoding strategies per se, we were interested in areas involved in self-initiating elaborative semantic processing which was not necessary to perform the orienting task. We did so by presenting a specific encoding instruction (‘related?’) orienting towards semantic analysis of object triads

with a varied number of relationships, and another encoding question (‘smaller?’) which oriented the participant away from semantic analysis. These experimental manipulations were intended to examine self-initiated (though not necessarily self-aware/intentional) elaborative processing. In the non-semantic encoding condition, any semantic analysis performed by the participant was self-initiated (rather than externally cued). Because it is unlikely that extensive semantic analysis will be performed in unrelated (zero-link) triads during non-semantic encoding (as there are no existing semantic associations to consider), any cluster that shows greater activity in the non-semantic > semantic contrast, while still being modulated by relatedness, would be good candidates for the self-initiation of elaborative semantic encoding processes.

2.4.1 Behavioral Effects: For the encoding task, we found a reaction time modulation of the encoding conditions and the number of semantic links. The encoding condition effects indicate that participants were slower to perform the non-semantic encoding task. This may represent either additional processing time to form and evaluate mental images, or it may reflect an increased difficulty selecting a definitively correct response for the non-semantic encoding question (in cases where object size was similar). With regards to the modulation of RT by the number of semantic links, this may be viewed as evidence that explicit semantic analysis was performed for both the semantic and non-semantic encoding questions. However, the magnitude of the RT differences from relatedness were quite small (although strongly statistically significant, $p = 0.004$), and it is not possible to rule out the effects of implicit and automatic semantic priming facilitating task performance for both encoding questions (rather than self-initiated semantic evaluation).

While recognition memory performance was increased for the semantic compared to the non-semantic encoding question, we did not observe the expected effects of the number of

semantic links on recognition accuracy. While other studies have found that increasing semantic links resulted in better recognition memory (Addis & McAndrews, 2006; Lepage et al., 2000), those studies utilized verbal stimuli. Differences between our results and previous studies are likely due to our use of high quality color photographs of objects rather than verbal stimuli, differences in task related to the inclusion of a second non-semantic encoding question, or the fact that we presented each triad twice during encoding.

2.4.2 Activity related to semantic analysis: The results of our semantic encoding contrast (semantic > non-semantic encoding) showed a widespread activity related to semantic analysis. This pattern of results fits well with a recent meta-analysis of neuroimaging studies examining semantic process of verbal stimuli (Binder, Desai, Graves, & Conant, 2009), which reported a widespread pattern of activity including bilateral parietal activity (extending into the mid-temporal regions on the right), and activity in the PFC. There is a strong similarity between the parietal and mid-temporal results of our study and the activations in the meta-analysis (Binder et al., 2009), though we observed activations related to semantic analysis of pictures which were not present in the meta-analysis of verbal material. For example, we observed activity in the posterior insula and sub-cortical areas (including bilaterally in the basal ganglia and the amygdala, and the anterior hippocampus on the left). These activations may be related to stimulus type (as we used triads of complex, verbalizable pictures, rather than purely verbal stimuli), or to the specifics of our particular task and contrasts.

2.4.3 Activity related to semantic analysis in the non-semantic encoding condition: We examined areas more active for non-semantic encoding (with the non-semantic > semantic encoding contrast), and performed an inclusive masking conjunction analysis to identify regions which are likely involved in the self-initiation of elaborative processing. This revealed clusters of

activity in the left DLPFC (around BA 9/46), and the left and right inferior parietal lobes in the SMG, which were significantly modulated by semantic relatedness in the non-semantic encoding condition. These same areas were observed following both the first and second presentation of the triads, suggesting that the observed results are robust neural responses.

When examining the non-semantic > semantic encoding contrast, the DLPFC activity had a right sided-dominance (a larger cluster of activation). However, we found that activity in the left DLPFC was modulated by relatedness, while activity on the right DLPFC was not. This may suggest a laterality effect, in which the right DLPFC is somehow more involved in the cognitive operations necessary for the non-semantic encoding task, while the left DLPFC may be more involved in the self-initiating of semantic analysis in the non-semantic encoding condition. Another possibility is that the right DLPFC, or another brain region, initiates semantic analysis during the non-semantic encoding task for all triads, regardless of the number of semantic relationships. Such a region would show greater activation for non-semantic > semantic encoding, but no modulation as a function of the number of relationships. Examining the results for the non-semantic > semantic encoding contrast does not suggest a region that is a better candidate for self-initiation of encoding strategies than the DLPFC. Other active areas included bilateral SMA (BA 6), bilateral parietal (which we discuss further below), and small occipital activations. Activity in the DLPFC has been associated with executive functioning and higher-order mental operations such as monitoring and manipulating short-term representations and the control of planned behaviours and cognition (Petrides, 2005), while activity in these other areas are not typically independently associated with elaborative processes and high-level complex cognitive operations.

Considering only the pattern of activation and the beta value for the inferior parietal activity, one could argue that these regions make as good a candidate as the DLPFC for the self-initiation of encoding strategies. However, we do not believe that this is the most parsimonious explanation . Lesion evidence has implicated the prefrontal cortex, but not the parietal lobes, in the self-initiation of encoding strategies and memory performance (Gershberg & Shimamura, 1995; Hirst & Volpe, 1988; Incisa della Rocchetta & Milner, 1993; Stuss et al., 1994). Instead, we favor an explanation based around the role of the parietal lobes in attentional control. Dual-attention theory has been used to explain activation in the parietal lobes associated with successful encoding (Uncapher & Wagner, 2009) and during memory retrieval (Cabeza, Ciaramelli, Olson, & Moscovitch, 2008). Dual attention theory divides the roles of the dorsal and ventral parietal lobes into separate fronto-parietal systems (e.g., Behrmann, Geng, & Shomstein, 2004; Corbetta, Patel, & Shulman, 2008; Corbetta & Shulman, 2002), with the dorsal parietal lobes involved in top-down goal directed attention and the ventral parietal cortex (the inferior parietal lobe) is involved in bottom-up attention, including the detection of behaviorally relevant stimuli that is salient and/or unexpected. Our conjunction analysis pointed to activity within the ventral parietal lobe, more specifically within the supramarginal gyrus (SMG).

The ventral parietal lobes capture relevant cues, and can signal the need for a change in the locus of attentions (Cabeza, 2008). Based on our results, we suggest that the ventral parietal lobes signal the need to allocate attentional resources towards semantic analysis, more-so when such semantic analysis is not task relevant. During the semantic encoding task, these relationships are already being evaluated so there is less need for increased activity in the parietal bottom-up attentional system. In the case of zero-link trials, which can be quickly rejected during the semantic encoding condition (as evidenced by our encoding reaction time data), there is

relatively little parietal activity (see Beta values in Figure 5). However, during the non-semantic encoding condition, a certain level of attentional orientation must remain, as the semantic links are being analyzed in conjunction with the actual task demands (visualizing the object in real space and making a size judgment). This causes either an increase in the amount or duration of neuronal firing resulting in a larger increase in the hemodynamic response.

We therefore propose that the left DLPFC (in association with the parietal cortex) is a good candidate region for the self-initiation of elaborative semantic encoding, and thus may be an area involved in the general self-initiation of efficient encoding strategies. Note that when we discuss “encoding strategies”, we do not necessarily mean a planned or intentional process. Instead, we are using the term encoding strategy to refer to any elaborative processing outside the direct requirements of the task that may promote successful memory formation. In the case of our study, we utilized a design in which semantic analysis was the most obvious and available form of elaborative processing which was available to participants. But similar effects could be examined using other potential encoding strategies. For example, it would be interesting to see if this region showed greater activations in word pairs which were easy to visualize interacting together as opposed to word pairs in which such a visualization strategy is less feasible, or in other controlled experimental designs which allowed the use of elaborative encoding strategies. This would add further evidence that this region of the DLPFC was indeed involved in the self-initiation of encoding strategies and elaborative processing beyond task requirements, and not specifically related to only the self-initiation of elaborative semantic encoding.

One issue that is difficult to clarify with fMRI data is the directionality of the relationship between the DLPFC and parietal activity. Indeed, the dual-attention theory posits separate dorsal and ventral frontoparietal networks in attention (Corbetta & Shulman, 2002), suggesting that the

relationship between our frontal and parietal activations is not a clear-cut direct functional relationship. However, the dorsolateral prefrontal cortex has been shown to be anatomically connected to the inferior parietal lobes in macaque monkeys (Petrides & Pandya, 1999). Two possibilities present themselves; the DLPFC may initiate the attentional orientation in the parietal lobes, or the parietal activity may influence the DLPFC activity. While our hypothesis that the DLPFC initiates elaborative encoding may seem to indicate that the first hypothesis is correct (that the DLPFC drives the parietal activity), this is suggestive of a top-down system of attentional control and would be more consistent had we observed dorsal parietal activity. Instead, we favor the second hypothesis, that the parietal SMG activity orients attention towards the relationships between items, and facilitates DLPFC activity. This does not imply that it is the SMG proper that is initiating elaborative encoding processes. Instead, the SMG orients attention towards the semantic relatedness features of the stimuli (during both semantic and non-semantic encoding), and that it is the DLPFC which actually initiates the elaborative encoding in which these relationships are actually subjected to semantic encoding, especially when this semantic encoding is not specifically required by the task.

While numerous other studies have examined the neural correlates of elaborative encoding strategies, this is the first study to focus explicitly on the self-initiation process during elaborative semantic encoding. In particular, this study is novel in that we utilized a controlled design which contrasts self-initiated elaborative semantic encoding to externally cued semantic analysis, as opposed to using retrospective measures (questionnaires) which focus on individual use of various elaborative encoding strategies. This design not only allows an examination of self-initiation contrasted to an externally-cued condition, but may also provide a useful paradigm for translation into studies on patient groups. Given that a lack of efficient encoding strategy use

has been related to memory decline in numerous groups (e.g. healthy aging with memory decline, Alzheimer's disease, Schizophrenia, frontal lobe lesions), an understanding of the neural correlates of the self-initiation process is important to understand the neurological deficits within these groups. By contrasting conditions with directed an undirected encoding and conditions with stimuli which lend themselves to elaborative encoding to those which do not, we should be able to examine self-initiation of memory encoding strategies across a range of both patient groups and healthy controls.

Chapter3: rTMS Studies of Memory

Functional imaging studies have resulted in a dramatic increase of our understanding of memory processes, and most especially how those processes are handled by the brain. However, functional imaging has the intrinsic drawback of being a correlational method; activity observed in response to a task may not be critical to the task itself. Thus, while we can determine which brain areas are activated by a task, it does not follow that those brain areas are necessary for that task. It is also difficult to determine specific functional roles within different brain areas using functional brain imaging, though sufficiently elegant experimental designs can help overcome this limitation. In Experiment 1, we established that activity in the DLPFC may be related to the use of volitional mnemonic strategies during our memory task (i.e. evaluating semantic relationships without being explicitly instructed to do so). However, it remains difficult using fMRI alone to determine if this activity is causative or correlational. That is, we are unable to determine if DLPFC activity initiates and directs the use of mnemonic strategies, or if that activity is secondary to another process modulated by a different brain region (to which our task or analysis is possibly not sensitive). It is also nearly always the case in fMRI studies that alternate explanations for the observed pattern of brain activity are possible. For example, our results may have been influenced by working memory effects (which is compatible with the DLPFC being involved in self-initiating elaborative encoding, which may involved increased working memory demands), or the overlap in activity detected by our conjunction analysis may have been coincidental.

Recent advances in trans-cranial magnetic stimulation (TMS) have allowed us to temporarily disrupt (or enhance) activity within a brain region during task performance. TMS works by firing a high-intensity magnetic pulse (typically around 1.5 Tesla) through the scalp

into the brain. One benefit of magnetic stimulation over electrical stimulation is that magnetic stimulation is not attenuated while passing through the scalp and skull. The magnetic pulse affects neurons beneath the site of stimulation, to a maximum effective depth of about 2 or 3 centimeters from the skull surface, depending on the characteristics of the TMS coil and the intensity of the stimulation. This limits TMS investigations to superficial cortical areas, as it is impossible to stimulate regions deeper within the brain (such as the insula or the hippocampus) using standard TMS coils. TMS also has the benefit of an extremely high temporal resolution, as a TMS pulse lasts only about 1 ms, and its direct effect on the underlying cortex lasts only about 60 ms (Allen, Pasley, Duong, & Freeman, 2007). When a train of TMS pulses is presented during a task, cortical activity in the affected area is disrupted, though the exact mechanism of this disruption is an area of active debate. Two main hypotheses have been suggested; TMS may reduce neural activity in the affected area (Harris, Clifford, & Miniussi, 2008), it may increase random noise in the underlying cortex (disrupting activity related to the task; Ruzzoli, Marzi, & Miniussi, 2010), or it may be some combination of both.

TMS is an especially useful tool because it allows a more direct examination of the role of a given brain region to a cognitive task. If we disrupt activity in an area of the cortex which is essential to the task, we should observe a decrease in task performance. Most studies of neural disruption use a repeated TMS procedure, in which a high-frequency (e.g. 10 or 20 Hz) train of TMS pulses is given during the critical phase of a task (e.g. during stimulus presentation for a memory task). However, it is worth remembering that disruption of one area of the cortex may have secondary effects on other cortical areas which are strongly connected to the disrupted area. The purpose of experiment 2 will be to use rTMS to disrupt activity in the PFC to help causally determine the role of the PFC in episodic memory function.

rTMS has been used fairly extensively in examining the role of areas in the pre-frontal cortex during working memory tasks. These experiments frequently target the DLPFC and VLPFC, areas of the frontal cortex also involved in long-term memory and important for our present discussions. Functional differentiations within the PFC for working memory tasks have been observed, with the VLPFC involved in non-spatial tasks, and stimulation of the DLPFC resulting in greater performance deficits for spatial tasks (Mottaghy, Doring, Muller-Gartner, Topper, & Krause, 2002). However, DPLFC stimulation still had an effect on both the spatial and non-spatial tasks (though note, a larger effect in the spatial task), suggesting the DLPFC may be generally involved in working memory processes. Stimulation of the left DLPFC has also been shown to have a negative impact on maintenance of verbal working memory (Osaka et al., 2007). Mottaghy, Gangitano, Krause, & Pascual-Leone (2003) used single pulse TMS to examine the timing of activity in the DLPFC and parietal cortex during a working memory (n-back) task. Task performance was impeded by TMS earlier in the parietal cortex than the DLPFC, and earlier in the right as opposed to left hemisphere. The maximum effect of TMS of the left DLPFC on task performance was found at 260 ms. Interestingly, the interference effects were very specific to that stimulation timing, and performance deficits were not found when stimulation occurred at 220 or 300 ms after stimulus onset, suggesting that activity in this region was only critical for a very short, specific time period.

Rossi et al. (2001) performed rTMS on the left or right DLPFC (inhibiting activity within the cortex) during encoding or recognition of complex visual scenes. They found that stimulation of the left DLPFC during encoding or right DLPFC during recognition resulted in an impairment in memory performance. This suggests a functional dissociation of the left and right DLPFC during this memory task, similar to that proposed by the HERA model (Tulving et al. 1994). In a

follow-up study, Rossi et al. (2006) performed stimulation on the right and left parietal cortex (which has been implicated in several neuroimaging studies of memory), but failed to find any disruption of memory performance from stimulation of the parietal cortex. Using the same task but examining the effects of 1000 ms trains of rTMS after different delays from stimulus onset, Rossi et al. (2011) stimulated 100, 200, 300, 400, or 500 ms after the onset of the stimuli (a complex scene). They found that stimulation of the left (but not the right) DLPFC after 500 ms post-stimulus during encoding resulted in a memory impairment. There was also the possibility that the level of impairment was modulated with the timing of stimulation onset, with later stimulation producing a greater memory deficit. However, rather than a random or counter-balanced design, the timing of stimulation onset was done across blocks, with later blocks having a later onset of rTMS stimulation. Thus, it is possible that order effects may have influenced their results. However, the fact that only the latest stimulation condition (500 ms) produced a memory deficit suggests that activity in the DLPFC during memory formation is not involved with early processes, such as perception or attention.

Examining related and unrelated word pairs, Sandrini, Cappa, Rossi, Rossini, & Miniussi, (2003) found that stimulation of either the left or right DLPFC during encoding impaired memory performance, but much more so for unrelated than related pairs. The authors interpreted this as a ‘novelty’ effect. However, given the above discussion on mnemonic strategies, it is possible to interpret these results (Sandrini et al., 2003) as evidence that the DLPFC plays a role in forming semantic relationships where none exist (as an effective memory strategy). When activity in the DLPFC is inhibited, participants may be less likely to form semantic relationships among unrelated words, and thus show a decrease in memory performance. This may be

consistent with the DLPFC as a higher-order executive control mechanism involved in selecting cognitive strategies for binding items together.

The notion that the results of Sandrini et al. (2003) may be related to the role of the DLPFC in forming semantic relationships is supported by the results of a more recent paper (Innocenti et al., 2010), in which participants performed a deep or shallow encoding task. For deep encoding, participants had to judge if presented words were living or non-living (a semantic analysis), while for shallow encoding, participants had to judge is the word contained the letter ‘e’. It was demonstrated that stimulation of the left DLPFC abolished the memory enhancing effect of deep encoding, substantially reducing performance in the deep encoding task to a level similar to the shallow encoding task, which was at near-chance levels.

Chapter 4: Experiment 2: The Dorsolateral Prefrontal Cortex Plays a Role in Self-Initiated Elaborative Cognitive Processing during Episodic Memory Encoding: rTMS evidence

Colin Hawco, Marcelo T. Berlim, and Martin Lepage

Contributions: Colin Hawco was the lead author, and was principally responsible for the design, analysis, and interpretation of the study (in collaboration with the other authors), and the primary author of the manuscript. Marcelo Berlim was involved in determining TMS stimulation parameters, and consultation on the overall study design, as well as review of the manuscript. Martin Lepage collaborated on all elements of the study and reviewed the manuscript.

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Abstract

During episodic memory encoding, elaborative cognitive processing has been demonstrated to improve later recall or recognition. While there has been multiple studies examining the neural correlates of encoding strategies, few studies have explicitly focused on the self-initiation of elaborative encoding. Repetitive transcranial magnetic stimulation (rTMS), a method which can transiently disrupt neural activity, was administered during an associative encoding task. rTMS was applied to the left dorsolateral prefrontal cortex (DLPFC) or the vertex (a region not involved in memory encoding) during presentation of pairs of words. Pairs were either semantically related or not related. Two encoding instructions were given, either cueing

participants to analyze semantic relationships (cued condition), or an instruction to memorize the pair without no specific strategy cues (the self-initiated condition). Participants filled out a questionnaire regarding their use of memory strategies and performed a cued-recall task. We hypothesized that if the DLPFC plays a role in the self-initiation of elaborative encoding we would see a reduction in memory performance in the self-initiated condition, particularly for related pairs. We found a significant correlation between the effects of rTMS and strategy use, only in the self-initiated condition with related pairs. High strategy users showed reduced performance following DLPFC stimulation, while low strategy users tended to show increased recall following DLPFC stimulation during encoding. These results suggest the left DLPFC may be involved in the self-initiation of memory strategy use, and individuals may utilize different neural networks depending on their use of encoding strategies.

4.1 Introduction

While areas in the medial temporal lobe have long been known to be involved in memory processes, there has recently been an increased interest in the role of the frontal lobes in long-term memory formation. Neuroimaging studies of item memory have often found a subsequent memory effect in the ventrolateral prefrontal cortex (VLPFC) for remembered items over forgotten items (Blumenfeld & Ranganath, 2007; Paller & Wagner, 2002). Although dorsolateral prefrontal cortex (DLPFC) activity has not been consistently shown in neuroimaging studies of subsequent memory for items, studies examining associative memory (remembering the relationship between two or more items rather than the items themselves) have often reported both VLPFC and DLPFC activity for successful associative memory formation (Blumenfeld et al., 2011; Blumenfeld & Ranganath, 2006; Murray & Ranganath, 2007). Interestingly, activity in the DLPFC has been shown to be increased for associative memory encoding compared to item encoding independent of subsequent memory performance (Achim & Lepage, 2005).

The DLPFC has been proposed to be involved in conscious planned control of behavior and cognition (Petrides, 2005) with several fMRI studies suggesting activity in the DLPFC during associative encoding may be related to working memory processes (Hales et al., 2009; Blumenfeld & Ranganath, 2006). Given that associative encoding may involve greater elaboration or executive control than item encoding, Blumenfeld et al. (2011) examined this issue utilizing a task which required effortful, elaborative encoding for both item and associative encoding. They observed greater activity in the DLPFC for remembered over forgotten memoranda for associative encoding only, while VLPFC activity was greater for subsequently remembered trials for both item and associative encoding. This suggested that DLPFC activity

was not simply the result of increased task demands and elaboration but was related to forming associations between the items.

Additional evidence regarding the role of the prefrontal cortex in memory comes from prefrontal cortex (PFC) lesions. PFC lesions can lead to deficits on tests of free recall (Dimitrov et al., 1999; Jetter et al., 1986; McAndrews & Milner, 1991; Moscovitch & Winocur, 1995b; Stuss et al., 1994) and cued recall (Vogel, Markowitsch, Hempel, & Hackenberg, 1987) without the severe amnesia associated with medial temporal lesions. While specific localization of memory deficits in PFC lesions is complicated by the heterogeneity of lesions, the most severe memory impairments are observed following damage to Brodmann's area (BA) 46 and 9 (the DLPFC) and BA 44 (part of the VLPFC) (Alexander et al., 2003). Interestingly, people with PFC lesions have been shown to have a deficit in self-initiating elaborative and effective memory encoding strategies related to their memory problems. For example, people with prefrontal damage do not typically engage in semantic clustering (Gershberg & Shimamura, 1995; Hirst & Volpe, 1988; Incisa della Rocchetta et al., 1995; Incisa della Rocchetta & Milner, 1993; Stuss et al., 1994), even though this is an effective memory encoding strategy, yet they are capable of performing semantic clustering when explicitly instructed to do so (Gershberg & Shimamura, 1995; Hirst & Volpe, 1988). As opposed to people with frontal lobe damage, healthy individuals will tend to spontaneously utilize elaborative encoding strategies during memory tasks. When examining verbal stimuli, some possible memory strategies include rote-repetition, binding the word into a semantic context (including categorization of words within lists), building a sentence from the word, or using mental imagery. Some strategies, such as sentence generation, are more effective than rote repetition (Dunlosky & Hertzog, 1998; S. Heinze et al., 2006), although rote repetition is still a reasonable memory strategy. Generally, the use of more elaborate and

efficient encoding strategies has been linked to better memory performance in healthy individuals (Camp & Maxwell, 1983; Christopher Hertzog et al., 2004; Shaughnessy, 1981).

Repetitive trans-cranial magnetic stimulation (rTMS) allows a more causative approach in that a functional hypothesis for a specific cortical region can be tested. In healthy participants, rTMS to the left DLPFC during memory encoding has been shown to reduce memory performance for complex scenes (Rossi et al., 2001; Rossi et al., 2011; Rossi et al., 2006), for unrelated (but not related) word pairs (Manenti, Cotelli, & Miniussi, 2011; Sandrini et al., 2003), and for word lists (Grafman et al., 1994). Reduction in memory performance following left DLPFC stimulation is similar for both verbal and non-verbal material (Gagnon, Schneider, Grondin, & Blanchet, 2011). However, laterality effects of rTMS stimulation of the DLPFC have been observed between encoding and recognition with left-side stimulation generally reducing performance during encoding and right-side stimulation reducing performance during retrieval or recognition (Manenti et al., 2011; Rossi et al., 2001; Rossi et al., 2011; Rossi et al., 2006; Sandrini et al., 2003). Together, this would suggest the effects of rTMS are specific to the memory processes being examined rather than general impairments in cognition. The results of rTMS studies provide compelling evidence that the left DLPFC is involved in encoding operations during a variety of conditions, rather than principally during associative encoding as suggested by the fMRI literature (Blumenfeld & Ranganath, 2006; Murray & Ranganath, 2007).

As mentioned earlier, another possible role for the DLPFC during encoding operations may be in the use of elaborative encoding strategies. The DLPFC is associated with high level cognitive functions and findings in people with prefrontal damage indicate a reduction in the self-initiation of effective elaborative encoding strategies. This fits with the fMRI literature that has shown the DLPFC to be mainly associated with successful encoding only for associative

memory tasks (tasks that promote the use of more elaborative encoding strategies which facilitate forming relationships among objects). While there is some evidence of memory strategy effects following DLPFC stimulation during memory retrieval (Manenti, Cotelli, Calabria, Maioli, & Miniussi, 2010), no previous study has used rTMS to examine elaborative encoding strategies.

To explore this, we conducted a study that examined the possible role of the left DLPFC on the self-initiation of elaborative encoding strategies during memory encoding. To do so, we utilized an associative memory task in which participants were instructed to remember pairs of semantically related or unrelated words. As the goal of our study was to examine self-initiation of elaborative encoding, we utilized two separate encoding instructions that oriented participants towards externally-cued or self-initiated elaborative encoding. If the DLPFC does indeed play an important role in the self-initiation of elaborative encoding, we would expect to see a reduction in memory performance following left DLPFC rTMS stimulation during the self-initiated condition (possibly larger for related pairs due to elaborative encoding of the relationship between the words) and no rTMS effects in the externally-cued condition. In contrast, if the DLPFC plays a more general role in encoding associations, we expected a generalized decrease in memory performance regardless of encoding condition. In order to control for non-specific effects of rTMS (sound and somatosensation), we utilized a within-subject crossover design comparing DLPFC stimulation to rTMS administered to the vertex, an area which has been used as a control site in other rTMS memory studies that has been shown to be comparable to a baseline condition (Innocenti et al., 2010; Rossi et al., 2011). Finally, participants answered a questionnaire on memory strategies and performed a cued recall test to assess the effects of rTMS on memory encoding and strategy use.

4.2 Methods

4.2.1 Participants: Only right handed participants between the ages of 18 to 35 who had native level proficiency in English, and no self-reported history of neurological or psychiatric disorders (including any history of seizures) were eligible to participate in this study. Forty participants were recruited for this study (16 males; mean age 22.8 ± 3.6). Participants were screened for TMS contraindications (such as the presence of metallic objects in the body) and signed an informed consent form prior to the experiment. There was no significant difference in either the gender or age of participants in each order group ($p = 0.13$ for age, independent samples t-test, $p = 0.33$ for gender, chi-squared test). Of the forty participants recruited, one chose not to complete the experiment due to discomfort during rTMS and four other participants were excluded due to extremely poor performance on the cued recall task (mean recall rate of 3.5%, 4.2%, 6.3%, and 6.9% for these individuals; see below for task details), resulting in a total of 35 with usable data.

4.2.2 Stimuli: Experimental stimuli consisted of pairs of related and unrelated words. All words were concrete visualizable nouns. In order to classify word-pairs as related, norms were collected from a group of 10 English speaking participants. Participants were shown a pair of words on a laptop, and rated the level of relatedness of each pair on a 7-point scale, with 1 being totally unrelated (e.g. hammer - apple), and 7 being very highly related (e.g. hammer - nail). Word pairs with mean relatedness scores above 4.5 and a standard deviation of less than 2.5 were considered to be semantically related. One hundred forty-four word pairs were created for the experiment (72 related and 72 unrelated).

4.2.3 Experimental Task: The experimental task was performed on an IBM laptop with a 17” screen, positioned approximately 0.7 meter from the participant’s eyes, using E-Prime 2.0. The experiment was divided into three parts: an encoding phase (during which rTMS stimulation was administered), a questionnaire assessing encoding strategies, and a cued-recall test.

4.2.4 Encoding Phase: Participants were presented an encoding instruction for 2 seconds, then a pair of words with the previous instruction for 2 seconds, and finally a fixation cross for 8 seconds between trials (Figure 1). rTMS was administered while the word pair was on the screen (see below). Encoding instructions oriented participants towards either externally cued elaborative encoding (the 'cued' condition) or self-initiated elaborative encoding (the 'self-initiated' condition). For the cued condition, the task instruction was 'related?'. Participants were instructed to indicate if the presented words were semantically related or not. For the self-initiated condition, participants were shown the task instruction 'memorize' and asked to make a button press once they read the words. We chose the non-specific instruction 'memorize' to ensure participants were free to utilize encoding strategies without an external prompt to do so (so any elaborative encoding was self-initiated). It was emphasized to the participants there would be a memory test later on and they would be tested on all of the word pairs (regardless of whether the task instruction was 'related?' or 'memorize'). So, the only difference between the 2 encoding conditions was if participants were explicitly instructed to judge relatedness (an effective memory strategy) or if they had to self-initiate semantic processing. If participants did in fact use semantic processing during the self-initiated condition, we hypothesized there would be a greater recall for related over unrelated word pairs, which should be similar to the cued condition.

Each word pair was associated with the externally cued encoding condition in half of participants and the self-initiated condition in the other half. The encoding phase was divided into two consecutive blocks of 72 trials (corresponding to the two rTMS blocks; DLFPC and Vertex stimulation) of 12.5 minutes in length.

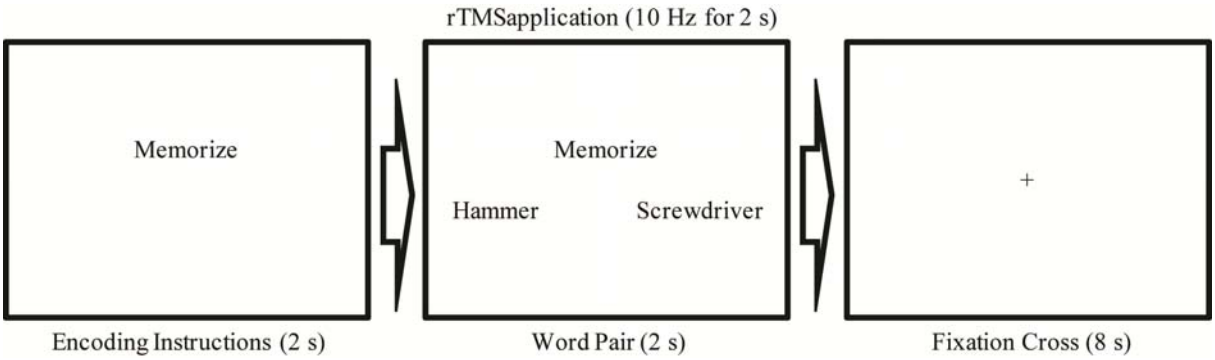

Figure 1: Schematic of encoding task. Participants were shown encoding instructions ('related? for cued encoding, or 'memorize' for self encoding trials) for 2 seconds, followed by the instructions along with the word pair for 2 seconds, and lastly a fixation cross for 8 seconds. rTMS was administered during word pair presentation.

4.2.5 Memory Strategy Questionnaire: Immediately after the encoding phase, participants were instructed to fill out a memory strategy questionnaire. The purpose of the strategy questionnaire was to determine if DLPFC stimulation had a direct effect on self-reported strategy use and to allow for a more detailed examination of how different strategy uses may have been affected by rTMS. Participants were informed that there were four types of trials during the experiment. For each of these separate conditions, they were asked to rate how often they used each of five different memory strategies on a numerical 7-point scale (with *1* corresponding to never, and *7* with always). These strategies were derived by considering other studies examining memory strategies (Dunlosky & Hertzog, 1998, 2001; C. Hertzog, McGuire, et al., 2010; Kirchhoff & Buckner, 2006).The five memory strategies were:

1. I considered how the words could be related to each other.

2. I imagined the objects described by the words interacting in some way.

3. I used prior personal memories associated with the objects.

4. I constructed a sentence with the two words.

5. I repeated the words to myself in my head.

Questions 1 to 4 can be considered elaborative encoding strategies, in that they include additional cognitive processing related to the stimuli. Each strategy was briefly explained to the participants. Participants were instructed to consider only word pairs presented during the second block of the encoding phase (corresponding to either DLPFC or vertex stimulation). We believed that participants would retrospectively report more accurately to more recent events (i.e. the second block of encoding). Furthermore, it would have been inappropriate to have participants complete the questionnaire after each block as exposure to memory strategies after the first block would have confounded any strategy related effects in the second block. Note, while participants responded to the memory strategy questionnaire with respect to either DLPFC or vertex stimulation, all participants received both types of stimulation during the experiment.

4.2.6 Cued Recall Phase: Recall began 30-35 minutes after the end of the second rTMS encoding block, to allow time for any potential carry-over effects of rTMS to wear off. Participants were presented a single word on the computer screen and instructed to indicate which word was paired with the presented word during the encoding phase. Participants responded verbally and then pressed the spacebar to proceed to the next trial. Participants were told to say ‘Pass’ if they were unable to recall the match to the presented word. Responses were coded as correct, incorrect, or pass.

4.2.7 rTMS Stimulation: High frequency rTMS was administered during the encoding phase using a Magstim Rapid2® magnetic stimulator (Magstim Company Ltd., U.K.) with a focal 70-mm figure-of-eight coil. The resting motor threshold was determined over the left primary motor cortex using the visualization method (Pridmore, Fernandes Filho, Nahas, Liberatos, & George, 1998) and the maximum likelihood strategy (Mishory et al., 2004). Coil positioning was determined by the 10-20 EEG system, such that F3 corresponds to the left DLPFC (Herwig, Lampe, et al., 2003; Herwig, Satrapi, & Schonfeldt-Lecuona, 2003) and the vertex corresponds to Cz. For DLPFC stimulation, the coil was placed flat against the scalp with the handle pointing 45° away from the midline; for vertex stimulation, the handle was pointed behind the participant with the coil flat on the head and the handle facing the participant's back. During word presentation, a 2 second train of 10 Hz rTMS was presented at the resting motor threshold, with a 10 second inter-train interval. Two bursts of rTMS were presented prior to the onset of the first word-pair to acclimatize participants.

Two separate blocks of rTMS were administered for each participant: one block stimulating the DLPFC and the other block stimulating the vertex (as a control). The vertex has been used as a control site in other memory-rTMS studies to account for non-specific TMS effects (somatosensation and noise) and memory performance; vertex stimulation has been found to be similar to a no TMS baseline condition (Innocenti et al., 2010; Rossi et al., 2011). The order of rTMS blocks (DLPFC and Vertex) was counter-balanced across participants with half of the participants receiving the DLPFC block first and half receiving the vertex block first.

4.2.8 Statistical Analysis: All statistical analyses were performed using PASW statistics 18.0. For ANOVAs, equality of variance was tested with Levene's test, and normality was confirmed.

Any results at $p < 0.05$ were considered significant, while results at $p < 0.1$ were considered marginally significant and fully reported.

4.3 Results

4.3.1 Encoding Phase: Encoding accuracy data was only analyzed for the cued encoding task (the 'related?' task instruction), as participants performed a judgment task which could be considered correct or incorrect. The mean accuracy for the cued encoding task was 93.4% for DLPFC trials and 91.3% for vertex trials. No significant difference in accuracy was found for relatedness, rTMS block, or rTMS by relatedness interaction (all $p > 0.1$). This indicated that TMS stimulation did not interfere with participant's ability to analyze semantic relationships.

4.3.2 Questionnaire Data: For this part, participants were separated into 2 groups (DLPFC or vertex stimulation in last encoding block) and then we compared the mean response for each question within the 4 types of trials (Figure 2). Since questionnaire data was highly skewed (positive for questions 1, 2, and 5; negative for questions 3 and 4), data were analyzed using Mann–Whitney U-tests. No significant effect of group was observed for any question (all $p >$ 0.1).

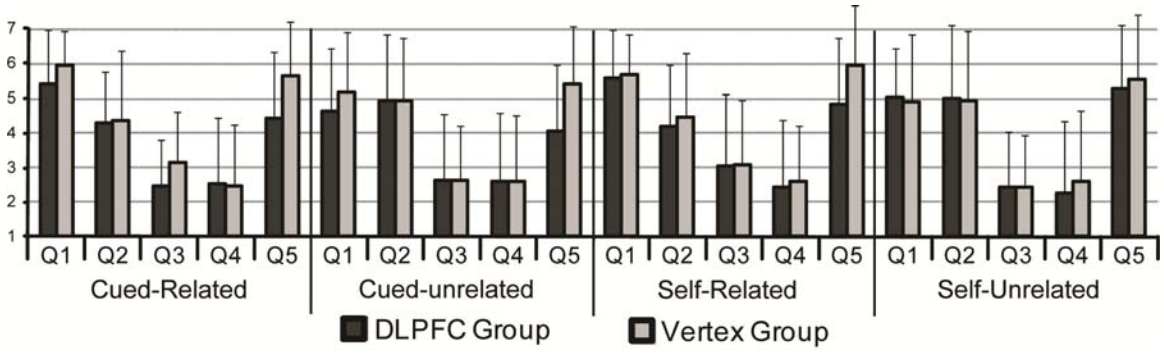

Figure 2: Mean (and standard deviations) of responses given on the memory strategy questionnaire. Participants responded with respect to the second encoding block, which corresponded to DLPFC stimulation for half of participants (n = 17), or the vertex block for the other half (n = 18).

4.3.3 Cued Recall Results: Overall cued recall results are presented in Figure 3. We performed a repeated measures MANOVA with encoding condition (cued, self-initiated) and rTMS (DLPFC, vertex)] as within-group factors. Due to a generally poor performance and a large number of participants with no correct answers, recall data for the unrelated word pairs was highly skewed (floor effect) and was not included in this analysis. Overall, we observed a significant main effect of encoding ($F_{(1,34)} = 0.38$, $p = 0.046$) with better recall for the cued condition vs. the self-initiated condition. There was no main effect of TMS ($F_{(1,34)} = 2.77$, $p = 0.543$) or an interaction ($F_{(1,33)} = 0.49$, $p = 0.825$).

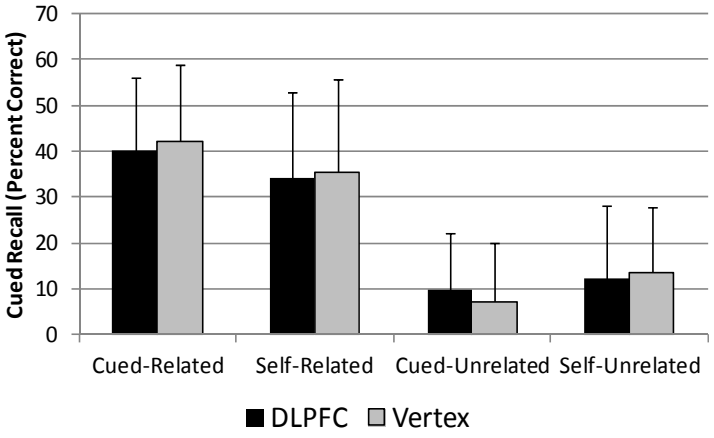

Figure 3: Cued recall results across the experimental conditions (mean and std for correct responses).

Since strategy use has been shown to be related to rTMS effects on the DLPFC during recognition (Manenti et al., 2010) we re-ran the MANOVA using "strategy use" as a covariate to determine if elaborative encoding strategies had any effect on performance. Strategy use was calculated as the mean response for questions 1 to 4 (the elaborative encoding strategies) from the questionnaire. We now observed a marginally significant TMS by encoding interaction

($F_{(1,32)}$ = 3.59, p = 0.067) but no main effect of encoding ($F_{(1,33)}$ = 1.07, p = 0.308) or TMS ($F_{(1,33)}$ = 2.01, p = 0.166). For completeness, we also performed a similar MANCOVA using Question 5 (repetition) as a covariate to determine if repetition strategy use would have a similar effect on performance; no significant effects were found (all p > 0.1).

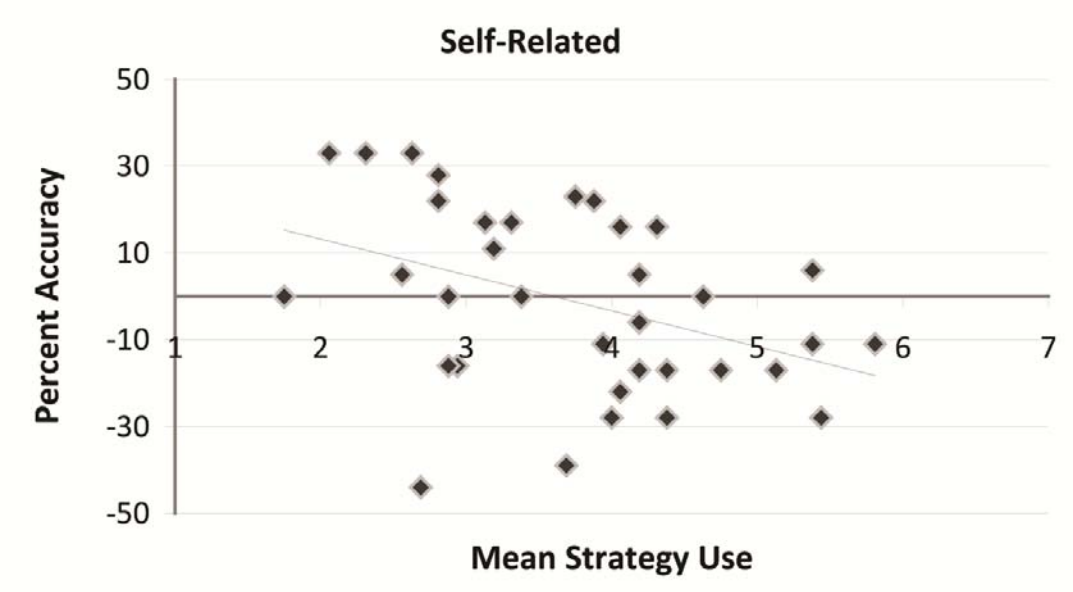

Figure 4: Scatter plots for difference scores of TMS (DLPFC - vertex) in cued recall performance and mean memory strategy use (for questions 1 to 4 on the questionnaire), in the self-related condition. A positive difference score indicated that participants had increased performance following DLPFC stimulation (compared to vertex), while a negative score indicates DLPFC stimulation during encoding reduced later cued recall performance. A significant correlation was only found for the self-related condition, using Spearman's Rho.

Given the above marginally significant interaction, further analyses were performed. As we were interested in the effects of TMS on the different task conditions, we calculated a difference score for TMS (DLPFC minus vertex) across each task condition (cued-related, cued-unrelated, self-initiated-related, and self-initiated-unrelated). These difference scores (representing the effects of TMS in each separate condition) were then correlated with strategy use for each participant using Spearman's Rho. There was a significant correlation with the self-

initiated-related condition (Rho = 0.41, p = 0.01; Figure 4); the other 3 conditions did not reach significance (all p > 0.1). This suggested the effect of rTMS on cued recall performance may be modulated by strategy use in the self-initiated-related condition.

4.4 Discussion

We performed a study using rTMS using a within-subjects cross-over design to test whether or not the DLPFC plays a role in the self-initiation of elaborative encoding strategies. We used two encoding conditions: one cued participants towards elaborative encoding ('related?' instruction) while the other did not orient participants towards any specific encoding strategy or elaborative encoding ('memorize' instruction, or self-initiated). To begin, we observed equally improved recall performance for related pairs over unrelated pairs of words in both the self-initiated and cued encoding conditions indicating participants did engage in at least some elaborative encoding (semantic clustering) during the self initiated condition. Therefore, the main difference between these two conditions was if elaborative encoding was cued or self-initiated.

We did not observe any overt effect of rTMS on strategy use. It was not clear whether this was because our rTMS conditions had no overt effect on strategy use or if the questionnaire was simply not sensitive enough to detect small changes in strategy use over a limited time window. For example, the participants' answers may be more of a reflection of how they would generally perform such a task rather than what they actually did during the second block of the experiment. However, we did observe an effect of TMS on cued recall for the self-initiated related condition. This suggested that DLPFC stimulation is indeed having an effect on encoding which is related to the use of memory strategies, in keeping with our hypothesis, and this effect

is specific to the condition in which strategy use is self-initiated. We might therefore infer that the DLPFC is involved in the self-initiation of elaborative encoding. However, it is not the clear effect we had expected to find, in which DLPFC stimulation would simply reduce later memory performance for the self-related encoding condition. Instead, participants with who made low use of memory strategies were more likely to have increased recall performance following DLPFC stimulation at encoding, while high strategy users showed reduced recall following DLPFC stimulation (in the self-related condition).

This finding shows that the effects of rTMS on the DLPFC may not be consistent across participants, but instead may differ across individuals according to specific factors (such as appropriate strategy use), and these differences may be modulated by experimental conditions. In another study using rTMS, right DLPFC stimulation during a recognition task has been found to reduce recognition for unfamiliar face-name pairs for people who reported using recognition memory strategies. In contrast, participants reporting not using strategies showed performance reduction following left DLPFC stimulation (Manenti et al., 2010). This suggests that strategy users and no strategy users may utilize different neural networks for task completion, at least for recognition memory. fMRI studies have also shown that individual differences in the pattern of brain activity may be related to individual strategy use during encoding (Kirchhoff & Buckner, 2006; Miller, Donovan, Bennett, Aminoff, & Mayer, 2012). Our results compliment these findings, in that we found that participants who make minimal use of memory strategies showed a different effect of DLPFC compared to vertex stimulation than high strategy users in the self-related condition. This suggests that different individuals may be utilizing different neural networks during task performance, depending on the how they perform the task. An important implication of our results is that individuals may have substantially different responses to rTMS

stimulation (as well as patterns of brain activity in neuroimaging studies), particularly for less structured tasks such as our self-initiated condition. We must therefore be careful in interpreting findings based on group means, which may reflect results from only a portion of participants or fail to show significance due to different patterns of activity across groups of participants. It may be more appropriate to seek out patterns of activity within groups of individuals within a given data set, and determine if those differences can be related to a relevant factor (such as strategy use or cognitive ability).

Our finding that rTMS had an effect in the self-related condition which was modulated by strategy use suggests that our hypothesis that the left DLPFC plays a role in self-initiation of encoding strategies. However, the effects were modulated by overall strategy use, suggesting that the relationship between left DLPFC and strategy use is not clear-cut. Instead, it suggests the possibility of differing neural networks across individuals, related to how much they utilize memory strategies. This may have particular relevance when considering clinical groups who may have a deficit in self-initiated strategy use, such as schizophrenia or Alzheimer's. Differences in neural activity in these individuals during cognitive tasks may reflect altered neural networks activated during tasks when individuals fail to utilize efficient strategies to perform a task.

Chapter 5: Concurrent TMS and fMRI.

New technology has made it possible and practical to perform TMS stimulation during an MRI scan. This new and exciting combination of techniques has only recently become available (Bohning et al., 1999; Bohning et al., 1998; Roberts et al., 1997, see Bestmann, Ruff, et al., 2008, for review). This combination offers a unique and exciting opportunity to take advantage of the high spatial resolution of fMRI and pair it with a method for causative changes in brain function (TMS). When considering the combination of TMS and fMRI, there is two ways these modalities can be combined: online and offline TMS-fMRI. In offline TMS-fMRI, TMS stimulation is applied outside the MRI scanner for a period of time. This results in long term changes in cortical activity which may persist for tens of minutes. The participant is then placed into the scanner and brain activity is measured. It is then possible to compare the effects of prolonged trains of TMS on brain function with a baseline, no TMS period. While offline TMS-fMRI studies have produced some interesting results, there are some limitations to these studies. For one, the time effects of TMS stimulation on cortical activity are limited, and the effects of stimulation may have a 'roll-off', in that the effects of TMS on cortical activity may slowly reduce over time during task performance.

In on-line TMS-fMRI, TMS stimulation is applied during a task, simultaneous with brain imaging. Because TMS pulses last only a brief time (approximately 1ms), pulses can be interleaved with MRI slice acquisitions. This technique poses some significant challenges. While the MRI compatible TMS coil has no ferrous-metallic components, the presence of the TMS coil inside the scanner results in a distortion of the fMRI signal (Weiskopf et al., 2009). Furthermore, when an actual TMS pulse is fired, there can be a dramatic effect on MRI signal for a short

period of time. This results in the loss of data for the slice during which the TMS pulse is fired. Thus, data for those slices will need to be replaced by interpolating data from other acquisitions.

A further challenge of combined TMS-fMRI is the choice of a baseline or comparison condition. TMS stimulation results in rather prominent non-specific TMS effects, particularly a loud sound during coil discharge, and somatosensory sensation over the site of stimulation. As fMRI analysis typically focuses on the contrast between different conditions, it is not generally appropriate to compare TMS stimulation to a no-TMS baseline condition, as this should evoke strong activations in auditory and somatosensory regions. It is therefore important to carefully design any combined TMS-fMRI study to ensure there is a valid baseline condition to address the research question being explored. However, with careful design and some technical sophistication in setup and analysis, combined TMS-fMRI studies are possible, and may prove to be highly useful in understanding brain function.

It has been demonstrated that TMS stimulation results not only in changes in neural activity directly over the site of stimulation, but also at distant cortical and sub-cortical sites (Paus et al., 1997). Most concurrent TMS-fMRI studies have, for historical reasons, focused on the primary motor cortex (M1). The advantage of stimulating M1 is that there is a direct and easily measurable behavioral consequence of such stimulation (motor activity), which can be used to validate the area of stimulation (Bestmann, Swayne, et al., 2008). It was demonstrated in these early studies that even relatively short bursts of TMS stimulation of M1 resulted in activity across multiple brain regions, including the supplementary motor and pre-motor cortices. Studies (Bohning et al., 2003; Bohning et al., 1999) have demonstrated that the effects of TMS on unstimulated regions is dependent on the magnitude of the stimulation, with higher intensity TMS stimulation resulting in greater changes in distant cortical regions. Activity at distant areas

of the cortex has also been observed even when the stimulated area does not show a clear BOLD change during TMS (Bestmann, Baudewig, Siebner, Rothwell, & Frahm, 2003, 2004; Bohning et al., 1999; Denslow, Bohning, Bohning, Lomarev, & George, 2005).

It has also been demonstrated that the effects of TMS stimulation can be dependent on the current state of the cortex. For example, when stimulating M1, differences have been observed between resting and muscle contraction (Strens et al., 2002; Fujiwara & Rothwell, 2004). These state-dependent effects of TMS stimulation have also been demonstrated in the visual cortex (Aurora, Ahmad, Welch, Bhardhwaj, & Ramadan, 1998), during spatial attention (Bestmann, Ruff, Blakemore, Driver, & Thilo, 2007), and during neural adaptation paradigms (Silvanto, Muggleton, Cowey, & Walsh, 2007). Ruff and colleagues (Ruff et al., 2008; Ruff et al., 2006; Ruff, Blankenburg, et al., 2009) demonstrated that stimulation of the parietal cortex has an effect on the visual cortex (areas V1-5), but that this activity was different when visual stimuli were being presented (therefore presumable altering the functional state of the visual cortex) as opposed to when there was no visual stimuli presented.

Very few studies have successfully performed combined TMS-fMRI in cognition. A recent study used combined TMS-fMRI to examine a hypothesis of left DLPFC function during working memory interference (Feredoes, Heinen, Weiskopf, Ruff, & Driver, 2011). This study examined the role of the DLPC in working memory maintenance and resistance to distracters, with a role in top-down control of more posterior regions. Participants were presented with stimuli (faces or houses) which had to be maintained in working memory. On some trials, a distracter from the other category (face distracters for house, and house distracters for faces) were presented, along with a burst of 3 pulses of TMS at 11Hz over the left DLPFC. The authors then examined activity in two a-priori selected posterior regions, the parahippocampal place area

and the fusiform face area. TMS was presented at either a high level of intensity or a subthreshold low-level intensity control. When the target stimuli were faces, and the distracter stimuli were houses, TMS caused a change in neural activity specifically in the fusiform face area. In contrast, house targets with face distracters resulted in changes only in the parahippocampal place area. TMS had no effect on these regions in the absence of a distracter. This double-dissociation demonstrates that the DLPFC modulates activity for distracters in the fusiform face area for face targets and the parahippocampal place areas for house stimuli. This study represented an excellent use of combined TMS-fMRI to test an existing hypothesis of neural connectivity and function. By combining a causal technique (TMS) with fMRI, the authors were able to directly demonstrate the functional connectivity between the DLPFC and distant posterior regions during task performance. An important point of this study is that the focus was not on disrupting brain function and observing a change in task performance, as is typically the case in TMS. Instead, the authors were interested in changes in distant regions following TMS stimulations. When two regions are interacting, the gates of communication are open, allowing for an alteration of activity from TMS stimulation.

The purpose of Experiment 3 was to adapt a TMS-fMRI design for the study of cognition, particularly for memory encoding. As described above, the choice of a baseline task to compare with TMS stimulation was an important consideration in designing a study. A further issue is that the available MRI compatible TMS coil was only designed for a maximum of 3 TMS pulses per second within the scanner. This is an important point, as the effect of TMS on a cortical region may be very time specific. Therefore, if we stimulate during the wrong time window, we may not observe an effect (as our stimulated region may not be involved in the task during that time window). Given the limits of the TMS coil, and the difficulties in comparing

TMS stimulation to a no-TMS stimulation condition, an experimental design was conceived in which we would alter the onset timings of TMS during an encoding task, by presenting TMS stimulation during different time windows. By doing so, we hoped to observe task-specific changes in distant brain regions following left DLPFC stimulation, and that these changes would be specific to certain time windows. In this way, we could infer temporal information about when specific regions were communicating with the left DLPFC. This also overcomes the problem of the non-specific effects of TMS stimulation (sound and somatosensation), in that we are comparing the effects of the same TMS stimulation across brief time windows.

This approach may represent a significant technique for understanding brain function and the interactions between brain regions. In many respects, this technique could be considered a means of achieving high temporal resolution brain imaging (as we can vary the onset of TMS across very precise time windows), despite the fact the BOLD signal measured by fMRI is a physiological signal with a time scale in the seconds (as opposed to milliseconds). The purpose of Experiment 3 was to test such a design and demonstrate that time-specific changes in distant brain regions could be observed following left DLPFC stimulation.

Chapter 6: Experiment 3: Time Varying the Onset of TMS Stimulation during Concurrent fMRI: A Method for High Temporal Resolution Measurement of Interactions between Brain Regions

6.1 Introduction

Since the inception of functional magnetic resonance imaging (fMRI), there has been an explosion of studies examining the neural correlates of a variety of cognitive tasks. While fMRI has been an extraordinarily useful tool in understanding human brain function, it has some fundamental drawbacks as a research tool. For one, fMRI analysis is correlational in nature. While we can observe specific regions of the brain which are active during a given task, it is not always clear that those regions are causally involved in the task. That is, if that region of the brain was removed (by a lesion, etc), participants may still be able to perform the task. For example, while the parietal lobes are consistently observed to be active in studies of memory (Cabeza, 2008; Wagner, Shannon, Kahn, & Buckner, 2005), lesions to the parietal lobes (even when overlapping areas found active in neuroimaging studies) do not produce obvious memory deficits (Simons et al., 2008). Another intrinsic limitation of fMRI studies is poor temporal resolution. While recent advances in imaging have allowed for fast data acquisition, in some cases as fast as one whole brain scan every 100 ms, (Lindquist, Zhang, Glover, & Shepp, 2008), the BOLD signal measured by fMRI is still an intrinsically slow signal. Furthermore, the time course of the BOLD signal can be strongly influenced by local physiology (vasculature and capillary distribution). This can complicate any attempt to gain useful temporal information from fMRI. However, it is certainly an important and relevant question to understand which brain

regions are interacting during task performance, and the timing of those interactions between regions.

In contrast to fMRI, transcranial magnetic stimulation (TMS) allows for a causative examination of the role of a specific brain region with a high temporal resolution. TMS studies work by presenting a train of magnetic pulses during task performance, which disrupts or disorganizes brain activity at the site of stimulation during task performance. TMS can be delivered with a high level of temporal accuracy, and chronometric single pulse studies have been used to determine the specific timing of involvement of brain regions during task performance. For example, Mottaghy et al. (2003) administered single TMS pulses to the left or right dorsolateral prefrontal cortex (DLPFC) and left or right inferior parietal cortex during a working memory (n-back) task, and found highly temporally specific effects (within 40 ms) of TMS on task performance across regions. TMS studies have been tremendously useful in providing causative evidence of the role of specific brain regions in cognitive tasks, although such studies generally require a reasonable hypothesis of what the stimulated brain region is actually doing during a given cognitive task. It is also difficult to be certain that any observed behavioral effects following TMS stimulation can be attributed to the specific region being stimulated. While the main effect of TMS is to alter activity in the region being stimulated, changes in the stimulated region can result in modulation of neural activity in distal regions of the brain, which may affect participant's performance on the task being examined.

For some time, it has been possible to conduct concurrent TMS-fMRI studies (Bohning et al., 1999). However, due to the technical challenges and the previous lack of commercially available MRI compatible TMS coils, only a relatively small number of studies have performed concurrent TMS stimulation while scanning brain activity using fMRI. However, MRI

compatible TMS coils have become more readily available, leading to a recent increase in studies performing combined TMS and fMRI. TMS-fMRI is an exciting research technique in that it allows for an examination of the interaction across brain regions during task performance.

When stimulating the primary motor cortex, even short bursts of TMS can produce changes in distant cortical regions (Bohning et al., 1999; Bohning et al., 1998), and the effects of TMS on distant regions was related to the intensity of stimulation (Bohning et al., 2003; Bohning et al., 1999). Furthermore, the effect of TMS stimulation of a given region on distant cortical areas is modulated by the state of cortical activity or the specific task being performed (Aurora et al., 1998; Bestmann et al., 2007; Feredoes et al., 2011; Fujiwara & Rothwell, 2004; Ruff et al., 2008; Ruff et al., 2006; Ruff, Blankenburg, et al., 2009; Silvanto et al., 2007; Strens et al., 2002). This demonstrates that TMS can be used to probe task-specific functional networks, in that the effects of TMS stimulation on distal brain regions are dependent on the interactions between regions during that specific task.

The purpose of this study is to demonstrate a technique combining TMS and fMRI to examine time-specific and task-specific interactions across cortical regions during a cognitive task (associative memory encoding). The dorsolateral prefrontal cortex (DLPFC) is involved in the successful encoding of associations between objects (Blumenfeld et al., 2011; Blumenfeld & Ranganath, 2006, 2007; Murray & Ranganath, 2007; Sommer, Rose, Weiller, & Buchel, 2005; Summerfield et al., 2006). However, large and diverse activations in other areas of the cortex are often also observed during encoding tasks. From fMRI alone, it is not clear how these regions are interacting during task performance. However, it has been suggested that the DLPFC plays a role in high-level control of cognitive operations during associative encoding (Blumenfeld &

Ranganath, 2006). We might therefore suppose that the DLPFC will interact with different brain regions at different times during the course of encoding.

In order to examine the temporal dynamics of DLPFC interactions with other brain regions during memory encoding, 3 pulses of TMS at 10 Hz was presented to the left DLPFC during an associative encoding task. The timing of the onset of TMS stimulation was varied, with the onset of stimulation occurring at 200 ms, 600 ms, or 1000 ms after stimuli onset. This results in three non-overlapping time windows of TMS stimulation. There was also a no TMS baseline condition. In order to have a condition which could be contrasted within each TMS stimulation condition, we presented pairs of objects which were either semantically related or unrelated to each other. If we observe that the effects of TMS on a distant cortical region is limited to a specific time window, it demonstrates that the DLPFC is communicating with that region during that specific time window and the changes in cortical activity in distant regions is not caused by non-specific TMS side effects (such as noise or somatosensation).

6.2 Methods

6.2.1 Participants: Twelve participants (four females, average age 21.8 years, age range 19-26) were recruited for this study. Inclusion criteria were that all participants were right handed, aged 18-35 year old, native-level English proficiency, and no history of neurological or psychiatric disorders. One participant declined to complete the study due to discomfort associated with TMS, and another participant's session was cancelled due to technical problems with the experimental presentation software, resulting in a total of ten data sets included in the analysis.

6.2.2 Experimental Task: The experimental task was presented using E-prime software 2.0 (build 2.0.10.182) on a PC running windows 7. Stimuli consisted of pairs of high quality

color photographs of common objects (tools, kitchen items, fruit, etc)of objects taken from the Bank of Standardized Stimuli (Brodeur et al., 2010). Half of the object pairs were semantically related to each other (e.g. axe - saw), and half were unrelated (e.g. backpack - lime). Participants were instructed to examine the object pair and judge which of the objects is larger in real life. Behavioural data for the size task was not recorded due to necessities in how E-prime was set up to trigger the TMS pulses. Relatedness and size judgements were normed by asking five English speaking participants (who did not participate in the TMS-fMRI study) to judge which object of the pair was larger, and if the pairs were related. Pairs were only included in the experiment if 4 out of 5 of these individuals judged the pair to be related, and agreed on which object was larger.

During each trial, participant's saw a fixation cross for 2 seconds (which served as a warning that the stimuli were about to appear), followed by the object pair for 2 seconds, and a blank screen inter-trial interval, which lasted from 4.4 to 11.2 seconds. The experiment was divided into two runs of 60 trials, each lasting 12.5 minutes. Prior to the onset of the first experimental trials, two 'TMS acclimation' practice trials were presented, in which a pair of images depicting the same object was presented along with a train of TMS stimulation, to acclimate participants to the TMS stimulation prior to the first experimental trial.

Participants were informed that they were performing a memory study, and explicitly told that there would be a post-fMRI memory test for the association between objects. Following the fMRI encoding task, participants were removed from the scanner. Approximately 30 minutes after the end of the last encoding run, participants were given a cued recall test. Participants were presented with a single object from a pair which was presented during the encoding phase, and verbally indicated which object was paired with that object during encoding. Any reasonable description of the paired object was accepted as correct. In the case where the participant could

not remember which object was paired with the presented object, they were instructed to say "pass".

6.2.3 fMRI Parameters: : Echo-planar images were collected on a Siemens 3T Tim trio MRI (TR = 3000 ms, TE = 30 ms, slice acquisition time TA = 100ms, 30 slices of 5 mm thick, 64 x 64 voxel plane with an FOV of 256 mm, giving 4 mm x 4 mm x 5 mm voxels, and an interleaved slice order acquisition). Each BOLD run was preceded by 4 volumes that were discarded to allow a magnetic steady state, and included 250 whole brain volumes and 60 experimental trials. Following the two EPI sequences, an anatomical scan was performed. The anatomical scan was a sagital 3D FLASH (TR = 20 ms, TE = 4.99 ms, FOV 256 mm, 1mm x 1mm x 1 mm voxels). The anatomical scan lasted for 7.5 minutes.

6.2.4 TMS stimulation: TMS was administered using a Magstim Rapid2® magnetic stimulator (Magstim Company Ltd., U.K.) with an MRI compatible focal 70-mm figure-of-eight coil. Prior to entering the MRI the resting motor threshold was determined over the left primary motor cortex using the visualization method (Pridmore et al., 1998). All subsequent TMS stimulation was presented at the motor threshold.

During the encoding phase inside the MRI, trains of TMS consisted of three TMS pulses spaced 100 ms apart (10Hz frequency). The TMS coil was placed over EEG 10/20 electrode site F3, which corresponds to the left DLPFC (Herwig, Lampe, et al., 2003; Herwig, Satrapi, et al., 2003), with the coil placed flat against the scalp and the handle pointing 45° away from the midline. The TMS coil (and the participant's head) was held in place inside the MRI coil with MRI compatible foam padding which was packed around the coil and participant. The onset of the TMS train relative to the onset of the object pair was varied, such that the train of TMS pulses could start at 200ms, 600ms, or 1000ms after stimuli onset. Each TMS onset condition

was presented during 30 trials (15 related and 15 unrelated object pairs). There were also 30 trials of a no TMS baseline condition intermixed with the TMS trials. Because TMS pulses had an adverse effect on MRI slice acquisition, the onset of the stimuli (and as such, the onset of TMS) was jittered such that the slice of MRI data affected by the TMS pulses was equally distributed across TMS onset conditions.

6.2.5 fMRI Data Analysis: fMRI data was analyzed using SPM8. The first step of preprocessing was to replace data from slices affected by TMS pulses. Slices affected by the TMS pulses were replaced by interpolating data for that slice from the previous and subsequent TR, as has been done in previous studies (Bestmann, Ruff, et al., 2008; Feredoes et al., 2011). fMRI data was then motion corrected, normalized to the default SPM EPI template (and transformed in 2mm x 2mm x 2mm voxels), and smoothed with an 8mm Gaussian kernel. Data was then analyzed with a standard linear model, using the HRF plus derivative and dispersion. Event onset was defined as the onset of the object pair. Eight types of events were defined in the analysis, with separate events for the related and unrelated pairs for each of the four TMS conditions (noTMS, 200ms, 600ms, and 1000ms).

Significant fMRI activation was defined as a cluster of at least eight contiguous voxels with a t-value above 4.29 (which corresponds to $p < 0.001$ uncorrected for multiple comparisons). Three sets of contrasts were performed. In the first set, we contrasted related > unrelated pairs (and vice versa) separately in each TMS condition (resulting in four t-maps). The second contrast compared the noTMS condition to each TMS condition, separately for related or unrelated word pairs (resulting in six t-maps). Note that not all of these contrasts were independent, as the related noTMS condition was included in three contrasts, and the unrelated noTMS was included in the three other contrasts. These t-maps from these contrasts were then

visually examined to identify clusters of activity in which there might be a time-specific TMS effect. For example, if a cluster was observed in the related > unrelated for the 200ms condition, but not for noTMS, 600ms, or 1000ms. The t-maps were visualized at threshold of 20 voxels above $t = 3.29$ (corresponding to $p < 0.005$ uncorrected). Using this sub-threshold visualization made it possible to identify regions with a trend towards activation, increasing our understanding of TMS modulated activity in that region. These sub-threshold activations were not considered significant and were utilized for visualization purposes only. Beta values for the 8 experimental conditions (related or unrelated pairs across the 4 TMS conditions) were then extracted from a region of interest of 11 resampled voxels within those clusters.

6.3 Results

6.3.1 Cued Recall Results: Mean overall accuracy for cued recall was 20.4%. Because data did not follow a normal distribution, non-parametric statistics were used (Wilcox Ranked Sum test). Cued recall performance was significantly higher for related pairs (mean accuracy 35%) than unrelated pairs (mean accuracy 5.9%), $Z=-2.7$, $p = 0.007$. To address the effects of TMS stimulation, we compared the noTMS condition to each of the 200ms, 600ms, and 1000ms conditions, separately for related and unrelated pairs. There was a significant difference between the noTMS and 1000ms condition for related pairs, $Z = -2.04$, $p = 0.041$. There were no other significant differences (all $p > 0.1$). Results for the cued recall test are presented in Table 1.

Table1: Cued Recall Results (percent accuracy)

	Related	Unrelated
noTMS	34.8	5.2
200ms	38.5	8.9
600ms	42.2	7.4
1000ms	24.4	2.2

6.3.2 Overall fMRI results: Significant fMRI activations from the contrasts comparing related to unrelated pairs separately for each TMS condition are presented in Table 1. Significant clusters from the contrasts comparing the effects of each TMS condition to the noTMS condition are presented in Table 2 for related pairs and Table 3 for unrelated pairs. In these 10 contrasts, 87 clusters were present.

6.3.3 Details of Selected Clusters of Activation: In order to understand the patterns of significant activity, Beta values from significant clusters were visualized, as described above. Results from the ten contrasts were used as a guideline to identify potentially interesting regions, as we were specifically interested in regions in which a specific effect of TMS was observed (as opposed to clusters which were activated by multiple TMS conditions, suggesting non-specific TMS effects). Activity from selected regions is presented, to demonstrate that we can in fact observe condition and time specific effects of TMS in relevant regions of the cortex.

6.3.3.1. Hippocampus Activation: A cluster the right posterior hippocampus was noted in the Unrelated > Related, 200ms contrast, suggesting that the left DLPFC was in communication with that region of the hippocampus shortly after stimulus onset. This right hippocampal activation (including Beta values for all conditions) is presented in Figure 1.

Table 2: Related vs Unrelated Contrasts

Cluster Size	Peak t value	x	y	z	BA	Location
NoTMS Condition						
Related>Unrelated						
No Clusters						
Unrelated > Related						
129	9.24	-36	-76	-22	19	Inferior Occipital/Cerebellum
89	8.81	-38	-48	-30	20/NA	Inferior Temporal/Cerrebellum
30	7.18	-4	18	-4	25	Anterior Cingulate
28	7.01	68	-46	12	22	Superior Temporal Gyrus
25	6.8	-18	30	24	32	Anterior Cingulate
13	5.57	26	-56	62	7	Superior Parietal Lobule
9	4.79	8	24	62	6	Superior Frontal Gyrus
8	4.48	-36	-88	12	19	Middle Occipital Gyrus
200ms TMS Condition						
Related>Unrelated						
13	5.7	-44	-40	0	22	Superior Temporal Gyrus
15	5.36	-6	-30	-38		Cerrebellum
Unrelated > Related						
8	6.47	34	-34	-8	NA	Hippocampus
13	6.27	36	-48	-14	37	Fusiform Gyrus
74	6.14	-22	-96	-2	18	Middle Occipital Gyrus
16	5.69	18	46	-4	10	Medial Frontal Gyrus
28	5.66	-28	-90	24	19	Cuneus
20	5.26	38	-96	4	19	Middle Occipital Gyrus
600ms TMS condition						
Related>Unrelated						
20	6.07	-58	4	6	22	Superior Temporal Gyrus
19	6	-12	-32	-18	NA	Cerrebellar Penduncle
24	5.43	-60	-4	20	4	Precentral Gyrus
Unrelated > Related						
No Clusters						
1000ms TMS condition						
Related>Unrelated						
47	8.66	24	-38	-44	NA	Cerrebellum
21	6.4	16	26	6	NA	Caudate Head
8	5.24	20	-16	10	NA	Ventral Lateral Nucleus
9	5.03	20	8	28	NA	Caudate Body
8	4.82	-10	26	2	NA	Caudate Head
14	6.94	38	-88	16	19	Middle Occipital Gyrus
15	5.56	56	20	32	9	Middle Frontal Gyrus
11	5.15	-16	-106	6	18	Cuneus
Unrelated > Related						
14	6.94	38	-88	16	19	Middle Occipital Gyrus
15	5.56	56	20	32	9	Middle Frontal Gyrus
11	5.15	-16	-106	6	18	Cuneus

Table 3: Related Pairs of Objects

Cluster Size	Peak t value	x	y	z	BA	Location
No TMS > 200ms						
9	6.19	18	-102	18	18	Cuneus
200ms > noTMS						
317	12.66	40	0	-10	13	Insula
19	8.94	70	-36	14	22	Superior Temporal Gyrus
83	7.28	-46	-8	-8	22	Superior Temporal Gyrus
11	7.28	10	32	0	24	Anterior Cingulate
15	6.27	-6	38	0	24	Anterior Cingulate
12	6.11	-6	-24	-26	NA	Pons
14	5.73	40	-28	32	2	Postcentral Gyrus
19	5.54	26	-72	60	7	Superior Parietal Lobule
16	5.4	-30	18	38	9	Middle Frontal Gyrus
41	5.08	-36	-48	46	40	Inferior Parietal Lobule
13	5.06	40	56	4	10	Inferior Frontal Gyrus
8	4.99	-2	10	64	6	Superior Frontal Gyrus
8	4.96	-4	34	54	8	Superior Frontal Gyrus
8	4.88	-8	-34	-4	27	Parahippocampal Gyrus
8	4.59	-52	-32	16	41	Superior Temporal Gyrus
No TMS > 600ms						
No activations						
600ms > noTMS						
67	7.32	12	18	-6	NA	Caudate Head
19	6.19	0	-98	4	18	Cuneus
28	6.09	-4	32	54	8	Superior Frontal Gyrus
46	5.99	38	42	24	10	Middle Frontal Gyrus
65	5.94	-4	26	-4	24	Anterior Cingulate
16	5.79	44	-40	62	2	Postcentral Gyrus
23	5.57	26	-24	8	NA	Thalamus
30	5.27	52	-42	52	40	Inferior Parietal Lobule
13	5.15	40	-68	-28	NA	Cerrebellum
13	5.11	10	48	4	10	Medial Frontal Gyrus
9	4.86	0	18	62	6	Superior Frontal Gyrus
No TMS > 1000ms						
110	7.78	-24	-98	10	19	Middle Occipital Gyrus
1000ms > noTMS						
15	7.59	-12	0	-10	NA	Medial Globus Pallidus
34	6.47	12	-54	-42	NA	Cerebellar Tonsil
20	5.99	42	-20	-6	13	Insula
43	5.88	-34	-82	18	19	Middle Temporal Gyrus
12	5.81	-22	18	-8	NA	Putamen
9	5.23	40	54	6	10	Inferior Frontal Gyrus
12	4.99	-50	-66	16	39	Middle Temporal Gyrus

Table 4: Unrelated Pairs of Objects

Cluster Size	Peak t value	x	y	z	BA	Location
No TMS > 200ms						
15	6.02	-14	28	24	32	Anterior Cingulate
16	5.23	42	20	8	45	Inferior Frontal Gyrus
200ms > noTMS						
38	6.63	60	-2	-14	21	Middle Temporal Gyrus
75	6.58	-2	-40	2	NA	
43	6.49	-56	-28	12	41	Superior Temporal Gyrus
18	6.09	-42	2	-4	13	Insula
20	5.23	48	-12	-4	22	Superior Temporal Gyrus
11	4.75	50	0	-10	38	Superior Temporal Gyrus
No TMS > 600ms						
22	7.41	68	-46	12	22	Superior Temporal Gyrus
217	7.31	30	26	38	9	Middle Frontal Gyrus
30	6.24	-14	-78	-36	NA	Cerrebellum
600ms > noTMS						
22	6.95	2	-40	0	NA	Culmen
9	5.94	-56	10	32	9	Inferior Frontal Gyrus
No TMS > 1000ms						
115	8.07	-18	-98	6	18	Middle Occipital Gyrus
69	7.59	16	46	18	10	Medial Frontal Gyrus
114	6.92	-20	22	28	9	Medial Frontal Gyrus
12	6.23	24	4	-4	NA	Putamen
24	6.2	14	34	32	9	Medial Frontal Gyrus
17	5.98	8	-24	12	NA	Thalamus
100	5.46	28	36	28	9	Middle Frontal Gyrus
12	4.97	30	62	6	10	Superior Frontal Gyrus
1000ms > noTMS						
22	5.41	-54	-50	52	40	Inferior Parietal Lobule

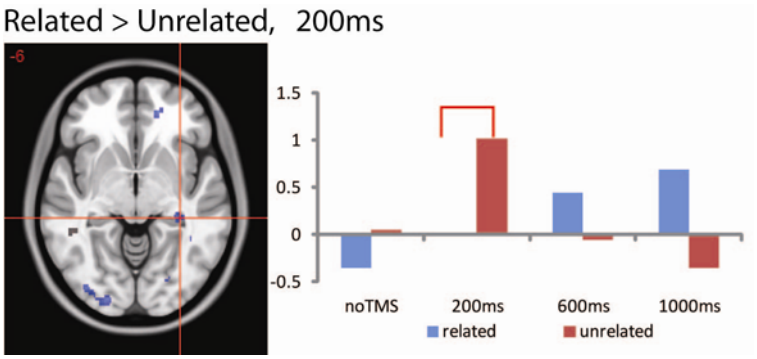

Figure 1: Selected right hippocampal activation from the Unrelated > Related, 200ms condition. Positive t-values (indicating Related > Unrelated) are shown in red, and negative t-values (indicating Unrelated > Related) are shown in blue. The t-map is displayed at a using a t-value of 3.24 (corresponding to $p < 0.005$ uncorrected) for visualization purposes. Bar graph shows the average Beta values across participants for each condition.

6.3.3.2 Insula and Superior Temporal Activations: For related pairs, a prominent activation in the right insula was observed in the 200ms > noTMS contrast, with a smaller activation in the left insula. For unrelated pairs, an activation was observed in nearby region of the right superior temporal lobes for the 200ms > noTMS contrast. These activations are shown in Figure 2. This shows a disassociation of activity in these adjacent regions across conditions (related or unrelated pairs) occurring early after stimuli onset (prior to 600ms), but no activity related to modulation of the left DLPFC by TMS in later time windows.

6.3.3.3 Cingulate and Medial Frontal Activity: Significant differences in activity were observed in the anterior cingulate cortex for related pairs in the 600ms < noTMS contrast, the 200ms < noTMS contrast, and the unrelated > related pairs in the 200ms TMS condition. This demonstrates that left DLPFC activity is modulating with the anterior cingulate for related pairs over a prolonged period, ending prior to 1000ms post-stimuli onset. For unrelated pairs, differences were observed in the superior medial frontal cortex for the contrasts 200ms > noTMS

and 600ms > noTMS, but not for 1000ms > noTMS. These cingulate and medial frontal activations are shown in Figure 3.

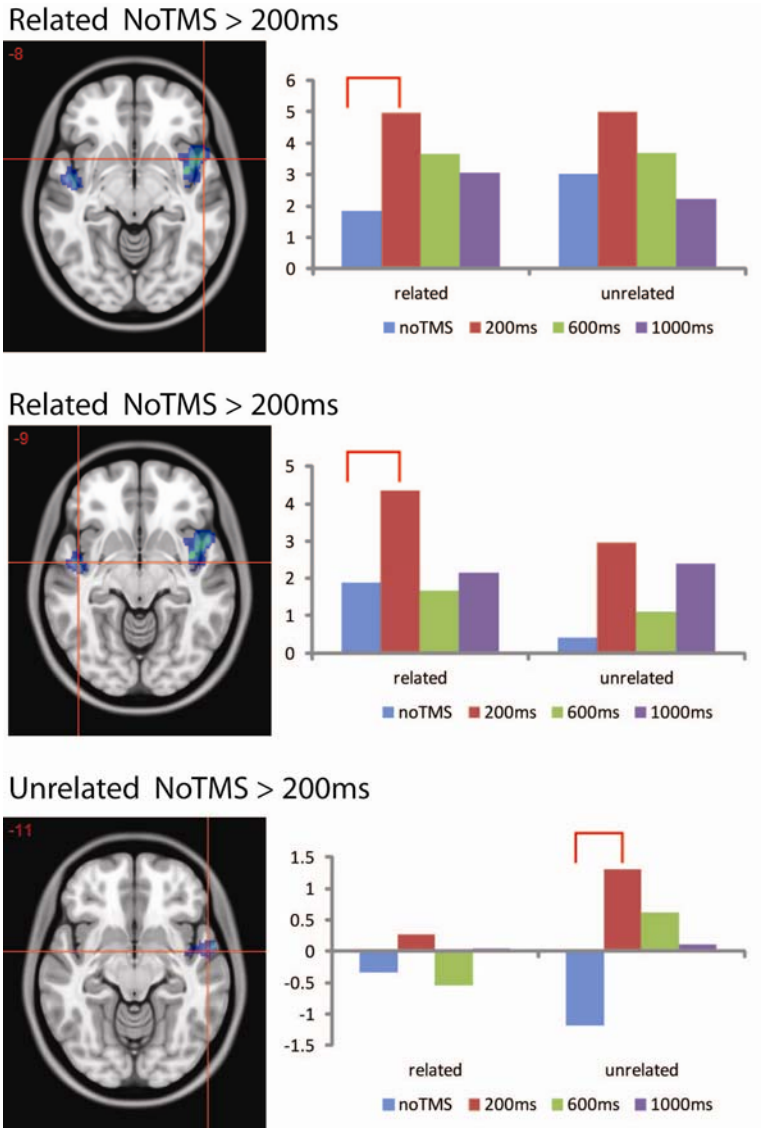

Figure 2: Selected Insula and superior temporal activations Positive t-values (indicating noTMS > 200ms) are shown in red and negative t-values (indicating 200ms > noTMS) are shown in blue. The t-map is displayed at a using a t-value of 3.24 (corresponding to $p < 0.005$ uncorrected) for visualization purposes. Bar graphs show the average Beta values across participants for each condition. Statistically significant differences are indicated by a red line.

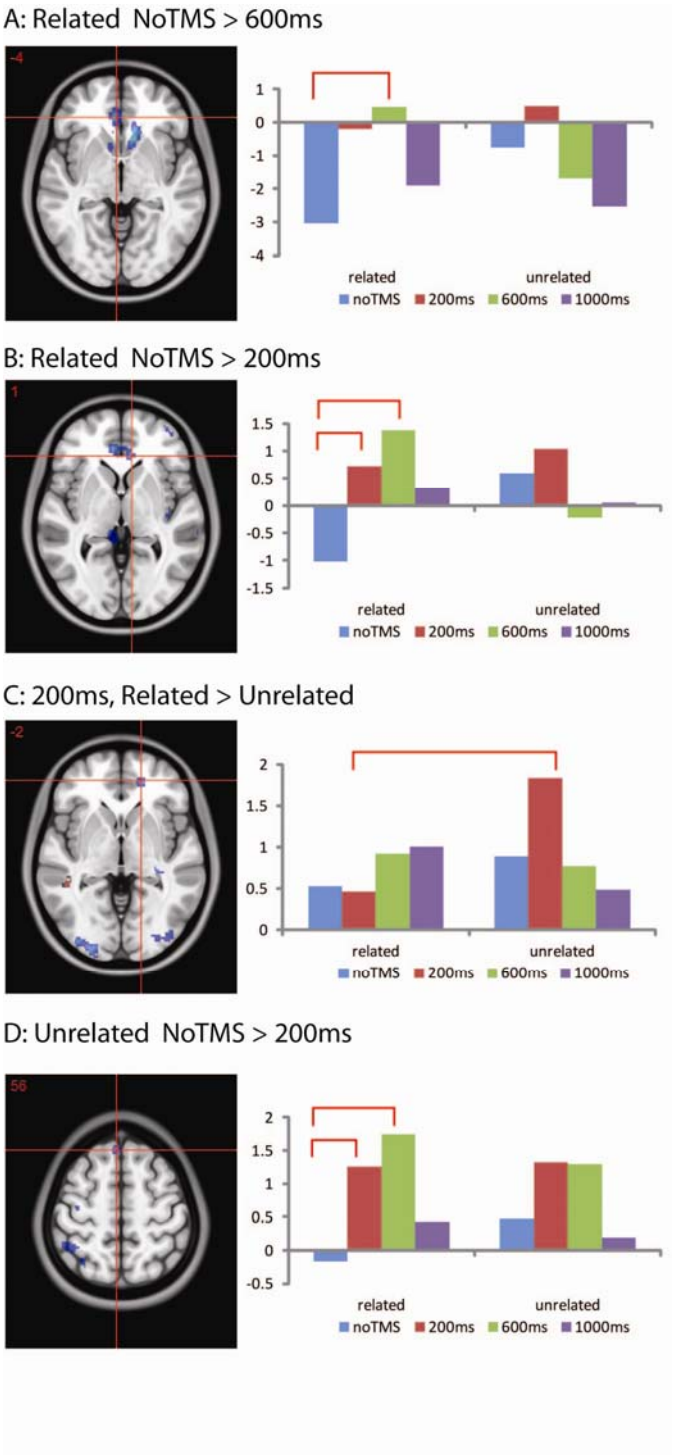

Figure 3: Selected anterior cingulate and medial frontal activations. Positive t-values are shown in red and negative t-values are shown in blue. The t-map is displayed at a using a t-value of 3.24 (corresponding to $p < 0.005$ uncorrected) for visualization purposes. Bar graphs show the average Beta values across participants for each condition. Statistically significant differences are indicated by a red line.

6.3.3.4 Parietal Activity: Activity was also observed in the parietal cortex, a region which is frequently found to be active in memory encoding studies. Two parietal clusters were identified in the noTMS < 200ms for related pairs, in the left inferior parietal cortex and right superior parietal cortex (the post-central gyrus). Beta values for these clusters are shown in Figure 4. There is a clear difference between the noTMS and 200ms TMS conditions for related pairs in both regions, as well as some suggestion of a (non-significant) effect of 600ms TMS in the right inferior parietal activation. There where no apparent numerical differences in Beta values in the unrelated pairs, suggesting the modulation of parietal activity in these regions by the left DLPFC is specific to related pairs.

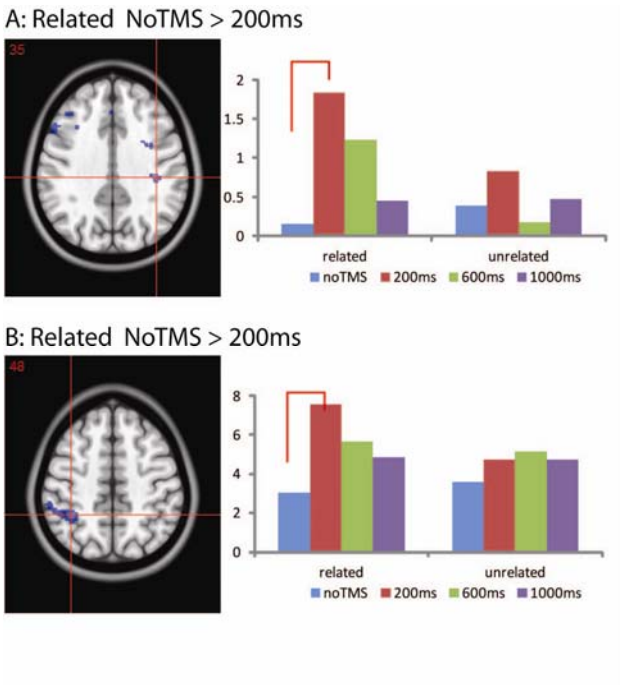

Figure 4: Selected parietal activations. Positive t-values are shown in red and negative t-values are shown in blue. The t-map is displayed at a using a t-value of 3.24 (corresponding to $p < 0.005$ uncorrected) for visualization purposes. Bar graphs show the average Beta values across participants for each condition. Statistically significant differences are indicated by a red line.

6.3.3.5 Selected Non-specific Effects: Not all regions showed clear effects of TMS, even when a given area was significantly active for a single contrast. Some representative areas where selected to demonstrate this phenomenon, from the left frontal cortex, the caudate nucleus, and the cerebellum (which had active clusters in several contrasts). These regions are shown in Figure 5. The caudate activation was observed in the noTMS < 600ms contrast for related pairs. This region appears to show a non-specific effect of TMS for related pairs. There is a numerical but statistically insignificant difference between related and unrelated pairs for the noTMS condition (and some sub-threshold caudate activation was observed in proximal areas in the caudate for the related < unrelated, noTMS contrast). The Beta values for this region suggest that left DLPFC stimulation increases caudate activity to a level similar to that observed in unrelated pairs, but this change occurs across all TMS conditions (even though significant effects were only observed at 600ms). Indeed, the absolute magnitude of the effect at the 200ms condition was larger than the 600ms condition, though the 200ms condition was not significant due to increased variability. Even though the 200ms and 1000ms contrasts did not reach significance, it is difficult to draw any conclusions with regards to the effects of TMS of the left DLPFC on this region due to ambiguous results. A similar ambiguity is observed in the selected cerebellar activation for unrelated pairs (Figure 5). A region of the left prefrontal cortex was also identified. This region was significantly active in the noTMS related < unrelated contrast, and in contrast of noTMS > 1000ms for related pairs. There was also a subthreshold activation (at $p < 0.005$) in the noTMS > 200ms for related pairs. Examining Beta values in this region suggests that TMS to the left DLPFC causes a non-specific reduction of activity in this region for unrelated pairs. While it may suggest an overall effect of TMS, no specific temporal information can be determined. Even a claim that the left DLPFC is in communication with this region for a prolonged period during

the processing of unrelated pairs is difficult to justify due to the lack of clear statistical effects, and it is likewise difficult to draw any conclusions on temporal specificity.

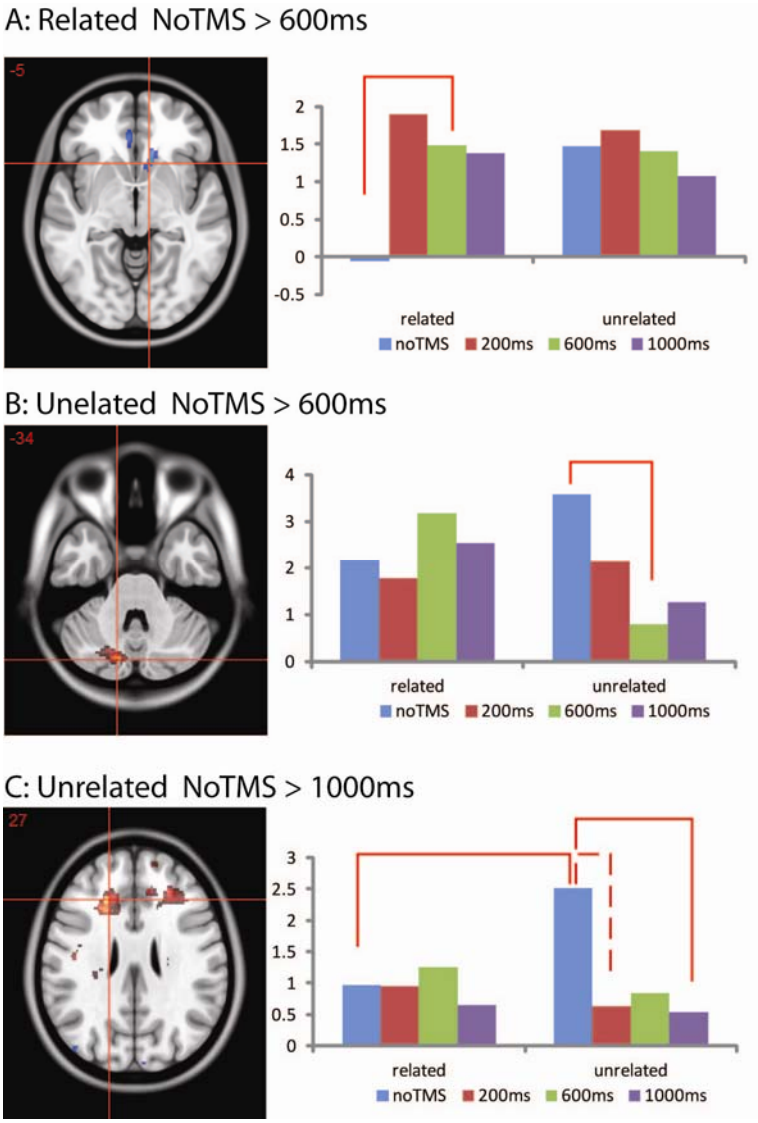

Figure 4: Selected areas showing non-specific or ambiguous effects of TMS in A: the Caudate nucleus, B: the Cerebellum, and C: the medial frontal lobes. Positive t-values are shown in red and negative t-values are shown in blue. The t-map is displayed at a using a t-value of 3.24 (corresponding to $p < 0.005$ uncorrected) for visualization purposes. Bar graphs show the average Beta values across participants for each condition. Statistically significant differences are indicated by a red line. The dashed red line indicate a sub-threshold difference, at $p < 0.005$ uncorrected.

6.4 Discussion

The purpose of this study was to demonstrate the utility of time-varying the onset of trains of TMS during fMRI acquisition as a method for examining interregional connections with high temporal resolution. Previous TMS-fMRI studies have demonstrated that the effects of TMS on distal brain regions are specific to the functional state of the cortex, indicating that TMS-fMRI can be used as a technique to measure the interactions between regions during different experimental conditions (Aurora et al., 1998; Bestmann et al., 2007; Fujiwara & Rothwell, 2004; Ruff et al., 2008; Ruff et al., 2006; Ruff, Driver, & Bestmann, 2009; Silvanto et al., 2007; Strens et al., 2002). While we also observed state-specific effects of TMS, in the observed differences between related and unrelated pairs, we expanded this into effects which were specific to time as well. This demonstrates that time-varying TMS trains can be used to elucidate temporal information on the interactions between regions in different task conditions. As the presented TMS stimulation resulted in a direct change in cortical activity in the left DLPFC, any changes we observed in distal regions are most likely causatively related to the modulation of left DLPFC activity. This suggests a direct measure of connectivity. The ability to observe changes in distant regions in response to stimuli from temporally specific time windows suggest that concurrent TMS-fMRI can be used to achieve high temporal resolution fMRI, overcoming intrinsic limits in the temporal resolution of fMRI related to the characteristics of the BOLD signal. This study represents a feasibility study of the utility of an exciting new technique to investigate the interaction across brain regions.

One interesting phenomenon was observed in our data: several of the clusters affected by TMS stimulation were in regions which did not show a difference across our encoding conditions (related or unrelated word pairs). For example, the clusters in the insula was not significantly activated in the related > unrelated noTMS contrast. Without the inclusion of the TMS

conditions, we would not have observed any task-related differences in these regions when contrasting related and unrelated pairs. But the observed effect in the right hippocampus suggests that left DLPFC is modulating activity in the right posterior hippocampus for unrelated pairs, specifically during the time period shortly after trial onset (the 200ms condition). This adds a new piece of information on the interaction across brain regions during encoding, which would not have been obvious without TMS-fMRI.

In some cases, the effects of TMS occur over more than one TMS stimulation condition, as is the case in some clusters of the medial frontal lobes. This suggests either a prolonged interaction between these regions and the left DLPFC, or that the interaction occurs in a time window which crosses two TMS timing conditions. For example, if the DLPFC was interacting with a region in the medial frontal cortex from 400 to 800 ms, we might expect to observe changes in activity in that region in both the 200ms and 600ms condition (both of which partially cover that time window). It is also reasonable to suggest that there may be some level of temporal variability across participants in the interactions between brain regions. That is, while the left DLPFC may communicate with a given region in the time window covered by the 1000ms condition for some participants, this communication may start earlier in other participants and partially overlap the 600ms TMS condition. This explains some of the results in which we observed visual but not statistical effects of TMS in time windows adjacent to condition which produced significant activity (such as in the 600ms condition for related pairs in the inferior parietal activation in Figure 4, part A). This may also present the impression that the effects of TMS are linear. But this linearity may be an artefact of the fact that we have a prominent change in one condition, some modulation driven by a sub-population of participants in the adjacent condition, and no effects in the third condition, giving the appearance of linearity.

That is to say, the appearance of a linear change is largely a result of their being three TMS conditions. In this study, we chose distinct and non-overlapping time windows in order to produce the clearest results, and to limit the number of conditions. Future studies may refine the temporal information in some regions by using overlapping time windows (e.g. 3 pulses of 10Hz stimulation starting at 400ms, 500ms, 600ms, and 700ms), or presenting single pulses across a wider range of onset times. Single pulse TMS has been used successfully in several behavioural TMS studies (Mottaghy et al., 2003) . In such a study, it would be important to be mindful of individual differences in the timing of interactions with distant brain regions.

Some activated areas did not show a clear temporal effect of TMS. In some cases, such as the left frontal cluster shown in Figure 5, there is the suggestion that TMS stimulation in one encoding condition changes brain activity to a level similar to the other encoding condition. It may be tempting to attribute meaning such similarities in activation (Beta) levels, but care must be taken in such interpretations. It is difficult to draw any clear conclusions, and in these cases, the observed changes in brain activity may be related to non-specific TMS effects. It is important to limit conclusions to regions in which we can observe time specific effects of TMS, as any such effects are not likely to be related to the non-specific side effects of TMS (somatosensation and noise).

One final note of caution is worth considering. In some cases, we observed TMS increasing activity (as measured by changes in Beta values) in a given region, while a decrease in Beta values was observed in other regions. While this may be related to factors such as inhibitory of excitatory connectivity between regions, our understanding of the neurophysiology of TMS and TMS-fMRI is not sufficient at present to draw any conclusions in this regards. However, an increasing understanding of how TMS stimulation modulates neural activity may allow such

conclusions in the future, which will further increase the utility of time-varying TMS-fMRI, and TMS-fMRI in general.

This study has demonstrated the feasibility of presenting TMS stimulation during different time windows during fMRI acquisition as a method to gain high temporal resolution causative information on the interaction between brain regions. This proof-of-principle study lays the groundwork for future research in this direction. This is a particularly exciting avenue of research, as it may allow for causative, high temporal resolution examinations of the interconnections and interactions between brain regions. This is difficult to do with most currently available fMRI techniques, as the timing of the BOLD signal is influenced by local physiology more than the timing of neural activity. Time-varying TMS-fMRI can be considered a method of achieving high temporal resolution fMRI.

Chapter 7: Conclusions and Future Directions

Our hypothesis was that the DLPFC plays a role in self-initiating elaborative encoding memory strategies. We began by devising a design philosophy on how to create a task which would allow us to examine the self-initiation process during encoding strategy use. We concluded we would require a design in which we had a condition that was amicable to strategy use vs. a condition which was not (related vs. unrelated stimuli), and a contrast of conditions in which strategy use was cued or uncued/self-initiated (semantic vs. non-semantic orienting questions in the fMRI study). We then found regions in the brain which were perturbed by both of these conditions in the appropriate direction by performing a conjunction analysis on our data. We found activity in the left DLPFC and left and right supramarginal gyrus.

While we interpreted these results as good evidence that the left DLPFC was involved in self-initiating elaborative encoding, the issue was still not resolved. While fMRI is a very useful research tool for understanding the role of specific brain regions in performing tasks, it is still a correlational technique. That is, we can never be certain that an activated region is critically involved in the task at hand. We therefore performed a follow-up study using rTMS, a technique which allows us to perturb activity in a small region of cortex and observe the behavioral effects of removing that region from the cortical circuit involved in task performance. Using a task design derived from the same design principles as our first study, we found evidence that left DLPFC stimulation (in a region similar to that observed in experiment 1) reduced memory performance only in the condition in which self-initiated elaborative semantic encoding was relevant (the self-initiated related condition), but only in participants who made greater use of memory strategies. We also found the interesting finding that in a subset of our sample (who generally underutilized elaborative encoding strategies), left DLPFC stimulation appears to

improve memory. This suggests the possibility that these individuals are utilizing a distinct neural network then 'high strategy users'. Regardless of the fact that the findings of this study were not a simple relationship of DLPFC stimulation reducing performance in the self-initiated related condition, this study (especially combined with experiment 1) provides compelling evidence that the left DLPFC plays a role in self-initiating elaborative encoding strategies, at least for evaluating semantic relatedness.

Our third study combined TMS and fMRI to leverage the strengths of each technique to understand the neural networks involved in task performance. As we wished to utilize a simple task design (as the critical manipulation here was TMS stimulation during different time points), we presented related and unrelated object pairs in a condition similar to the non-semantic (self-initiated) condition in experiment 1. This study provided unique technical and analytic challenges, but was ultimately successful. The preliminary results from this study suggest that we can identify time-specific effects of brief bursts of TMS stimulation on to the left DLPFC on distant cortical regions. For example, we identified a region in the posterior right hippocampus which showed a reduction in activity only for unrelated pairs and only during the 200ms TMS condition. This suggests it is feasible to use TMS-fMRI to better understand some of the networks (and the timing of communication between regions of those networks) involved in task performance during associative encoding.

While we have demonstrated some novel and interesting findings, further work remains to be done. Firstly, we have utilized task designs examining stimuli which were semantically related or unrelated. This manipulation was chosen because semantic relatedness is known to facilitate later memory performance, and should be utilized by nearly all participants. However, we cannot extend our current findings to other types of encoding strategies, such as visualization.

It is therefore necessary to conduct further studies to determine if the left DLPFC plays a supramodal role in initiating elaborative encoding strategies, or if it is specific to semantic analysis. Such a study would probably best be conducted using brain imaging (fMRI), and utilizing a design which manipulated the feasibility of utilizing different types of memory strategies. For example, visualization is another effective memory strategy which is frequently used while encoding pairs of words (as evidenced from the questionnaire results of Experiment 2). In order to understand if the DLPFC plays a supramodal role in self-initiating elaborative encoding, we utilize an experimental design with pairs of words, and manipulating visualizability and relatedness of the word pairs. So, we could present semantically related and unrelated word pairs, and pairs of words which could be visualized interacting and pairs in which visualization was not feasible (for example, abstract words), and include conditions such as related-visualizable, related-nonvisualizable, unrelated-visualizable and unrelated nonvisualizable, as well as encoding conditions orienting towards either strategy, or not towards a relevant strategy. While such a design would require careful consideration within the context of the existing body of literature to avoid confounding factors (such as using concrete objects for visualizable stimuli and abstract words for nonvisualizable stimuli), results of such task design could determine if the left DLPFC is involved in self-initiating different elaborative encoding strategies or is specific to elaborative semantic encoding.

Another important step to consider in any future studies on this issue is the importance of collecting data on participant's use of encoding strategies. Given the results of Experiment 2, we have proposed the possibility that low strategy users utilize a distinct neural network compared to high strategy users. If this is the case, it may be an important source of inter-subject variability which can have a significant effect on the results of any fMRI study. Establishing if high and low

strategy users do in fact utilize different neural networks during task performance will be interesting on a purely theoretical level (and may have implications for patient populations which under utilize memory strategies), as well as being an important consideration in any group analysis of brain imaging data.

A second but highly relevant branch of future research involves extending these findings to patient populations that show a deficit in self-initiating elaborative encoding strategies. For example, patients with schizophrenia demonstrate verbal memory deficits that appear to be at least somewhat related to a deficit in the use of elaborative encoding strategies, such as semantic clustering. For example, Brebion et al. (1997) presented patients with schizophrenia and healthy controls with lists of words which were ether unrelated or which could be divided into categories. Patients were less likely than controls to use the semantic properties of the words to encode them, and benefited less than controls from the use of semantic relatedness (although both patients and controls benefited from utilizing semantic relatedness). Patients were also observed to have overall poorer performance than controls, regardless of the effects of semantic relatedness. Vaskinn et al. (2008) compared patients with schizophrenia who had relatively normal memory performance to patients who were more severely impaired, and noted that more impaired patients made less use of semantic clustering in list learning. Chan et al. (2000) noted that both patients with schizophrenia and healthy controls benefited from an external cue to utilize semantic encoding strategies. The overall pattern of results from the literature in semantic clustering in schizophrenia is that these patients make less use of semantic clustering strategies than healthy controls, but benefit from semantic clustering when they do use such strategies, and improve memory performance when cued to use semantic relationships. This suggests these

patients have a deficit in the self-initiation of the use of effective memory strategies during learning.

Our experimental design philosophy could easily be adapted to examining the neural correlates of self-initiating elaborative semantic encoding in schizophrenia as compared to controls, utilizing a design similar to Experiment 1 (though perhaps with pairs of pictures, as object triads may be too complex a stimulus for effective studies on clinical populations with memory impairments). By comparing patients to healthy controls, we can determine if patients show reduced activity in the left DLPFC compared to controls, and if this reduction is only present in patients who show a particular deficit in the use of elaborative encoding strategies. An alternate approach is to examine patients who make use of elaborative encoding as opposed to those who do not, and observe how these patient subgroups differ from each other (and possibly how that pattern of results differs from healthy controls that are high or low strategy users). In addition to applying our paradigm to patients with schizophrenia, it is also possible to use this design to examine other clinical groups who may have a deficit in memory related to elaborative memory strategy use, such as memory decline in healthy aging and Alzheimer's disease.

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