Perceiving Oldness in Parietal Cortex: fMRI Characterization of a Parietal Memory Network

Adrian Gilmore
Washington University in St. Louis

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WASHINGTON UNIVERSITY IN ST. LOUIS

Department of Psychological and Brain Sciences

Dissertation Examination Committee:
Kathleen B. McDermott, Chair
Ian G. Dobbins
Nico U. F. Dosenbach
Steven E. Petersen
Henry L. Roediger, III

Perceiving Oldness in Parietal Cortex:
fMRI Characterization of a Parietal Memory Network
by
Adrian Warham Gilmore

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Adrian W. Gilmore

Washington University in St. Louis

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ABSTRACT OF THE DISSERTATION

Perceiving Oldness in Parietal Cortex:

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by

Adrian W. Gilmore

Doctor of Philosophy in Psychology

Washington University in St. Louis, 2016

Professor Kathleen B. McDermott, Chair

The manner in which the human brain recognizes certain stimuli as novel or familiar is a matter of ongoing investigation. The overarching goal of this dissertation is to improve our understanding of how this may be accomplished. More specifically, work contained herein focuses on a recently described “parietal memory network” (PMN; Gilmore et al., 2015) that shows opposite patterns of activity when perceiving novel or familiar stimuli: deactivating in response to novelty, and activating in response to familiarity. Critically, our understanding of this network is based on explicit memory tasks, in which subjects are deliberately instructed to learn or remember information to perform the experimental task. The aim of this dissertation is to determine if the same opposing patterns of activity are present in task conditions in which no explicit orientation to stimulus history is required (i.e., implicit memory conditions).

In Chapter 1, I review evidence that links activity within the PMN to encoding and retrieval processes, and describe how the perception of novelty and familiarity may explain various observations from prior literature. In this chapter I discuss several techniques that utilize functional magnetic resonance imaging (fMRI) to measure activations within the brain. These
include single experiments utilizing blood oxygen level dependent (BOLD) activity as a means of associating specific behavioral phenomena with specific neural correlates; meta-analyses of many such fMRI studies; and the use of BOLD correlations in the absence of explicit task conditions to estimate the functional network structure of the human brain. It is from the work reviewed in this chapter that this dissertation’s empirical questions were derived.

In Chapter 2, I discuss experimental data collected under implicit memory task conditions. This was designed to assess the degree to which activity predicted by explicit memory tasks is recapitulated under implicit conditions. Subjects observed stimuli multiple times, making simple semantic judgments during each presentation. The BOLD responses within each subject were measured for each presentation of each stimulus. PMN regions demonstrated two of three predicted patterns of activity: they deactivated relative to a resting baseline when initially processing a stimulus, and they increased in activity across multiple item presentations. Predicted above-baseline activations during final presentations were not observed. This suggests that existing hypotheses describing PMN functions should be revised in a way that suggests a more prominent role for attention in producing familiarity-related activations.

In Chapter 3, the task data from Chapter 2 are compared to an individual with superior memory abilities. This individual (ND) is a “memory athlete” who has trained extensively in the use of mental imagery as a tool for rapid learning. When comparing him to the control group characterized in Chapter 2, we found no appreciable differences in neural activity in the implicit memory task. These findings are consistent with those observed in prior literature that suggest memory athletes do not possess unusual memory skills outside of the tasks they specifically train (Maguire et al., 2002; Ramon et al., 2016).

In Chapter 4, resting-state functional connectivity (RSFC) MRI data are examined to
estimate the functional network organization of all participants examined in Chapters 2 and 3. The PMN and several control networks were localized using this independent approach, and the activity within regions of each network was compared using data from the implicit memory task. Results suggest that the implicit memory task produces very similar activity in PMN and adjacent default mode network regions, and suggests that the task itself is not a practical means of localizing the PMN within single subjects.

Chapter 5 serves as a summary of the results from Chapters 2-4. In this chapter I place key findings of the dissertation in a broader context and suggest future directions that might be taken to better understand the PMN. An updated hypothesis of PMN function is proposed to better account for possible attentional affects on network activity, and several future directions are considered.
Chapter 1: Memory retrieval, parietal cortex, and brain networks

Abstract

The manner by which the human brain learns and subsequently recognizes stimuli is a matter of ongoing investigation. In this chapter, I summarize evidence from single experiments, meta-analyses, and resting-state functional connectivity studies to argue that a network of parietal regions is broadly involved in human learning and memory. These regions are located in the precuneus (PCU), mid-cingulate cortex (MCC), and posterior inferior parietal lobule/dorsal angular gyrus (pIPL/dAG). A number of memory-related effects are observed in the BOLD responses of these regions: During encoding, the level of activity present can predict subsequent item memory; at retrieval, activity in this network differentiates between correctly identified old and correctly identified new items. Furthermore, the direction of activity in this network differs for old and new items: novel stimuli lead to deactivation, while familiar stimuli lead to above-baseline activation. Reflective of its extensive involvement in human memory processing, this network has recently been described as the “parietal memory network.” This chapter concludes with discussion of a preliminary framework for understanding the functional significance of the network, and it is from this framework that the experiments described in Chapters 2 to 4 are derived.
1.1 On Memory

Psychologists have studied the construct of memory since the field’s inception. Ebbinghaus (1885/1964) famously spent years learning and re-learning nonsense syllables, plotting learning and forgetting functions, and paving the way for generations of future scientists to add clarity and detail to our understanding of how we, as humans, learn and remember. In the decades that followed, our understanding of basic aspects of memory has grown enormously, and today we appreciate that retrieving a memory can either be a phenomenologically rich or extremely vague experience (James, 1890; Tulving, 1985); that memory can impact our behaviors in both automatic and intentional manners (Warrington & Weiskrantz, 1970; Jacoby, 1991); and that multiple systems, both neural and cognitive, appear to support the broad range of actions that can collectively be referred to as “memory” (Tulving, 1983, 1985; Alvarez & Squire, 1994; McDermott et al., 2009). At the risk of understatement, it has become clear that memory is a complicated thing.

Its complication poses practical problems. Identification and discussion of hypothetical constructs has been productive, but our lack of understanding the processes that make up these constructs continues to pose a challenge. Further, commonly discussed components of memory (e.g., encoding, retrieval) are highly interactive, making basic “laws” of learning and memory difficult or impossible to articulate (Roediger, 2008). For instance, universally “superior” encoding strategies are effectively nonexistent; the efficacy of any one strategy is based on how information is retrieved (e.g. Tulving & Pearlstone, 1966; Tulving & Thomson, 1973; Craik & Tulving, 1975), as well as what materials were used and what population is being assessed (Jenkins, 1979).

With the advent of functional neuroimaging, the neural correlates of cognitive processes
could be assessed *in vivo* in humans. Memory-related questions, such as how one might predict whether a given experience would be remembered or forgotten (Brewer et al., 1998; Wagner et al., 1998), and how successful and unsuccessful retrieval differed in their neural signatures (Buckner et al., 1998), were among the first questions asked by scientists when it became possible to do so. Unfortunately, as was presaged by the results of decades of cognitive psychological experimentation, the answers to many of these questions are an unsatisfying “it depends.” Neural correlates supporting the successful encoding of information vary not only by the materials used (Kelley et al., 1998), but the means by which one attempts to learn materials (Otten & Rugg, 2001a; Uncapher et al., 2006) or how one is later tested on them (Otten, 2007). Likewise, the neural correlates of successful retrieval vary based on the nature of the encoded material (Wheeler et al., 2000), the subjective experience of remembering (Wheeler & Buckner, 2004; Yonelinas et al., 2005), and the type of retrieval task required (e.g., McDermott et al., 2009; Kim, 2013; Frithsen & Miller, 2014).

In the remainder of this introductory chapter, I review evidence of a recently described cortical network that may prove helpful in clarifying at least some components of how the brain encodes or retrieves information. More specifically, this network has been associated with the concept of familiarity (Gilmore et al., 2015), which can be defined as an automatic and somewhat general effect of having prior experience with a particular stimulus (Jacoby, 1991). Through further study of this network, we may gain important insights into how we can differentiate between stimuli that we have encountered previously, and those that we are experiencing for the first time. The network is located predominantly in parietal cortex, and so it is important to first understand the various ways in which parietal cortex has been linked with learning and memory.
1.2 Parietal cortex contributes to memory processes in multiple ways

Early functional imaging studies focused on the frontal and medial temporal lobes, but over time parietal cortex has come to be strongly associated with processes related to human memory (Wagner et al., 2005; Olson & Berryhill, 2009; Nelson et al., 2013b). Perhaps most famously, effects related to whether a stimulus is recognized to be old or new are frequently observed in parietal cortex (Figure 1.1) (Wagner et al., 2005; Simons et al., 2008; Kim, 2013). Other research, however, has found that parietal cortex is associated with a wide range of memory effects that extend well beyond this old/new (“retrieval success”) effect. These include observable differences in BOLD activity:

Figure 1.1. Old/new (retrieval success) effects are strongly associated with parietal cortex. A) Retrieval success effects are most reliably associated with lateral and medial parietal cortex. B) A bar graph of recognition-related effects across numerous cortical regions. Lateral and medial parietal cortex show effects most consistently. Figures adapted with permission from Wagner et al. (2005) and Simons et al. (2008). Abbreviations: IPS = intraparietal sulcus; IPL = inferior parietal lobule; APFC = anterior prefrontal cortex; VLPFC = ventrolateral prefrontal cortex; DLPFC = dorsolateral prefrontal cortex; Thal = thalamus; MTL = medial temporal lobes.
for the encoding of materials that will later be remembered, as compared to those that will later be forgotten (Brewer et al., 1998; Wagner et al., 1998; Otten & Rugg, 2001b; Wagner & Davachi, 2001; Kim, 2011);
during conditions in which participants are intentionally encoding materials as compared to intentionally retrieving materials (McDermott et al., 1999);
based on the number of times an item has been presented during intentional encoding conditions (Nelson et al., 2013a);
based on the number of times an item has been presented during explicit retrieval conditions (Jessen et al., 2001);
for new items that are falsely believed to be old (false alarms) as compared to old items that are falsely believed to be new (misses) (Wheeler & Buckner, 2003);
based on how confident one is in their recognition memory decision (Yonelinas et al., 2005);
based on how novel or familiar a given item is reported to be during recognition memory decisions (Hutchinson et al., 2015); and
based on whether judgments are based on recollective details or are driven by processes related to item familiarity (Dobbins et al., 2002; Dobbins et al., 2003; Wheeler & Buckner, 2004; Frithsen & Miller, 2014).

Driven by findings such as those described above, multiple hypotheses have been forwarded to account for the role of parietal cortex in memory (Wagner et al., 2005; Cabeza et al., 2008; Cabeza et al., 2012a; Shimamura, 2014). Each can account for some effects, but so far none can account for all of these patterns. Many of these hypotheses only focus on retrieval, and were not intended to explain effects related to encoding. A separate, but potentially larger issue relates to
how each hypothesis treats (or rather, fails to consider) functional neuroanatomy. Most of these hypotheses describe only lateral parietal contributions, and ignore the medial surface, which is also very strongly associated with both encoding and retrieval processes (Figure 1.1B). Exacerbating the medial/lateral concern is the mosaic nature of parietal cortex (Figure 1.2). It contains many distinct functional areas, each with its own patterns of connectivity and profile of functional responses (Nelson et al., 2010; Seghier et al., 2010; Yang et al., 2014; Bzdok et al., 2015), yet these are not considered to any significant degree in extant hypotheses. At best, several research groups have recognized a basic dorsal/ventral distinction (e.g., Cabeza et al., 2008; Vilberg & Rugg, 2008), which seems to generally support results that track familiarity- and recollection-supported retrieval decisions, but some of these same researchers have explicitly rejected the notion of distinguishing between distinct functional areas when describing parietal

Figure 1.2. Numerous putative areas can be localized on the lateral and medial surfaces of parietal cortex. Different colors on each example figure refer to distinct areas, but colors are not meant to be consistent across each dataset. Figures adapted from Nelson et al. (2010), Seghier et al. (2010), Yang et al. (2014), and Bzdok et al. (2015).
contributions to human cognition (Cabeza et al., 2012a; see Nelson et al., 2012; Cabeza et al., 2012b for subsequent discussion).

Given the functional and anatomical heterogeneity within parietal cortex, I argue that attempting to postulate an all-encompassing theory at this time is impractical. Instead, it appears to be more fruitful to find a smaller, more tractable target for which hypotheses can be generated. Recently, a review of meta-analyses of fMRI task data, along with examination of a number of resting-state functional connectivity analyses, has pointed to a small network that appears to be an ideal candidate for such a targeted analysis.

1.3 Three parietal regions are strongly associated with human memory

Meta-analyses can identify regions most consistently associated with a task or condition of interest. Further, by virtue of surveying a large number of datasets, meta-analyses effectively nullify the peculiarities or idiosyncrasies specific to any single experiment, and instead highlight general trends in the literature. Meta-analyses of tasks focusing on encoding or retrieval have independently implicated the regions within precuneus (PCU), the mid-cingulate cortex (MCC), and the posterior inferior parietal lobule, near the dorsal crown of the angular gyrus (pIPL/dAG), as being strongly associated with human memory (Figure 1.3, left). These three regions are, depending on the analysis, either those most strongly associated with retrieval success effects (Nelson et al., 2010) or are among those most strongly associated with such effects (McDermott et al., 2009; Kim, 2013; Spaniol et al., 2009). These same regions have also been associated with encoding-related activity, being among those first reported to demonstrate negative subsequent memory (nSM) effects (Otten & Rugg, 2001b; Wagner & Davachi, 2001; Kim, 2011). That is,
Figure 1.3. fMRI task and functional connectivity data converge on a small 3-node network. Left: Meta-analyses of task data highlight consistence recruitment of the precuneus (PCU), mid-cingulate cortex (MCC), and posterior inferior parietal lobule/dorsal angular gyrus (pIPL/dAG) in memory encoding and retrieval tasks. Right: Independent network estimates based on functional connectivity data identify the same regions as being members of a distinct functional network. Figure taken, with permission, from Gilmore et al. (2015).
less activity within these regions is associated with a greater likelihood of later retrieval.

The observation that PCU, MCC, and pIPL/dAG are commonly implicated in both encoding and retrieval is noteworthy, but they are associated with one another even when humans lie quietly at rest. Recent examinations of the intrinsic network structure of the brain, as estimated by resting-state functional connectivity (RSFC) MRI suggest that these regions form a distinct functional network. Unlike traditional task designs, in which behavioral variables are manipulated, RSFC MRI capitalizes on observations that regions that tend to co-activate during task conditions also tend to correlate with one another even when one is quietly at rest (Biswal et al., 1995; Greicius et al., 2003; for recent reviews, see Wig et al., 2011; Power et al., 2014). Multiple RSFC investigations, conducted using different analysis streams and overseen by different research groups, converge upon a distinct network of regions consisting of the PCU, MCC, and pIPL/dAG (Figure 1.3, right). These same regions have recently been shown to have similar changes in their connectivity profiles across the lifespan (Yang et al., 2014), which is one means by which these three regions appear distinct from the adjacent default mode network (DMN) regions with which they are sometimes (mistakenly) associated (e.g., Vannini et al., 2011). The relative positions of PMN and DMN regions are illustrated in Figure 1.4.

In summary, both task fMRI and RSFC MRI experiments have identified a small network of three regions within parietal cortex. These same regions have been associated with both the successful encoding of information into, and successful retrieval of information from, long-term memory. As a result of the robust association between PCU, MCC, and pIPL/dAG regions in the literature—with one another as well as with memory-related processes—these regions have been termed the Parietal Memory Network (PMN) (Gilmore et al., 2015). This small network is well
1.4 Negative subsequent memory effects

nSM effects are observed when activity within a given region at encoding is negatively correlated with the probability of later retrieval. With respect to a resting baseline, this can translate to either greater \textit{deactivation} being associated with encoding \textit{success}, or greater \textit{activation} being associated with encoding \textit{failure} (Daselaar et al., 2004). PMN regions, as well as adjacent DMN regions, appear to show the former pattern (Daselaar et al., 2009; de Chastelaine & Rugg, 2014).

Our understanding of nSM effects is still somewhat poor, but most hypothetical.
explanations are attentional in nature. For example, nSM effects within frontal regions are thought to reflect inefficient stimulus processing (Otten & Rugg, 2001b). A similar explanation has been offered for deactivation within DMN regions. Here, it has been argued that DMN activity reflects inefficient resource allocation, and thus greater degrees of deactivation reflect a suppression of task-irrelevant processing (Lustig et al., 2003; Daselaar et al., 2004; Buckner et al., 2008).

With respect to the PMN, we have argued that the degree of deactivation may reflect the perception of a stimulus’ novelty, at least within the context of a single experimental task setting (Gilmore et al., 2015). Greater attentional capture coupled with a stronger sense of novelty (and greater deactivation) is accompanied by more extensive and/or elaborative encoding, resulting in better subsequent memory performance on average.

1.5 Repetition enhancement

As stimuli are repeatedly processed, PMN regions show a pattern of repetition enhancement. That is, neural activity increases as a single stimulus (or perhaps, specific set of stimulus features) is repeatedly encountered (Henson et al., 2000; Segaert et al., 2013). In this way, it can be considered the opposite of repetition suppression (i.e., neural priming) in which activity is reduced upon multiple item presentations (e.g., Desimone et al., 1995; Schacter & Buckner, 1998; Grill-Spector et al., 2006).

One recent example of repetition enhancement effects being observed within the PMN, reported by Nelson et al. (2013a), is presented in Figure 1.5. Participants were tasked with learning associated pairs of words. Activity was measured during an initial encoding period and at a final encoding period, with an interposed task that manipulated the experiential history of
Figure 1.5. Regions within the parietal memory network show trial-wise repetition enhancement effects and "flip" about baseline. BOLD activity within each member region increases across multiple item presentations, changing from an initially deactivated state to one of above-baseline activation. Explanation of figure labels: “Initial encoding” represents a first exposure to an item; “Final encoding without restudy” represents a second encounter with an item; “Final encoding with restudy” represents a third encounter with an item; and “Final encoding after test” indicates that participants initially studied an item, and had an intervening test prior to the final restudy period. Figure taken, with permission, from Gilmore et al. (2015). Coordinates are listed in MNI space.

Different word pairs. Initial presentation was associated with deactivation within all 3 PMN regions. The final encoding condition was always associated with greater activity than this initial encoding, but the extent of the difference was strongly affected by item history. Items encoded twice showed less of an increase than did items that were encoded three times, and these in turn did not show as strong of an increase as did items that were tested between the encoding periods. This indicates that PMN activity is strongly modulated by recent item history, suggesting in this case that both the raw number of exposures to a particular item, as well as the task required for a given exposure, can modulate the degree of repetition enhancement observed.
In the broader literature, several different hypotheses have been proposed to account for repetition enhancement effects, but no consensus has emerged. Of potential relevance here is one suggestion that repetition enhancement may reflect the formation of a memory trace (Henson et al., 2000). In the case of the PMN, this would be better recast as the association of a given stimulus within a given experimental context, and might therefore be restated as accompanying an item’s progression from “contextually novel” to “increasingly familiar.”

Repetition enhancement, as a general effect, is not restricted to the PMN. However, within the PMN it manifests with a very distinctive property: PMN regions “flip” from a deactivation during initial encoding to activation above baseline activation upon repeated exposure to a stimulus. This has been termed the “encoding/retrieval flip,” and was described in several studies that assumed PMN regions to be members of the DMN (Vannini et al., 2011; Vannini et al., 2013; Huijbers et al., 2012; Huijbers et al., 2013).¹

1.6 Retrieval success effects as variable forms of repetition enhancement

One way in which repetition enhancement can be observed is in the form of retrieval success effects, which were also used as a basis for defining the PMN (Figure 1.3). However, the degree to which PMN regions activate during retrieval seems to be somewhat task dependent. For example, the number of times an item has been recognized over the course of an experiment impacts the magnitude of the BOLD response in the PMN (Jessen et al., 2001). Furthermore,

¹ The term “encoding/retrieval flip” has also been used to describe regions exhibiting both nSM and positive retrieval success (Daselaar et al., 2009). This usage of the term captures activity patterns in a broader expanse of cortex than the meaning adopted here.
whereas the presence and direction of retrieval success in other parts of cortex appears to be sensitive to the frequency of old and new items (Herron et al., 2004; Aminoff et al., 2015), regions within the PMN do not emerge in analyses manipulating this factor. Combined with the results of Jessen et al. (2001), these findings suggest that PMN regions are not sensitive to the general task conditions in which a retrieval attempt takes place, but rather are sensitive to the experience one has with specific stimuli in the course of an experiment. Consistent with a “prior-experience” account, activity within PMN regions is correlated with the perceived familiarity of a given stimulus, and scales linearly with the subjective confidence that an item is old or new (Yonelinas et al., 2005; Kim, 2013; Hutchinson et al., 2015). Collectively, these findings suggest that retrieval success effects are reflective of different degrees of repetition enhancement\(^2\) in PMN regions, and thus may be distinct from retrieval success effects described elsewhere in the brain.

### 1.7 A preliminary functional account of the PMN

To date, a single hypothesis has been forwarded to account for the manner by which activity in the PMN may relate to human memory (Gilmore et al., 2015). This hypothesis assumes that activity within the PMN signifies the perceived novelty or familiarity of a given stimulus. Deactivations accompany novel stimuli, and activations accompany stimuli perceived to be familiar. This hypothesis appears to parsimoniously describe all of the effects described

\(^2\) The use of “repetition enhancement” in this manuscript refers to situations in which numerically greater activity is present at a later presentation (when compared to an earlier presentation). This is used without respect to resting baseline activity, and therefore includes situations in which task-induced deactivation levels are reduced across multiple presentations (i.e., when a negative value becomes less negative), as well situations in which value of zero or higher becomes increasingly positive.
thus far. However, it does require that novelty be considered the same as a lack of familiarity, and this is not a universally accepted definition of “novelty” (Habib et al., 2003; Daselaar et al., 2006; Kafkas & Montaldi, 2014).

1.7.1 Deactivations and novelty

We have argued that deactivation within the PMN represents stimuli that are novel within an experimental context (Gilmore et al., 2015). There are two important parts to this hypothesis. The first portion, which fits a large amount of experimental evidence, is that the network should deactivate across a range of task conditions in which novel stimuli are presented. This may occur during an initial encoding period (either intentional or incidental), or it may occur during a retrieval period in the form of novel lures that are presented to a subject. The second portion of this hypothesis offers a specific boundary condition for this effect: the novelty should be considered within the context of the current experimental setting. A stimulus such as a word may have been encountered numerous times across one’s lifespan, yet deactivation should still be observed when it is initially experienced in a scanner or testing room.

If greater attentional capture is associated with a stronger perception of novelty or familiarity, we can use this account to explain the negative subsequent memory effects observed in PMN regions. However, the properties of a stimulus responsible for the strength of its perceived novelty are not understood, and they may depend on surface features of an item, or they may depend on factors related to the ongoing task conditions. A surface feature account is intuitively plausible, and it is already known that surface features can impact the degree to which items are subjectively experienced as familiar (e.g., Whittlesea et al., 1990). Currently, the exact feature dimensions responsible are not understood. The second possibility (related to task conditions) also has some degree of support; unpublished work by McDermott and colleagues...
suggests that orienting individuals to semantic features of items is associated with greater deactivation within most PMN regions than is orientation to phonological or orthographic features (Figure 1.6).

![Graph showing signal change in different brain regions](image)

**Figure 1.6.** Unpublished data from two independent datasets suggests that initial encoding conditions can impact deactivations within the parietal memory network (PMN). Attending to semantic features of words is associated with less activity within PMN regions than is attending to phonological features of items. Attending to orthographic features leads to greater activity levels than does attending to phonological features.

### 1.7.2 Activation and familiarity

Just as deactivations within the PMN are thought to reflect an *absence* of familiarity with a given stimulus, above-baseline activation accompanies the experience that one has encountered an item previously. This likely results from some kind of match between one’s current perception and a representation from long-term memory. This does not assume that the PMN is
causally involved in the decision-making process, but rather that is it *reflective* of the degree to which a current representation is matching one that has previously been encoded and stored. This hypothesis has not been tested directly, but it can account for the degree that PMN regions are monotonically more active as one becomes more certain of their recognition decision or when stimuli are reported to be more familiar as compared to less familiar. One can also observe PMN regions in previous datasets that attempt to isolate regions thought to support familiarity-related processes (Yonelinas et al., 2005; Vilberg & Rugg, 2008).

Recognition-related activation within the PMN need not require an intentional retrieval attempt. This is evident in findings from (Nelson et al., 2013a), where the encoding/retrieval flip is seen even though participants are actually just encoding and re-encoding materials (Figure 1.5). However, it is clear that the degree of activation can certainly be affected by task conditions. This is evident when comparing the green and orange bars in Figure 1.5, but extends to other experimental conditions as well. In situations where participants are cued to expect a novel stimulus, but instead are confronted with a familiar (previously studied) item, greater pIPL/dAG activity is observed than in cases where participants are cued to expect the familiar stimulus (Jaeger et al., 2013). This may more broadly suggest that violations of expectation potentiate activity with one or more PMN regions, and this will need to be examined more specifically in future work.

### 1.8 Outstanding questions of PMN function

Our understanding of the PMN is still in its infancy. The hypothesis forwarded by Gilmore et al. (2015) reviewed a large area of the literature, but insufficient time has lapsed to begin to adequately test the novelty/familiarity hypothesis. I will now identify several
outstanding questions related to this network. These questions are meant to be answered by work described in later chapters of this dissertation, but by no means should this be considered an exhaustive list of “known unknowns” (for other outstanding questions related to PMN function, see Gilmore et al., 2015)

1.8.1 How does the PMN behave under incidental memory conditions?

All of the work that has been considered to formulate the novelty/familiarity hypothesis was conducted under explicit memory conditions. That is, participants were always either intentionally encoding materials in preparation for a later test, were always explicitly attempting to retrieve materials on a test, or both. However, we have hypothesized that neither explicit encoding nor retrieval is a necessary condition for deactivation to novelty or activation to familiarity. It seems that some amount of activation observed within the PMN can be driven by task, but in general it appears as though one can expect at least weak activation even in the absence of any explicit retrieval condition. Of course, it may well be the case that deactivations are not observed if participants are never directed to encode an item, and we may not observe activations within the PMN if participants were never instructed to consider their past experience with an item. To address this, one can easily invoke the logic used in incidental memory tasks, such as those used to study priming. In such cases, participants are asked to make decisions without being directed to their prior experiences, yet those very experiences can alter participant behaviors. For example, participants routinely show faster response times when repeatedly making judgments about the same stimulus (Schacter, 1987; Roediger, 1990; Roediger & McDermott, 1993). This is a phenomenon known as behavioral priming, and can be accomplished without explicit orientation to a previous time in which a given decision was made.
In this dissertation, I investigate how PMN regions respond during an implicit memory task. Participants were shown pictures of faces, pictures of scenes, or words, and were asked to make a simple semantic decision about each stimulus. Each stimulus was presented three times, and the semantic task was identical in each presentation. BOLD activity was measured for each presentation of each stimulus type. Results suggest that implicit memory conditions continue to exhibit initial deactivations and repetition enhancement within the PMN, but that the degree of activation appears to be very low or non-existent upon repeated exposures. The procedures employed and specific results of this experiment are discussed in Chapter 2.

1.8.2 Can training affect PMN responses?

An interesting approach to understanding the function of a system is to look at “outlier individuals.” For instance, a great deal was learned regarding the function of the medial temporal lobes by studying patients such as HM or KC, who had severe damage to these regions (Scoville & Milner, 1957; Tulving, 1985). On the other end of the spectrum are individuals who have highly superior memory abilities. For some of these individuals, this appears to be a natural ability, as in the case of those with Highly Superior Autobiographical Memory (LePort et al., 2012). For others, superior memory abilities are learned. Such is the case with “memory athletes” who have extensively trained in the use of visual imagery to rapidly encode (and later retrieve) large amounts of information extremely quickly. These individuals participate in highly competitive national and international tournaments (e.g., The USA Memory Championships, http://www.usamemorychampionship.com; The World Memory Championships, http://www.worldmemorychampionships.com) to fight for the title of “best memorizer.”

Surprisingly little research has been conducted on memory athletes in general, and even less has occurred in the context of cognitive neuroscience. A notable exception is work
conducted by Maguire et al. (2002), who found that athletes performed normally on standard cognitive batteries, did not have enlarged or shrunken brain structures, and were “special” only insofar as they used more effective strategies than normal individuals. In the context of PMN research, studying memory athletes may provide a valuable means of determining if the fundamental processing that occurs within the PMN can be altered in some way by “overtraining” encoding or retrieval processes. One might hypothesize, for instance, that memory athletes should show particularly large levels of repetition enhancement, as they have trained themselves to be very effective encoders and are often able to retrieve information very vividly as a consequence of the techniques they use.

In this dissertation I present data from a single memory athlete who was asked to perform the same task described in Chapter 2. Behavioral and neural responses during the task are compared to a control group consisting of the other participants who participated in this research. In general, at least with respect to the implicit memory task, the athlete was generally within the range of normal responses both behaviorally and neurally. More complete results of this comparison are presented in Chapter 3.

1.9 On the utility of single-subject analysis

The work presented in this dissertation is focused on questions related to the PMN. However, it differs from many experiments in that it is not primarily based on a large group analysis strategy. Instead, large amounts of data were collected from a small number of individual subjects. The rationale for this choice is discussed below.

The backbone of fMRI studies of human memory has been built on group-level analyses. Typically, data from 10-30 participants are averaged together, and results are described in one of
several standardized atlas spaces (e.g., the Talairach atlas, described in Talairach & Tournoux, 1988). This approach has provided (and continues to provide) valuable insights into human cognition, but is not without its limitations. Most notably, there exists considerable anatomical and functional variability across individual subjects, and even sophisticated registration algorithms cannot prevent substantial smoothing from occurring in group analyses (Devlin & Poldrack, 2007; Van Essen & Dierker, 2007). This places practical limits on our ability to localize very specific effects to very specific regions of cortex.

In group-level analyses, this is expected, accepted, and not especially problematic. However, transformations required in group analyses necessarily obscure individual variability, and this variability is critical for more precisely mapping brain-behavior relationships (Laumann et al., 2015). However, in cases where one wants to focus on a specific individual—as is the case in this dissertation with the memory athlete—the expected, accepted variability is in fact quite problematic. In these situations, alternative strategies are necessary. Here, it is more appropriate to focus on a very small number of subjects and collect many observations for each individual (e.g., Gonzalez-Castillo & Saad, 2012; Kay et al., 2015).

For practical purposes, each individual participant had approximately 10 participants’ worth of task data collected. In addition, each subject had 5 hours of resting state data collected, which is well above recently established guidelines concerning how much data needs to be collected to fully minimize intra-individual variance (Laumann et al., 2015). The result of this data collection strategy was to effectively collect a full experimental dataset for each participant, and therefore build a useful distribution against which one memory athlete could be compared.
1.10 On the agreement between different MRI methodologies in the localization of brain networks

A final component of this dissertation involves a comparison of how a single individual’s PMN may be localized using task-based fMRI data, and how that compares to the location and extent of PMN regions as they might be described by resting-state functional connectivity (RSFC) MRI.

Over the past decade, the prevalence of studies incorporating RSFC has increased substantially. As described earlier in this introductory chapter, RSFC uses fMRI methods to measure changes in the BOLD signal over time, but does so for completely different reasons than traditional task fMRI. Whereas task fMRI correlates changes in the BOLD signal with discrete events, RSFC MRI examines spontaneous fluctuations in the BOLD signal in the absence of explicit task conditions. These spontaneous fluctuations are not random across the cortex. Rather, they are distributed such that regions within distinct functional systems tend to show highly correlated spontaneous BOLD activity even when one is quietly at rest (Biswal et al., 1995).

An obvious question concerning RSFC is the degree to which the network maps it produces overlap with those derived from experimental task settings. To the extent that RSFC is indicative of a history of task-based coactivation, one would hypothesize a strong agreement between task-based and RSFC-based descriptions of a network, assuming a task can be made sufficiently specific and incisive. Some evidence supports that this is likely the case. For example, recent work by Laumann et al. (2015) used RSFC to locate putative areal boundaries in a single individual’s brain, and found that (task-based) retinotopic estimates of V1, V2, and V3
locations corresponded strongly with the (RSFC) boundary-based estimates.

In short, there is strong reason to expect that the contrast map generated by well-design tasks should show strong agreement with an RSFC-generated description of the same network being recruited to perform a given task. What this agreement allows for is an easy means of identifying the degree to which a given task may serve as a network localizer. In a general sense, if a task map coincides well with a single network map, then one can assume it to be a useful means of identifying that network in an individual. In the specific case presented here, I will examine the agreement between the implicit memory task carried out by participants in the experiments contained in this dissertation, and each individual’s PMN as it is identified by RSFC. If agreement is strong, then the task can serve as a very straightforward means of localizing the PMN, thereby enabling a diverse collection of researchers to define regions of interest in a consistent manner for future experiments.
1.11 References


Chapter 2: Assessing parietal memory network responses under incidental memory task conditions

Abstract

It has been hypothesized that irrespective of task conditions, the parietal memory network (PMN) deactivates in response to perceived stimulus novelty, and activates in response to perceived stimulus familiarity through a process of repetition enhancement. However, this hypothesis was generated from data collected under various conditions in which stimuli were explicitly encoded or retrieved. In this chapter, we describe results from a task in which no explicit memory component was present. Ten highly-sampled subjects made basic semantic judgments about stimuli that were presented to them multiple times. We found that we could localize PMN regions within individual subjects by comparing whole-brain neural activity across multiple stimulus presentations. However these regions only exhibited a subset of the hypothesized response patterns. Deactivations were observed during initial stimulus presentations, and repetition enhancement effects were evident across multiple viewings, but above-baseline activation for repeatedly presented (i.e., familiar) items was not present. These data suggest that PMN responses to familiar stimuli are more variable than previously thought, and that network activity appears to be more sensitive to the salience and/or task-relevance of stimulus familiarity than was previously believed.
2.1 Introduction

The Parietal Memory Network (PMN) has only been recently described in the literature, but appears to be involved in both the encoding of information into, and retrieval of information from, human memory (Gilmore et al., 2015). Across numerous studies, initial exposure to stimuli is associated with deactivation within the PMN, and subsequent item presentations (typically retrieval conditions) are associated with activations (e.g., Vannini et al., 2011; Nelson et al., 2010; Nelson et al., 2013). PMN regions therefore not only show patterns of repetition enhancement, but in memory experiments can actually “flip” their response direction relative to a resting baseline. A recently-proposed novelty/familiarity account has suggested that the PMN is not involved in encoding or retrieval per se, but rather is responding to the perceived novelty or familiarity of a given stimulus (Gilmore et al., 2015).

The hypothesis, as forwarded, makes clear predictions that the demands of a specific task should not impact the basic “flip” within PMN regions. Rather, the demands should impact the magnitude of responses, but not their directions relative to baseline. Data depicted in Figure 1.6 suggest that an encoding task can alter the degree of deactivation within PMN regions, while tasks in which the expectation of familiarity is manipulated have similarly affected the amplitude (but not direction) of responses at retrieval (O'Connor et al., 2010; Jaeger et al., 2013). In general, one may therefore expect the salience of novelty or familiarity to modulate the magnitude of the BOLD response in PMN regions, but there is little evidence to suggest that encoding should be associated with above-baseline activations or retrieval with deactivations.

In this experiment, we adopted an implicit memory paradigm with the intent of directly testing the predicted flip within PMN regions. Subjects were instructed to make semantic judgments about stimuli that were each observed multiple times (Figure 2.1). The decisions
required no explicit episodic memory component and were semantic in nature. By incorporating an implicit memory procedure, we were able to directly assess whether or not PMN regions continued to deactivate to novel stimuli, show repetition enhancement effects upon repeated exposures to a stimulus, and show clear activations at retrieval. Across individuals, we observed repetition enhancement effects across stimulus exposures, and deactivations in PMN regions accompanying initial stimulus presentations. However, the hypothesized activations during final stimulus presentations were not present. These findings suggest that initial characterizations of the PMN overemphasized the importance of familiarity \textit{per se}, and underemphasized the role of attention to that familiarity, in producing above-baseline activation.

2.2 Materials and methods

2.2.1 Subjects

Data were obtained from a total of 10 subjects, 2 of whom were members of the research team responsible for collecting these data. All subjects were recruited from Washington University and the surrounding area as part of the “Midnight Scan Club” (MSC) initiative. The subjects are therefore labeled MSC01-MSC10. Specific demographic information for all subjects is included in Table 1. To briefly summarize, the average subject was 29.1 years of age (range 24-34), was highly educated (average years of education: 20.7; range 17-28), and had IQs of approximately 125 (range: 117-138) as determined by the Kaufman Brief Intelligence Test (Parker, 1993). Half of the 10 subjects were female. All subjects were right-handed with normal or corrected-to-normal vision. Informed consent was obtained from all subjects in accordance with standard Washington University human research practices. Monetary compensation was
Table 2.1. Demographic information for all MSC subjects

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age</th>
<th>Gender</th>
<th>Years of Education</th>
<th>KBIT Verbal IQ score</th>
<th>KBIT Nonverbal IQ score</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSC01</td>
<td>34</td>
<td>M</td>
<td>22</td>
<td>129</td>
<td>125</td>
</tr>
<tr>
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<td>34</td>
<td>M</td>
<td>28</td>
<td>129</td>
<td>130</td>
</tr>
<tr>
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<td>112</td>
</tr>
<tr>
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<td>28</td>
<td>F</td>
<td>22</td>
<td>127</td>
<td>130</td>
</tr>
<tr>
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<td>27</td>
<td>M</td>
<td>20</td>
<td>102</td>
<td>132</td>
</tr>
<tr>
<td>MSC06</td>
<td>24</td>
<td>F</td>
<td>17</td>
<td>119</td>
<td>125</td>
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<td>27</td>
<td>F</td>
<td>21</td>
<td>129</td>
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</tr>
<tr>
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<td>M</td>
<td>19</td>
<td>135</td>
<td>115</td>
</tr>
<tr>
<td>MSC10</td>
<td>31</td>
<td>M</td>
<td>19</td>
<td>135</td>
<td>132</td>
</tr>
</tbody>
</table>

| Average | 29.1 | n/a | 20.6 | 124.9 | 124.8 |

provided to the 8 subjects who were not members of the research team. All sessions for all subjects were collected at the same time of day (i.e., midnight).

2.2.2 Materials

*Faces:* Face stimuli consisted of 240 photographic images of male and female faces (120 of each), taken from the following publicly available electronic databases: The Psychological Image Collection at Stirling’s 2D face set (http://pics.stir.ac.uk); the CNBC Tarrlab “Face Place” stimulus repository (http://wiki.cnbc.cmu.edu/TarrLab; Righi et al., 2012); the Park Aging Mind Laboratory Face Database (http://agingmind.utdallas.edu/facedb); and Libor Spacek’s Facial Images Database (http://cmp.felk.cvut.cz/~spacelib/faces; Hond & Spacek, 1997). To avoid potential differences in stimulus properties across image sets, no scan run used faces from more than 1 source. All face images were resized to a 4:3 aspect ratio, and were presented as a 600 x 450 pixel image in the center of the screen (overall screen resolution: 1024 x 768 pixels).

*Scenes:* Scene stimuli consisted of 240 photographic images of indoor and outdoor scenes
(120 of each), taken from a larger laboratory stimulus set originally assembled by Hank Chen. These images were originally obtained using Google image searches (images.google.com). All images were 800 x 600 pixels or larger in size to ensure sufficiently high quality for each image, and no humans were visible in any of the pictures. Scenes were cropped to a 4:3 aspect ratio and presented as a 600 x 450 pixel image in the center of the screen. An additional 24 images (12 indoor, 12 outdoor) were used in a make-up session for MSC02 to replace a task run corrupted by a software malfunction.

Words: Word stimuli consisted of 240 nouns taken from the English Lexicon Project database (http://elexicon.wustl.edu; Balota et al., 2007). Words ranged from 5-8 characters in length, were 1-4 syllables in length, and had an average HAL frequency rating (Lund & Burgess, 1996) of 5781.9 (range: 20-34727). Words were divided into “abstract” and “concrete” groups based upon their concreteness ratings, determined by the MRC Psycholinguistic database (http://www.psych.rl.ac.uk/MRC_Psych_Db.html; Wilson, 1988). Abstract words were defined as having a concreteness rating below 350 ($M = 292$; range: 204-349), while concrete words were defined as having a concreteness rating above 525 ($M = 606$; range: 530-662). Specific properties for each word are included in Table A.1.

2.2.3 Implicit memory task paradigm

The implicit memory task (IMT) data were collected as part of a larger protocol, which included the collection of anatomical data, rest data (which will be discussed in Chapter 4), and several other in-scanner tasks that are not considered here. In the IMT, subjects made binary decisions about scenes, faces, and words, each of which were presented multiple times (see Figure 2.1). Stimulus types of each category were separated into different scan runs and the order of runs was counterbalanced across all 10 data collection sessions for each subject such
Figure 2.1. Design of the implicit memory task. In separate scan runs, participants made semantic decisions about faces, scenes, or words. Each stimulus was presented 3 times, and the same decision was made each time a given stimulus was observed. All stimuli were presented once before any were presented twice, and all were presented twice before any were presented for a third time.

that the presentation order was not systematic across sessions and stimulus types. As there were three runs per session, a total of 30 task runs were collected for each subject. An exception to this was MSC10, for whom only 27 task scans were available for analysis.

In each task run, subjects viewed 24 stimuli, three times each. All stimuli were presented a single time before any were repeated, and all stimuli were shown twice before any were presented for a third time. Stimulus order was shuffled between presentations to produce a different presentation order and ensure an approximately equal delay between occurrences across all items. Each stimulus was presented for 1700 ms against a black background, followed by a jittered inter-stimulus interval (ISI) ranging from 500-4900 ms. During the ISI, a white fixation cross (48-point Arial type) was presented in the center of the screen, and subjects were instructed to relax, clear their mind, and await presentation of the next stimulus.

For scenes, subjects were instructed to indicate whether they were viewing an indoor or outdoor scene. For faces, they were instructed to indicate if the face was male or female. For words, they indicated if they thought the word was abstract or concrete. For verbatim instructions
given for each task, see Appendix A. Subjects had 2200 ms from the onset of each stimulus to make the appropriate response for that stimulus type (e.g., indoor/outdoor for scenes). They were instructed to disregard the number of times they had previously seen an item and simply perform the task as described.

2.2.4 Analysis of behavioral data

Responses to stimuli were scored for accuracy and response time (RT). These were analyzed with ANOVAs and t-tests using SPSS software version 23 (http://www-01.ibm.com/software/analytics/spss/). Effect sizes are reported using partial eta squared ($\eta^2_p$) for $F$-statistics and Cohen’s $d$ for $t$-statistics (Cohen, 1988). When correction for multiple comparisons was required, a Bonferroni correction was employed. To ease reader interpretation of statistical test significances, the $p$-values presented were multiplied by the number of tests employed and should be compared against a constant $\alpha = .05$. This is mathematically equivalent to dividing $\alpha$ by the number of tests, but provides a consistent referent for determining significance. $P$-values corrected in this manner are recorded as $p_{(corrected-N)}$, where $N$ is the number of tests for which the value is being corrected.

2.2.5 MRI data acquisition

All data were acquired using a Siemens MAGNETOM Tim Trio 3.0T scanner using a 12-channel Matrix head coil (Erlangen, Germany). Subjects were situated in the scanner with foam pillows to help maintain subject comfort and stabilize head position. Four T1-weighted sagittal Magnetization-Prepared Rapid Gradient Echo (MP-RAGE) structural images were obtained for each subject (TE = 3.74 ms, TR(partition) = 2400 ms, TI = 1000 ms, flip angle = 8º, 224 slices with 0.8 x 0.8 x 0.8 mm voxels, FOV = 256 x 256) (Mugler & Brookerman, 1990). Four T2-weighted sagittal turbo spin echo structural images (TE = 479 ms, TR = 3200 ms, 224 slices with
0.8 x 0.8 x 0.8 mm voxels, FOV = 256 x 256) were also obtained for each subject. Gradient field maps were collected to estimate inhomogeneities in the magnetic field for each subject in each scanning session. An auto align pulse sequence protocol provided in the Siemens software was used to align the acquisition slices of the functional scans parallel to the anterior commissure-posterior commissure (AC-PC) plane. Slices collected were therefore parallel to the slices in the Talairach atlas (Talairach & Tournoux, 1988). Functional imaging was performed using a BOLD contrast sensitive gradient echo echo-planar sequence (TE = 27 ms, flip angle = 90°, in-plane resolution = 4 x 4 mm). Whole brain EPI volumes (MR frames) of 36 contiguous, 4mm-thick axial slices were obtained every 2200 ms. The first 4 functional images of each scan were discarded to allow for T1 equilibration effects.

A headset with noise-canceling headphones was used to reduce in-scanner noise for all subjects. The headset was equipped with a microphone that allowed subjects to communicate with researchers throughout each scanner session. An Apple iMac computer (Apple, Cupertino, CA, USA) running PsyScope software (Cohen et al., 1993) was used to display stimuli. An LCD projector (Sharp model PG-C20XU) was used to project stimuli onto a MRI-compatible rear-projection screen (CinePlex) at the head of the bore, which the subjects viewed through a mirror attached to the head coil (maximum field of view = 21° of visual angle).

2.2.6 fMRI data preprocessing

Imaging data from each subject were pre-processed to reduce noise and to maximize across-session registration, using methods described in Laumann et al. (submitted). Data from each session were corrected for within- and across-scan movement using a rigid-body rotation and translation algorithm (Snyder, 1996), and were intensity-normalized to a mode 1000 across the whole brain to allow for comparisons across runs and subjects (Ojemann et al., 1997).
Transformation of functional data to an atlas space (711-2B) was computed by registering the mean intensity image from each subject’s first functional scan to atlas space via the average T1- and T2-weighted images ($n = 4$ for each image type). All other BOLD runs for each subject were linearly registered to this first session. Atlas transformation, distortion correction using a mean field map (Laumann et al., 2015), and resampling to a 3 mm isotropic atlas space were combined into a single interpolation step using the `applywarp` tool in FSL (Smith et al., 2004). Subsequent analyses were performed on the atlas-transformed data within and across subjects.

2.2.7 GLM-based fMRI data analysis

Time series data were analyzed using a general linear model (GLM; Friston et al., 1994; Miezin et al., 2000), in which the data for each time point in each voxel are treated as the sum of all effects present at that time point. The time course of activity for effects in each condition was modeled as a set of delta functions following the onset of each coded event (Ollinger et al., 2001a; Ollinger et al., 2001b). This approach assumes that all events associated with a specific condition evoke the same BOLD response, but makes no assumptions of what the shape of that response might be. Regressors reflect distinct task conditions as well as effects of non-interest, the specifics of which are described below.

2.2.8 GLM creation

Each IMT scan consisted of 117 frames (121 before discarding the first 4 frames of each scan, to allow for T1 equilibration effects), and runs were concatenated into a single time series for each subject (3510 MR frames in length). Nine conditions of interest were coded for in the GLM, one for each Presentation (1, 2, or 3) of each stimulus type (Face, Scene, or Word) (e.g., Face Presentation 1, Face Presentation 2, Face Presentation 3, Scene Presentation 1, etc.). As each condition was modeled over 8 time points (capturing 17.6 s of BOLD activity following
stimulus onset), the total number of regressors related to task conditions was 72. In addition, regressors of non-interest included a trend term to account for linear changes in signal for each run, and a constant term modeling the baseline signal for each run. A total of 132 columns were therefore in the design matrix.

2.2.9 **Analysis and visualization software**

Image processing was performed using Washington University’s in-house fMRI processing software (FIDL; http://www.nil.wustl.edu/~fidl/) written in IDL (Research Systems, Inc.). Statistical maps were sampled from volume to surface space and projected onto a partially inflated surface representation of the human brain using Connectome Workbench software (Marcus et al., 2011). All coordinates are reported in MNI152 space.

2.2.10 **Single-subject ANOVA and t-test parameters: Single stimulus analyses**

A multi-step approach was taken to identify voxels sensitive to repetition enhancement effects in the IMT (summarized in Figure 2.2). First, a Presentation (1-3) x Time Point (1-8) ANOVA was conducted to identify voxels that were sensitive to effects of stimulus repetition. In order to correct for multiple comparisons and achieve a whole-brain familywise error rate (FWE) of $p < .05$, only voxels with a $z$-score exceeding 3, and that were contiguous with at least two other such voxels, were considered to be significant (McAvoy et al., 2001).

Within each voxel identified by the Presentation x Time Point ANOVA, a $t$-test was conducted to provide information about the directionality of the difference across presentations. More specifically, a paired-samples, two-tailed $t$-test compared activity between Presentation 3 and Presentation 1 across Time Points 3-5 (5.0-12.5 s following trial onset). These time points were selected based on visual inspection of time courses reported previously in putative PMN regions (Nelson et al., 2010; Nelson et al., 2013). Significance was set at a $|z| > 1.96$. 

39
Figure 2.2. Graphical depiction of fMRI data analysis stream. 1) Raw statistical maps were generated for each subject by conducting a Presentation (1-3) x Time Point (1-8) ANOVA for each stimulus type (or across multiple stimulus types). 2) Each map was corrected for multiple comparisons to achieve a whole-brain $p < .05$, based on methods outlined by McAvoy et al. (2001). 3) Within each surviving voxel, a $t$-test was conducted between Presentations 3 and 1, comparing activity during Time Points 3-5 for each condition. Z-scores exceeding $\pm 1.96$ ($p < .05$) were required for voxels to be considered significantly different between Presentations. 4) A peak finding algorithm located local maxima based on the $t$-test. Putative PMN regions of interest (ROIs) were created for each subject by drawing 4 mm radius spheres around the closest peak within 15mm Euclidian distance of a priori coordinates (determined by averaging coordinates from McDermott et al. (2009) and Nelson et al. (2010) datasets). Example data are taken from subject MSC01’s IMT data for scenes.
(corresponding to an uncorrected $p < .05$) for each voxel. All voxels considered significant at this point therefore showed a significant interaction of Presentation Number and Time Point, and also showed significantly different activity between Presentation 3 and Presentation 1 during their peak response period.

2.2.11 ROI definition

An automated peak searching algorithm (peak_4dfp) written by Avi Snyder searched the difference maps for peaks, around which spherical ROIs were drawn. Peaks under 10 mm apart were consolidated via coordinate averaging. ROIs were then obtained by centering an 8-mm diameter sphere about the identified coordinates. Putative PMN ROIs were identified by selecting the closest ROI to each canonical PMN region (left pIPL/dAG, left PCU, MCC) as well as homotopic coordinates on the right hemisphere for pIPL/dAG and PCU. Time courses were extracted from each ROI by averaging activity across all included voxels.\(^3\) Regions centered in white matter or CSF were not considered for analysis. In 5 cases, this led to putative PMN regions being rejected. In all such cases, the next-closest ROI that fit the above criteria was selected.

2.2.12 Single-subject ANOVA and \(t\)-test parameters: Multiple stimulus analyses

In addition to examining PMN responses for each individual type of stimulus, responses were examined when collapsing across stimulus categories. This was done in two ways: Preliminary analyses raised a concern that faces behaved slightly differently than did scenes or words, so the main multi-stimulus analysis averaged activity only across Scene and Word

\(^3\) Subjects were variable with respect to the number of ROIs identified using the criteria discussed above. Figures in this chapter depicting time courses from different ROIs (e.g., Figure 2.10) reflect this inconsistency.
conditions. For the sake of completeness, a second analysis was conducted that examined activity when collapsing across all three categories (Figure A.1). Analyses of multi-stimulus responses were conducted as previously described, with one exception: After conducting the Presentation x Time Point ANOVA and correcting for multiple comparisons, a Presentation x Stimulus Type x Time Point ANOVA was also conducted and corrected for multiple comparisons using the same parameters ($z > 3; k \geq 3$). This image was applied as an exclusive mask to the Presentation x Time Point ANOVA, therefore removing any potential voxels that show different patterns of priming or enhancement for different types of stimuli. After this masking, a $t$-test was conducted as described above, as were peak detection and ROI generation.

### 2.2.13 Group ANOVA and $t$-test parameters: Single stimulus analysis

As a supplemental analysis, subjects were analyzed as a group in addition to being examined individually. Due to the nature of the data, the group analysis differed somewhat from the manner it was conducted at the single-subject level. Whereas fixed-effects maps were generated for each subject in their individual analysis, at the group-level subjects were treated as random effects.

Excepting this difference, the same GLMs that created each individual’s maps were carried forward for use in the group analysis. As before, an initial Presentation x Time Point ANOVA was conducted to identify voxels that were sensitive to stimulus repetition effects. The map was corrected for multiple comparisons as with single subjects ($z > 3; k \geq 3$), but this resulted in a map that found significant effects across virtually the entire cortex. Therefore, a new $z > 10$ threshold was selected for the initial ANOVA map. Procedures for the $t$-test and ROI definition that followed the initial ANOVA were identical to those described previously.
2.2.14 Group ANOVA and $t$-test parameters: Multiple stimulus analyses

Analyses of effects across multiple types of stimulus required an additional step of exclusively masking voxels that showed an interaction of Stimulus Type x Presentation x Time Point. For the group-level analysis, the statistical requirement of this second ANOVA was set to $z > 10$, to match the initial Presentation X Time Point ANOVA for group-level analysis. Procedures for the $t$-test and ROI definition that followed the initial ANOVA were identical to those described previously.

2.3 Behavioral Results

2.3.1 Subjects were accurate in their classification judgments

Subjects were effectively at ceiling in their classifications for all types of stimuli (Figure 2.3). On average, they responded correctly on 97.3% ($SEM = 0.19\%$) of trials. Focusing on individual stimuli, faces were correctly classified as male or female 98.5% of the time ($SEM = \ldots$)

![Figure 2.3. Subject accuracies during the classification of different stimulus categories. Overall, participants were effectively at ceiling for all types of stimuli.](image)
0.21%), scenes were correctly classified as indoor or outdoor 97.0% of the time (SEM = 0.17%),
and words were correctly classified as abstract or concrete 96.5% of the time (SEM = 0.43%).

**Subjects showed priming as they repeatedly judged the same stimuli**

Subjects showed behavioral priming as they repeatedly made the same type of judgment for each stimulus. Response time data suggest that no practice effects were present across sessions (Figure 2.4, top). A 3 (Presentation number) x 10 (Session number) ANOVA indicated an expected main effect of presentation ($F_{(2,10.1)} = 89.80, \eta^2_p = .909, p < .001$; Greenhouse-Geisser corrected for nonsphericity), with RT means of 879.2 ms, 814.6 ms, and 789.8 ms for Presentation 1, 2, and 3, respectively across the group. There was no main effect of session ($F_{(9,81)} = 1.17, \eta^2_p = .115, p = .326$), or interaction of presentation number by session number ($F_{(18,162)} = .93, \eta^2_p = .094, p = .542$).

When considering each type of stimulus separately, largely consistent results were also obtained (Figure 2.4, bottom). Each stimulus type was associated with clear behavioral priming across presentations (smallest obtained $F_{(2,18)} = 13.12, \eta^2_p = .593, p < .001$; obtained for faces). In addition, neither scenes nor words showed any effect of Session ($F_{(9,81)} = 1.01$ and 1.29, respectively, $p_{(corrected-3)'s} \geq .765$), though there was a small effect of Session for faces ($F_{(9,81)} = 2.63, \eta^2_p = .226, p_{(corrected-3)} = .030$), which remained significant after Bonferroni correction for

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4 Recall that stimuli were repeated within a given run, but not across multiple runs.
5 An earlier version of the model also included an Age covariate. However, this was not a significant predictor of between-subjects performance ($F_{(1,8)} = .756, \eta^2_p = .086, p = .410$) and did not significantly interact with any other factors. Age was therefore not included in further analyses.
Figure 2.4. Average reaction times across sessions. No practice effects were observed, although Face judgments were slightly faster during middle sessions than early or late sessions.

multiple comparisons (across the three stimulus types). This was driven by slightly faster RTs during the middle sessions as compared to the beginning or end sessions. There was no significant interaction of Presentation and Session for any of the stimulus types (largest obtained $F_{(18,162)} = 1.38$, $\eta^2_p = .133$, $p_{(corrected-3)} = .441$; obtained for faces).

2.3.2 The degree of priming differed between subjects

Although all subjects exhibited behavioral priming (as defined by a reduction in RTs across stimulus presentations), both the initial RTs and the degree of priming differed across subjects as items were repeatedly presented (Figure 2.5, top). A 10 (Subject) x 3 (Presentation number) ANOVA revealed a main effect of subject ($F_{(9,81)} = 86.30$, $\eta^2_p = .906$, $p < .001$), a main
effect of presentation \( (F_{(9,81)} = 268.70, \eta^2_p = .968, p < .001) \), and a significant Subject x Presentation interaction \( (F_{(18,162)} = 2.79, \eta^2_p = .236, p < .001) \).

When examining individual stimulus types separately (Figure 2.5, bottom), the two main effects of Subject and Presentation remained present (smallest effect of Subject: \( F_{(9,72)} = 36.98, \eta^2_p = .822, p_{(corrected)} < .001 \); obtained for scenes; smallest effect of Presentation \( F_{(1.3,11.4)} = 22.38, \eta^2_p = .713, p_{(corrected)} < .001 \), Greenhouse-Geisser corrected for nonsphericity; obtained for faces) but the interaction was no longer significant after Bonferroni correction for any of the stimulus types (largest obtained \( F_{(18,162)} = 2.73, \eta^2_p = .233, p_{(corrected)} = .078 \)).

![Diagram](image_url)

Figure 2.5. Average reaction times for each subject, across all stimulus types and within each type. All subjects showed behavioral priming, but the extent and progression of this priming differed across subjects.
2.4 fMRI Results

2.4.1 Statistical maps were generally similar across stimulus types

Statistical maps showing repetition enhancement and repetition priming effects are presented at the top of Figures 2.6-2.9. Visual inspection of the statistical maps for each stimulus type across all 10 subjects suggested a general consistency with respect to regions that showed repetition enhancement or priming. With the exception of MSC07, for whom no ROIs were identified based on the requirements outlined in the Methods section, all subjects exhibited repetition enhancement effects in one or more putative PMN ROIs. Subject-specific ROIs were typically <10 mm away from the a priori coordinates used to define each (see Table A.2 for one example of ROI locations). None of the stimulus categories recruited significantly more ROIs on average than did the others, but there were numerical difference between the categories. Faces ($M = 1.7, \text{SEM} = .60$) were associated with activity differences in slightly fewer ROIs than either scenes ($M = 3.0, \text{SEM} = .66$) or words ($M = 2.7, \text{SEM} = .66$). Paired comparisons across all 10 subjects found that after correcting for multiple comparisons, faces were marginally worse than scenes ($t_{(9)} = 2.90, d = .92, p_{(corrected-3)} = .054$), but were not significantly worse than words ($t_{(9)} = 2.37, d = .75, p_{(corrected-3)} = .13$). The number of regions associated scenes and words did not differ ($t_{(9)} = 1.96, d = .62, p_{(corrected-3)} = .24$).

2.4.2 ROI analysis shows consistent deactivation during Presentation 1, with little activation evident during Presentation 3

The primary purpose of this experiment was to examine the pattern of PMN activity that might be observed under incidental memory conditions. Time courses derived from each subject-specific putative PMN ROI are presented in Figures 2.10-2.13. By definition, all ROIs showed repetition enhancement effects, but the degree to which Presentation 1 would be accompanied by
Figure 2.6. Voxelwise results for each subject when performing Face judgments task. Regions exhibiting repetition enhancement are shown in warm colors, and repetition suppression in cool colors. Statistical maps presented on partially inflated surfaces using Workbench software (Marcus et al., 2011).
Figure 2.7. Voxelwise results for each subject when performing Scene judgments task. Regions exhibiting repetition enhancement are shown in warm colors, and repetition suppression in cool colors.
Figure 2.8. Voxelwise results for each subject when performing Word judgments task. Regions exhibiting repetition enhancement are shown in warm colors, and repetition suppression in cool colors.
Figure 2.9. Voxelwise results for each subject when averaging activity across Scene and Word judgment tasks. Regions exhibiting repetition enhancement are shown in warm colors, and repetition suppression in cool colors.
deactivations, or Presentation 3 by activations, was undetermined. Activations and deactivations were assessed by comparing peak response activity to zero. To briefly summarize the results that follow, deactivations were widely observed during Presentation 1, but the expected activations were absent during Presentation 3.

**Faces**

For faces, all 5 ROIs showed numerically negative deflections from baseline upon initial item presentation, though the small number of subjects who showed face-related repetition effects prevented most of these effects from reaching significance (Figure 2.10). The one exception was the left pIPL/dAG ROI, which showed significant deactivation following Bonferroni correction ($t(4) = 7.08$, $p_{(corrected-5)} = .011$). After collapsing activity across all ROIs that emerged across all individuals, the deactivation was statistically significant ($t(6) = 4.17$, $p = .006$).

Activity during Presentation 3 was not significantly above zero (maximum $t$-value obtained: $t(3) = 3.99$, $p_{(corrected-5)} = .140$; obtained for right PCU). When collapsing activity across all ROIs that emerged across all individuals, the activation was significantly greater than zero ($t(6) = 4.22$, $p = .006$).

**Scenes**

As with faces, initial scene presentations were associated with negative deflections from baseline in all 5 PMN ROIs (Figure 2.11). Left pIPL/dAG and MCC both emerged as significant even following Bonferroni correction (respectively; $t(7) = 5.95$, $p_{(corrected-5)} = .002$; $t(4) = 7.61$, $p_{(corrected-5)} = .008$), though the left PCU did not survive this correction ($t(4) = 3.39$, $p_{(corrected-5)} = .144$). When averaging activity across all identified ROIs across all subjects, the deactivation was
significant \((t_{8} = 4.24, p = .003)\).

Figure 2.10. Time courses of BOLD activity when making Face judgments. ROIs show individual subject and average group activity during Presentation 1, Presentation 2, and Presentation 3. *\(p < .05\) (Bonferroni corrected) vs. 0

Scenes were not accompanied by any activations within the PMN relative to baseline. Instead, activity was numerically at or below zero. This was initially significant only in left pIPL,
but did not survive Bonferroni correction ($t(7) = 2.47, p_{\text{corrected-5}} = .213$). Averaging activity across all available ROIs of all subjects resulted in a nonsignificant tendency toward deactivation ($t(8) = 2.21, p = .058$).

Figure 2.11. Time courses of BOLD activity when making Scene judgments. ROIs show individual subject and average group activity during Presentation 1, Presentation 2, and Presentation 3. 
* $p < .05$ (Bonferroni corrected) vs. 0
Words

As with faces and scenes, word Presentation 1 tended to be associated with deactivations relative to resting baseline (Figure 2.12). The only ROI not to reach or approach significance following Bonferroni correction was right pIPL/dAG ($t_{(5)} = 1.55$, $p_{(corrected-5)} = .903$). Deactivation within left PCU was marginally significant ($t_{(5)} = 3.52$, $p_{(corrected-5)} = .084$), and all other deactivations remained significant (smallest obtained value: $t_{(3)} = -6.65$, $p_{(corrected-5)} = .034$; obtained for MCC). When averaging activity across all ROIs, Presentation 1 activity was significantly below zero ($t_{(7)} = 6.24$, $p < .001$).

Presentation 3 was not associated with any significant deviations from zero, even when combining data from all identified ROIs (largest obtained value: $t_{(5)} = 2.28$, $p_{(corrected-5)} = .357$; obtained for right PCU).

Multi-stimulus analyses

Although examining each stimulus type individually was possible with the current dataset, the original intent was to use the different stimuli as a means of increasing the total number of trials for each participant. The importance of the stimulus-specific examination reported above was to determine whether or not all stimuli behaved sufficiently similar to be combined into a single measure. Given that faces exhibited several qualitative differences as compared to scenes or words (recruiting slightly fewer ROIs overall, and showing hints of activation at Presentation 3), a conservative decision was made to combine only scenes and words. However, if all stimulus types are combined, the results are qualitatively similar to those described below (Figures A.1-A.2).
Figure 2.12. Time courses of BOLD activity when making Word judgments. ROIs show individual subject and average group activity during Presentation 1, Presentation 2, and Presentation 3. *$p < .05$ (Bonferroni corrected) vs. 0

**Combined scenes and words**

A major benefit to collapsing across scene and word stimuli was an improvement in ROI detection. Deactivations were very pronounced during Presentation 1, and only a single ROI
failed to remain significant following Bonferroni correction (Figure 2.13). This exception was the right pIPL/dAG ROI ($t(4) = 3.92, p_{(corrected-5)} = .086$). All other regions were significantly deactivated (lowest obtained $t$-value: $t(6) = 4.26, p_{(corrected-5)} = .023$; obtained for right PCU), as was the network as a whole ($t(8) = 8.53, p < .001$).

Figure 2.13. Time courses of BOLD activity when averaging across Scene and Word judgments. ROIs show individual subject and average group activity across Presentations. *$p < .05$ (Bonferroni corrected) vs. 0
During Presentation 3, only a single region approached a significant difference from zero. This was left pIPL/dAG, which exhibited deactivation that did not survive correction for multiple comparisons \((t_{(6)} = 2.85, p_{\text{corrected-5}} = .146)\).

### 2.4.3 pIPL/dAG and PCU regions tend to be recruited bilaterally

The PMN has been associated with regions in the left hemisphere, but in the current experiment we attempted to identify ROIs in both hemispheres. Examining the results of the combined Scene and Word analysis across subjects, one can see that if a left pIPL/dAG or PCU ROI was located, a homotopic right-hemisphere region was generally also identified (Figure 2.9). A significant correlation was observed both for pIPL ROIs \((r = .66, p = .040)\) and PCU ROIs \((r = .81, p = .005)\).

### 2.4.4 Group analysis of MSC01-MSC10

In addition to examining activity within PMN regions defined within each subject, supplemental analyses were conducted across the ten subjects as a group. Overall, the data from the group analysis are consistent with those obtained from individual subject’s ROIs: deactivations were observed upon initial Presentations and little deviation from baseline was evident at Presentation 3. Statistical maps and time courses from the group analyses are presented in Figures A.3-A.6.

### 2.5 Discussion

This work was meant to test straightforward predictions of PMN activity, as forwarded by Gilmore et al. (2015). The observations leading to these predictions were made under explicit memory task conditions, and here we examined whether or not they could extend to implicit task
conditions. Results clearly demonstrated that several of the expected effects were present, but one was very notably absent. The specifics and impact of these findings are discussed below.

2.5.1 The IMT was associated with repetition enhancement effects and deactivation—but not activations—within the PMN

Prior to this experiment, our understanding of PMN function was based on explicit memory tasks, which involve direct instructions to subjects that they will be required to learn materials, will be tested on them, or both (Roediger & McDermott, 1993). The IMT used in this experiment allowed us to test whether or not PMN activity would show the same general pattern under implicit memory conditions. The IMT was designed such that we could directly test three very clear hypotheses. PMN regions—which were to be localized within individual subject—were expected to show repetition enhancement effects (defined as greater activity during Presentation 3 than Presentation 1), to deactivate to novel stimuli (defined in this experiment as Presentation 1 stimuli), and to show activation for familiar stimuli (defined as Presentation 3 stimuli). More broadly, the IMT used here allowed us to assess the specificity of PMN activity in the absence of the usual retrieval orientation that accompanies repeated stimulus presentations in typical memory experiments.

2.5.2 Repetition enhancement is a basic property of PMN regions

With one exception, we were able to localize putative PMN regions in all subjects by requiring only that a region show repetition enhancement, and that these regions fall within 15mm of a priori coordinates (themselves based on group average coordinates derived from meta-analyses). Indeed, visual inspection of the maps depicted in Figures 2.6-2.9 suggests that repetition enhancement effects are fairly restricted in their spatial extent, falling generally (although not exclusively) in parietal cortex. Continued observations of repetition enhancement
effects in the IMT suggests they are a fairly basic property of PMN regions. Moreover, the results suggest that enhancement is likely driven by repetition _per se_, rather than the demands of any specific task. This is consistent with the hypothesized role of changes in familiarity driving changes in PMN activity (Gilmore et al., 2015).

### 2.5.3 Deactivations represent stimulus novelty within the context of an experiment

As with repetition enhancement effects, deactivations during Presentation 1 were both predicted and observed in PMN regions. Fairly little explanation appears to be required to account for the extension of deactivations to implicit memory conditions. The judgments made during Presentation 1 were not particularly remarkable in the context of encoding tasks, and fall easily under the purview “deep” encoding conditions (Craik & Lockhart, 1972). In any case, a broader point is that the IMT offers more experimental evidence that stimulus novelty, at least within the context of an experimental setting, is associated with deactivations in the PMN.

### 2.5.4 A lack of PMN activation suggests a prominent role for attention to stimulus familiarity

Of the three predicted PMN responses in the IMT, only above-baseline activation for familiar items was absent. An exciting feature of this result is that it suggests repetition enhancement and activation to be dissociable from one another in a way that was not previously appreciated. More specifically, it suggests that whereas enhancement and deactivation are apparently obligatory, the activation is likely driven by task requirements.

In the original description of PMN, Gilmore et al. (2015) posited that familiarity “is manifested as activation within PMN regions” (p. 540). On that same page, they later stated that “activity in [PMN regions] can be influenced by the degree to which the familiarity of an item captures one’s attention.” Data from the IMT are consistent with the latter statement, and suggest
that the former must be qualified with “under explicit memory conditions.” The IMT did not require participants to orient to any familiarity signals, and in fact the instructions suggested that the decision would be made without respect to one’s prior experience(s) with a given stimulus (Appendix 2.2). Biasing of attention, then, seems to be a far more important component of PMN activation for familiar items than was originally appreciated, although replication and extension of the results obtained in the IMT would be important to establish a better sense of the boundary condition for observing above-baseline activation in PMN regions.

2.5.5 Interpreting stimulus impact on IMT repetition effects

The IMT was designed to use multiple stimuli, largely for a very practical purpose of increasing the number of stimuli in the experiment. That said, sufficient data were collected for each stimulus type that they could be modeled separately. At a qualitative level, it appears that faces were worse than either scenes or words at evoking repetition effects in the PMN. For this reason, when collapsing across stimuli we elected to restrict our primary analysis to only scenes and words. This was done to be conservative, but should not be over-interpreted by readers of this work. Given that all three stimulus types were presented under very similar conditions, it would be foolish at this juncture to make wholesale conclusions about whether (and why) a given stimulus type may be “best” for localizing PMN regions. This particular question should be addressed in future work, and for now a more important conclusion is that all stimuli showed some degree of both deactivation and repetition enhancement.

2.5.6 PMN effects are observable bilaterally

One interesting finding from the current work was that PMN effects were observed bilaterally; either ROIs were identified in both hemispheres, or neither. Prior PMN discussion has focused on left hemisphere regions but this does not appear to reflect the broader
organization of the network. One possibility, raised by Gilmore et al. (2015), suggested that the use of verbalizeable materials may more commonly recruit left hemisphere regions, and that right pIPL or PCU may be recruited using materials that are less verbalizeable (which would largely mirror prefrontal stimulus effects as observed by Kelley et al., 1998; McDermott et al., 1999). However, several of the current findings speak against this possibility. Most notably, both within-individuals and at the group-level, words commonly recruited right pIPL and PCU (Figure 2.8; Figure A.4), and faces were clearly capable of eliciting activation in left pIPL and PCU (Figure 2.6, Figure A.2).

2.5.7 Potential limitations of the present work

The IMT employed here represents an important step in better understanding PMN function, but the design and analysis decisions employed here leave open several important questions. These will need to be addressed in future research.

Behavioral differences were present across subjects.

It is empirically the case that different subjects showed different levels of behavioral priming across stimulus presentations. An important question relates to how these individual differences may impact the differences in PMN activity across multiple item presentations. Given the small number of subjects included in this dataset, it is not practical to correlate differences in behavioral priming with differences in repetition enhancement. Future work optimized for this question will be needed to address this possibility.

A single threshold is probably not optimal for comparing across individuals

Another concern relates to how one can best compare activity across individuals. Here, a constant set of criteria was applied to each subject. This resulted in certain subjects for whom
most or all PMN regions could be localized (e.g., MSC02), and others in which few or no ROIs were identified (e.g., MSC07). If these criteria are greatly relaxed, many more regions are identifiable across subjects. Examples are provided in Figures A.7-A.10. These were generated without an initial ANOVA being conducted, and only compared activity at Presentation 3 and Presentation 1, with voxels being identified as significant if they show $|z| > 1.25$. The question, then, is how best to threshold data in the most useful way possible when comparing datasets derived from single subjects.

Unfortunately, the optimal methods for inter-individual comparison are not entirely clear. Several potential options include specifying a certain number of voxels, for instance the upper and lower 1000, and only carrying these forward as a means of region identification. Alternatively, one may attempt to consider only a certain percentage of voxels for each individual. Which specific choice is selected would depend on whether one values an equal number of observations per individual, or an equal proportion of significant voxels, across individuals. The answer may depend somewhat on the distribution of the statistical map across different subjects. Such comparisons were outside the scope of this dissertation work, but will be important to consider as the field moves forward in its study of single subjects.

**Are the subject-specific ROIs actually within the PMN, or are they within the DMN?**

A very natural concern is that the subject-specific ROIs identified using the current methodology may fall not within the PMN, but rather within adjacent (and much larger) DMN regions. Certainly the obtained patterns of deactivation are consistent with the “task negative” effects often observed within DMN regions (e.g., Shulman et al., 1997; Buckner et al., 2008), but the statistical maps presented in Figures 2.6-2.9 are somewhat equivocal in terms of the network(s) in which they appear to be located. This question will be addressed in Chapter 4,
when discussing how resting-state and task-based network maps relate to one another in describing the PMN.

**Are the IMT findings due, in part, to how stimuli were ordered?**

Another potential concern relates to the basic design of the IMT. All stimuli were studied a single time, before being observed a second time, and all were seen twice before any were seen a third time. This is analogous to traditional fMRI study designs, in which stimuli are encoded (or studied) prior to being retrieved (or restudied, etc.). However, IMT findings suggest that the orientation toward stimulus familiarity is likely a very important component of above-baseline activation in PMN regions. The current task design, which blocked presentations, may have reduced the salience of whatever familiarity was perceived, since all stimuli were examined on the context of others with similar histories. An alternative approach would be to adapt a paradigm more similar to continuous recognition, in which old and new items are intermixed. Although such experiments are not common in fMRI studies, there is at least one study that associates probable PMN regions with repetition enhancement effects in explicit continuous recognition (Jessen et al., 2001). Intermixing stimuli, and perhaps manipulating within-subjects blocks of explicit recognition memory and an implicit memory task such as the IMT used here, may provide insight into whether or not the blocked nature of the current task is responsible for some of the lack of activation across stimuli during Presentation 3.

**2.5.8 Conclusions**

In the present experiment, a fairly basic task was used to assess PMN activity under implicit memory conditions. Results suggest that the activations observed in previous experiments were very likely attributable to explicit subject orientations to retrieval. This provides an important boundary condition for the “flip” that was recently described as a core
component of the PMN (Gilmore et al., 2015) and suggests that more attention must be paid to
task conditions than has previously been argued.
2.6 References


Chapter 3: Assessing parietal memory network responses in a highly trained memory athlete

Abstract

Evidence used to characterize the Parietal Memory Network (PMN) was originally derived from tasks requiring explicit orientations to memory, which generally recruited healthy young adult participants. In Chapter 2 of this dissertation, we failed to observe certain predicted patterns of PMN activity under implicit memory conditions. In the current chapter, we report on behavioral and fMRI data collected from a highly trained “memory athlete” who performed the same implicit memory task used in Chapter 2. In this way we could determine whether or not intense training was associated with alterations in functional properties of the PMN. We observed little appreciable difference between the subject and a group of well-matched controls, both in terms of behavior and BOLD activity. These findings suggest that training, even in extremely large quantities, does not appreciably affect PMN activity. More broadly, these results also speak against general benefits that cognitive training may have, which has important implications during a time when companies are offering “brain training” games as a means of improving cognitive function.
3.1 Introduction

Activity within the Parietal Memory Network (PMN) has been hypothesized to reflect the degree to which an item is perceived as familiar (Gilmore et al., 2015). Novel items are thought to produce deactivations within the network, and familiar items activations above baseline. This “novelty/familiarity” hypothesis was formed as an attempt to concisely account for a large body of available literature, but as Chapter 2 demonstrated, gaps and errors are present in our (nascent) understanding of the PMN. Just as our understanding of the PMN was refined by the use of implicit memory task conditions, so too might new insights be gained from moving beyond the typically-studied population of healthy young adults.

There exists a wide range of populations with generally superior or inferior memory abilities. On one extreme would be patients with damage to their medial temporal lobes, who have dramatically impaired performance on (explicit) episodic memory tasks (e.g., Scoville & Milner, 1957; Tulving, 1985; Squire et al., 2004). On the other end of the spectrum, there exist individuals with highly superior memory abilities. Some, such as those with a condition known as Highly Superior Autobiographical Memory, appear to be naturally gifted with respect to retrieving information from their own lives (Parker et al., 2006; LePort et al., 2012), although they do not appear to differ from normal controls in “typical” laboratory list-learning tasks (LePort et al., 2012; Pathis et al., 2013).

For other individuals, superior memory abilities do not develop spontaneously, but are intentionally and effortfully trained. One category of such individuals is comprised of “memory athletes.” These are individuals who have trained extensively in the use of the Method of Loci (or more generally, the use of vivid mental imagery) as a means of rapidly encoding large amounts of information extremely quickly (Maguire et al., 2002; see also Luria, 1975 for
discussion of the Method of Loci). Memory athletes train for and participate in highly competitive tournaments with the aim proving themselves to be the best “memorizer” in their region or the world at large. One such individual, here termed “ND,” is a four-time winner of the US Memory Championships, and agreed to participate in a subset of the experimental protocol described in Chapter 2 (and to be identified in this research). In this chapter, we describe the results of data collected from this individual.

ND has trained extensively in order to win his competitions, in which he has accomplished feats such as memorizing 339 consecutive random digits in a five-minute period, and memorizing a shuffled deck of playing cards in 40.65 seconds (http://www.world-memory-statistics.com/competitor.php?id=691). He reports training one-to-two hours every day (ND, personal communication, March 21, 2016), and in the months leading up to a tournament, increases training to four-to-five hours per day (Hanna, 2012). Given his aggressive training schedule, ND appears to be a “best case” scenario if one is interesting in determining how extensive practice and training might alter something fundamental about one’s memory abilities. Such change should then be detectable using BOLD fMRI. Training related differences in memory athletes have been observed before, albeit without respect to the PMN. Rather, Maguire et al. (2002) found that the use of visual imagery caused observable differences to appear between memory athletes and controls in extrastriate visual cortex. In the current experiment, the IMT represents an opportunity to determine if changes are observable under conditions that differ from those in which ND trained. We could thus ask the question, “Does ND’s training lead to transfer in other memory domains such as one not requiring intentional retrieval?”

Given the recent rise of training regimens intended to protect mental health or boost cognitive function, such as those offered by Lumosity (http://www.lumosity.com/) or Posit
Science (http://www.brainhq.com/), understanding an extreme case of training may provide a sense of upper boundaries of what may be achieved. Typical users presumably expend far less effort in cognitive training than ND, so if it is a reasonable assumption that training can improve cognitive function, ND is a likely case in which real improvement might be observed. Results from the cognitive training literature are somewhat pessimistic, however—although some evidence suggests training can provide broad cognitive benefits (Hardy et al., 2015), the more general trend indicates that training does not transfer across task domains (Harrison et al., 2013; Redick et al., 2013; Zickefoose et al., 2013). That ND might show transfer effects was therefore a somewhat unlikely, but not ultimately forgone, possibility.

Properly assessing an individual such as ND requires a well-constructed control group. The ten Midnight Scan Club (MSC) subjects described in Chapter 2 provide a well-matched comparison group. Demographic features were similar, both ND and the MSC subjects were highly motivated, and the IMT data could be directly compared between ND and MSC individuals. This alleviated potential issues that might complicate comparisons, such as differences in data quantity or effective smoothing, that might complicate a typical individual-to-group comparison.

Two possible outcomes were hypothesized with respect to differences in PMN activity. In one case, ND’s training may have impacted how he learns and processes stimuli at a fundamental level. If this were the case, one could expect to see differences, behaviorally and/or neurally, when comparing him to a group of well-matched controls. On the other hand, if ND’s training has granted him expertise in a very limited domain that does not allow for broad transfer, then one may not expect him to differ significantly from controls. As will be demonstrated throughout the rest of this chapter, results support the latter hypothesis; ND did not
appreciably differ from a group of 10 healthy controls in almost any manner.

### 3.2 Materials and Methods

#### 3.2.1 Subjects

The subject of interest (ND) was a 31-year-old male memory athlete. He is an expert in using mental imagery (particularly the method of loci) to rapidly encode information into his long-term memory. He has won the USA Memory Championship (www.usamemorychampionship.com) four times and has placed highly in international memory competitions. He is right-handed, neurologically healthy, has completed 18 years of education, and possesses normal vision. Informed consent was obtained in accordance with standard Washington University human research practices, and he was monetarily compensated for his participation.

Data from ND were compared to task data from the 10 subjects in the MSC sample, details for whom are present in Chapter 2 (Table 2.1).

#### 3.2.2 Materials

Materials used were identical to those described in Chapter 2.

#### 3.2.3 Implicit memory task

The same implicit memory task (IMT) used for the MSC subjects (described in Chapter 2) was also used for ND, with the following modification: Task data were collected over 8 sessions instead of 10 sessions. To adjust for this change, ND was presented with four task runs instead of three for the first 6 scan sessions. The final task was a repetition of the first task type (i.e., if ND was initially tasked with judging faces for a given session, then his fourth IMT run
would also use faces, albeit with novel stimuli). In addition, two scanning sessions were
collected in a single day, once in the early afternoon and again in the evening. This means that all
of his data were collected over four days total, and therefore both the time of day and the rate of
scanning overall differed between ND and the MSC group. Other task parameters were
consistent with those described in Chapter 2, including the specific order in which stimuli
appeared in each run.

3.2.4 Analysis of behavioral data

Responses to stimuli were scored for accuracy and response time (RT). These were
analyzed with ANOVAs and t-tests using SPSS software version 23 (http://www-
01.ibm.com/software/analytics/spss/). A 95% confidence interval was computed for accuracy
and reaction time around the MSC group mean, and ND was said to be different if his mean fell
outside of this range.

3.2.5 MRI data acquisition

Data were acquired as described in Chapter 2.

3.2.6 Data preprocessing

Data were processed as described in Chapter 2.

3.2.7 GLM-based fMRI data analysis

GLMs were created as described in Chapter 2.

3.2.8 ANOVA and t-test parameters

Statistical tests were conducted as described in Chapter 2.

3.2.9 ROI definition

ROIs were defined as described in Chapter 2.
3.2.10 PMN ROI comparison

Several different steps were taken when comparing ND’s data to that of the MSC control group. First, the magnitude of the BOLD response was compared between ND and the MSC group in the left pIPL/dAG ROI. This ROI was selected because it was identified in ND as well as being the most commonly observed region showing repetition-related effects in MSC subjects. Based on observations made in Chapter 2, the magnitudes compared combined activity from the Scene and Word judgments. A 95% confidence interval was computed for the MSC group for the Presentation 1, Presentation 2, and Presentation 3 responses (averaging activity at Time Points 3-5 as a means of estimating the response magnitude). ND’s responses were considered significant if his point-estimated magnitude fell outside of the 95% confidence interval around the MSC group mean.

3.2.11 Comparison of number of significant voxels

In addition to examining potential differences in response magnitudes, we examined whether or not the total number of significant voxels identified in ND and the MSC group might differ. We examine this in three different ways. First, we counted all voxels that emerged as significant following the Presentation x Time Point ANOVA and subsequent t-test, as outlined in Chapter 2 (see Section 2.2.10; Figure 2.2). Then we calculated the mean and 95% confidence interval of this value for the MSC group and determined if ND fell within or outside of this range. We also conducted two similar analyses, using a more lenient means of identifying significant voxels. This second approach required only a t-test comparing Time Points 3-5 for Presentation 3 and Presentation 1 to differ with a $|z| > 1.25$. This was the same threshold used to generate Figures A.7 to A.10. We then compared the number of voxels identified as showing Presentation 3 > Presentation 1 effects (i.e., repetition enhancement effects), or voxels showing
either Presentation 3 > Presentation 1, or Presentation 1 > Presentation 3 effects (i.e., any difference between presentations). A mean and 95% confidence interval was computed for the MSC group, and ND’s values were compared to this range.

3.2.12 Correlating raw Presentation x Time Point ANOVA maps

A final approach to examining ND to the MSC control group was to compare the overall statistical image generated by the initial Presentation x Time Point ANOVA across individuals. The unthresholded images for each person were converted into a single vector of values representing all values for all voxels in each subject’s volume, and these vectors were then correlated across subjects. After calculating all pairwise correlations, the resulting values were submitted to a hierarchical clustering analysis using the linkage function in Matlab (The MathWorks, Natick, MA). This progressively linked all subjects in increasing order of dissimilarity. The correlations were then converted using Fisher’s $r$ to $z'$ transformation (Fisher, 1915), and average values were computed across all MSC pairings for each MSC subject. A separate mean was computed for all pairwise values between ND and each MSC subject. A group mean and 95% confidence interval was computed for the MSC subjects and was compared to ND’s $z'$ value to determine if he significantly differed from the group.

3.3 Behavioral Results

3.3.1 ND was less accurate than the MSC group in classifying experimental stimuli

Although he was extremely accurate in his responses, ND was slightly less accurate than the MSC group at classifying (Figure 3.1). Overall, he classified stimuli correctly on 95.4% of trials. In terms of specific stimuli, he classified faces correctly on 97.6% of trials, scenes on 96%
of trials, and words 93.1% of trials. These were, with the exception of Scene judgments, all outside of the 95% confidence interval range computed from the MSC group. Qualitatively, ND’s accuracy scores were also lower than the lowest-obtained MSC value for every stimulus.

**3.3.2 ND’s response times did not differ from the MSC group**

ND’s RTs showed a typical pattern of behavioral priming. Across all presentations of all different stimuli, ND fell within a 95% confidence interval calculated from the MSC group (Figure 3.2). Unlike accuracy, where ND was always below the 10 MSC participants, his RT values were always extremely close to the MSC mean as compared to most MSC members.
Figure 3.2. Behavioral response times in the implicit memory task for the MSC control group and for ND. ND does not differ from the group in his reaction times for any specific stimulus or for across stimuli. Error bars represent 95% confidence intervals. P1 refers to Presentation 1, P2 to Presentation 2, and P3 to Presentation 3.

3.4 fMRI Results

3.4.1 Combining data from the Scene and Word conditions resulted in a single PMN region being identified in ND

Activity related to stimulus repetition was assessed in ND as it was for the MSC group. Based on results from Chapter 2, the responses to Scene and Word judgments were combined and constituted the main analysis of interest. Voxelwise results and ROI time courses for ND are shown in Figure 3.3. The only identified region exhibiting repetition enhancement fell within left pIPL/dAG. This pattern was also present when looking at Face, Scene, or Word stimuli separately, and statistical maps for individual conditions are included in Figure B.1.
3.4.2 Activity in left pIPL/dAG did not differ between ND and controls

Activity within ND’s left pIPL/dAG ROI was then compared to the values derived from the MSC control group. Each of the 3 Presentations was examined separately. As shown in Figure 3.4, ND did not fall outside of the 95% confidence interval set around the MSC group’s mean. Furthermore, as was the case with ND’s response times, the magnitude of ND’s response for each presentation was much closer to the MSC group’s mean than were many members of the MSC group.

3.4.3 ND and the MSC control group did not differ in the number of significant voxels identified

ND did not differ significantly from the MSC group in terms of his response in left
Figure 3.4. BOLD response magnitude in MSC control subjects and ND. Across all 3 presentations, ND did not differ from responses observed in the MSC group. Error bars reflect 95% confidence intervals.

pIPL/dAG, but it may have been the case that ND’s overall activity pattern differed from that of the MSC group. To this end, the overall number of voxels identified by the ANOVA + t-test procedure was compared between ND and the MSC group. As shown in Figure 3.5A, ND had a relatively small number compared to many in the MSC group, but this value did not fall outside of the 95% confidence interval.

As discussed in Chapter 2, it’s possible that the threshold set for identifying significant voxels in the IMT was too stringent when considering the effects across all participants. Therefore, a much more lenient test was conducted in which voxels were considered to show repetition-related effects if a t-test of Presentation 3 and Presentation 1 magnitudes differed with a z-score exceeding 1.25. The number of significant voxels showing either repetition enhancement effects only (Presentation 3 > Presentation 1) or any form of repetition effect (Presentation 3 > Presentation 1 or Presentation 1 > Presentation 3) was again compared between
Figure 3.5. Number of significant voxels identified across stringent and lenient analyses, for both MSC controls and ND. A) ND did not differ from the control group when a more stringent ANOVA + $t$-test approach was used to identify voxels sensitive to stimulus repetition. B) This was also shown to be the case when more lenient $t$-test only approaches were used at a very low threshold ($|z| > 1.25$). Error bars represent 95% confidence intervals.

ND and the MSC controls. In both of these cases, ND did not fall outside of the 95% confidence interval computed around the MSC group mean. Statistical maps for a more lenient voxel selection, comparable to those shown in Figures A.7 to A.10, are presented in Figure B.2.

3.4.4 ND’s whole-brain activity during the IMT did not differ from the MSC group

A possible concern with the previous analyses is that thresholding of data was required, even in the case of the lenient voxel count. This introduces a point of nonlinearity in the analysis and makes any single result somewhat arbitrary. Therefore, a whole-brain pattern of significance values was compared between ND and the MSC group when considering the results of the initial Presentation x Time Point ANOVA, without any thresholding employed. Results of all pairwise
correlations between ND and all 10 MSC participants are shown in Figure 3.6A, and a hierarchical clustering of this matrix is shown in Figure 3.6B (for subject-specific maps, see Figure 3.6C). ND appears to be slightly less similar to the MSC participants than many are to one another, but his average pairwise correlation is not the smallest observed overall.

Figure 3.6. Unthresholded voxelwise ANOVA map correlations across the MSC controls and ND. A) Correlation matrix containing all pairwise correlation values across ND and all 10 MSC control subjects. For display purposes on-diagonal cells have been set to zero. B) Hierarchical clustering solution of the values displayed in A. C) Individual subject statistical maps resulting from the Presentation (1, 2, or 3) x Time Point (8) ANOVA.

To more directly determine whether or not ND was an outlier, the correlation values were converted from $r$ to $z'$ values, averaged across MSC subjects, and compared to ND’s converted
$r$-to-$z$ value. The 95% confidence interval around the MSC mean included ND’s $z' = .24$ (MSC range: $z' = .22-.36$). As such we can conclude that he is not an outlier in terms of his overall degree of similarity.

### 3.5 Discussion

In the present experiment, we compared a memory athlete to ten healthy controls under implicit memory task conditions. Overall, his stimulus judgments were less accurate but he did not differ in his response latencies. Analysis of fMRI data found no significant differences between ND and the MSC controls. These results largely agree with and extend those observed previously in the literature (Maguire et al., 2002), suggesting that expertise in memory athletes is fairly limited in its scope (see also Ramon et al., 2016). Implications of these results are now considered.

#### 3.5.1 ND’s similarity to the MSC group

When attempting to assess the abilities of a single individual, one must be mindful of the group to which the individual is being compared. ND was unique in that none of the MSC participants reported any attempts at training to improve their memory abilities. Across other dimensions, however, ND and the control group were well matched. The average MSC individual had completed 20.6 (± 3.1) years of education (Table 2.1), to ND’s 18, with four of the MSC subjects having completed 17-19 years. ND and the control subjects were therefore similar in their level of education. The MSC group was also well matched to ND in terms of age, with an average of 29.1 (± 3.3) years to his 31 years at the time of testing. Further, both the MSC group and ND were highly motivated, as evident by their willingness to participate in a very
demanding experimental protocol that occurred over multiple days. One outstanding question is how ND’s IQ may compare to the MSC group. As of writing this discussion, ND has agreed to take the same intelligence test that the MSC participants have completed (i.e., the Kaufman Brief Intelligence Test; Parker, 1993), but these data have not yet been collected.6

Given the aforementioned similarities, it seems that the MSC group is a reasonable comparison to ND. This observation does not suggest that the null results reported in this chapter should be over-interpreted. Very likely, given a task in which explicit learning and memory was required, differences would be observed between ND and the group, as has been observed previously between memory athletes and controls (Maguire et al., 2002). However, one interesting question raised by the current dataset concerns where the boundaries might exist for ND with respect to his special abilities. One might imagine, for instance, that his heavy training in recall and recognition type tasks would reveal neural differences in standard list-learning paradigms. However, ND may or may not differ under less constrained recall conditions, such as those involving autobiographical memory recall. This will need to be explored in future research, and the point at which ND’s training ceases to show behavioral differences from typical subjects may reveal important properties of the organization of human memory in general and retrieval processes in particular.

3.5.2 Massive training does not appear to transfer to implicit memory tasks

The idea of transfer—that skill in one domain might affect performance in another—has become something of a holy grail in popular psychology. “Brain training” programs, such as

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6 ND has been tested with a similar IQ test, using a shortened form of the Ravens Progressive Matrices (Kane et al., 2004). He scored above average on this metric (correctly responding to 14/18 items; Roediger et al., unpublished) and it is not expected that he will differ from the control group on the KBIT.
those offered by Lumosity or Posit Science, advertise gains not only within the tasks that one is required to perform, but also to cognitive performance in general (extending across attention, memory, etc.). Some have even claimed that their training programs can restore gray matter volume in older adults to teenage/young adult levels (Merzenich, 2012). The individual under investigation here trained himself for many hours per day (presumably under far stricter conditions than would apply to a typical brain training program user), and yet no evidence of transfer was found between two tasks that were in the same broad conceptual domain of learning and memory. Indeed, to the extent that he demonstrated any differences at all, these were trivial reductions in his accuracy in the classification task compared to the MSC group. Overall, the results of the current study agree with many in the literature that have failed to find evidence of general improvement based on focused cognitive training (Harrison et al., 2013; Redick et al., 2013; Zickefoose et al., 2013). It appears as though the expertise gained by memory athletes such as ND is actually very limited in its scope.

3.5.3 Conclusions

In the present experiment, the findings in Chapter 2 were effectively replicated in a highly-trained memory athlete. These data suggest that even massive, learning-focused training does not impact the PMN under implicit memory conditions. These data suggest that memory athletes have not fundamentally changed the structure or function of memory systems in a broad sense, but rather have gained a limited set of abilities in a relatively small cognitive space. These findings also suggest that programs intended to “train your brain” are likely not training it in a general sense (i.e., in terms of reorganizing brain networks or altering the BOLD responses of specific functional regions), since even extremely dedicated individuals will fail to show transfer
in nominally related cognitive tasks.
3.6 References


Chapter 4: Using resting-state functional connectivity to improve localization of implicit memory task results

Abstract

The time courses observed in putative parietal memory network (PMN) regions from Chapter 2 of this dissertation were reminiscent of those observed previously in default mode network (DMN) regions under explicit recognition conditions (e.g., Nelson et al., 2010): deactivating for initial presentations and—despite showing repetition enhancement—exhibiting no significant activation for subsequent presentations. In this chapter, resting-state functional connectivity (RSFC) was employed as an independent means of clarifying the network membership of the repetition enhancement effects observed in the implicit memory task (IMT). First, the whole-brain network structure for each of 11 subjects was estimated from RSFC data using the Infomap community detection algorithm. Regions of interest were defined from RSFC-defined PMN, DMN, and as a control, the frontoparietal control network. Time courses of activity associated with stimulus presentations in the IMT were correlated between the RSFC-defined region of each network, and those defined from local maxima in IMT analysis as reported in Chapter 2. This allowed us to determine if regions from a single network showed time courses that were particularly similar to those from IMT-defined regions (whose network membership was not known). In addition, the spatial overlap between the RSFC-defined networks and the task activation maps from the IMT was examined. Results suggest that regions within both the PMN and DMN show patterns of activity highly similar to those identified purely within the IMT data, although DMN regions were slightly better correlated in overall time course
patterns than were PMN regions. Furthermore, voxels within the DMN constituted proportionally more of the statistical maps for each subject than did PMN voxels. The findings in this chapter do not invalidate the conclusions reached in Chapter 2, but they do highlight the importance of utilizing multiple MRI methods when attempting to discuss activity patterns in the context of specific networks.
4.1 Introduction

The parietal memory network (PMN) is a sparse network that sits adjacent to the much larger default mode network (DMN) and frontoparietal control network (FPCN) regions (Gilmore et al., 2015; see also Power et al., 2011; Power et al., 2014b). Its proximity to large regions in other networks presents a challenge in studying the PMN, and requires one to be particularly careful in ensuring that a given activation is associated with the correct region of the correct network (Nelson et al., 2013). In Chapter 2, we observed that an implicit memory task (IMT) produced expected deactivations to novel stimuli, as well as repetition enhancement, in putative PMN regions. However, above-baseline activation for familiar stimuli (i.e., those that had been encountered multiple times in the context of the experiment) was not observed in these regions. As discussed in Chapter 2, this may reflect a shortcoming in our current understanding of what activity in PMN regions represents. Alternatively, this may indicate that the ROIs associated with the PMN were, in fact, located in a different network.

This concern is exacerbated when visually comparing the time courses obtained from ROIs identified from the IMT to those described in a meta-analysis of 8 retrieval success contrasts reported by Nelson et al. (2010). The ROI identification procedure used in Chapter 2 was based on a priori PMN coordinates, but at least in the context of the putative pIPL/dAG ROI, the time courses appear to be more similar to the DMN’s angular gyrus (AG) than the PMN’s pIPL (Figure 4.1). Of course, the implicit nature of the IMT means that a direct comparison to explicit recognition decisions is difficult (as was discussed in Chapter 2), meaning that the presented similarity should not be over-interpreted. Instead, a useful approach for determining whether or not the ROIs identified in Chapter 2 are located within the PMN or neighboring DMN lies in the use of resting-state functional connectivity (RSFC) MRI.
RSFC MRI analysis can leverage correlations in spontaneous BOLD activity to estimate the network structure of the brain (see e.g., Wig et al., 2011). The networks identified in rest data are thought to recapitulate both basic processing systems (e.g., the visual system) as well as higher-order control systems (e.g., the FPCN). Various methods have been used to identify functional networks from RSFC data, but one approach that has proven productive is the use of unsupervised community detection algorithms, most notably Infomap (Rosvall & Bergstrom, 2008).

In the present experiment, Infomap was used to estimate the whole-brain network structure of the MSC subjects as well as ND. Focusing in particular on the PMN, DMN, and FPCN, we investigated the degree to which the task-evoked statistical maps generated for
individual subjects in the IMT corresponded to any of these networks. If the pattern of BOLD
activation from IMT was more strongly correlated with the PMN than the DMN or FPCN, then it
would suggest the discussion in Chapter 2 was correct in its description of PMN functionality.
On the other hand, if the DMN or FPCN was found to correspond better to IMT results, it would
imply that the IMT should not be used as a major means of improving our theoretical
understanding of the PMN. The results described in this chapter support something akin to the
latter conclusion, though more generally suggest that the PMN and DMN behave very similarly
in the IMT.

4.2 Methods

4.2.1 Subjects

Data from 11 subjects (MSC1-10 and ND) were used in this analysis. These subjects
were described in Chapters 2 and 3.

4.2.2 Materials

Task-based definitions of the PMN were derived from the IMT, described in Chapter 2
(specifically, the combined Scene and Word analysis). See Chapter 2 for a complete description
of the task design. For resting-state scans, a white fixation cross was presented on a black
background (48-point Arial type).

4.2.3 Resting-state protocol

During resting-state scans, participants were asked to lie as still as possible while fixating
on a centrally-presented crosshair. It was emphasized that participants should try as best they
could to remain awake during the resting-state scan. The exact instructions read to each
participant before each resting-state scan are included in Appendix C. All MSC participants had 10 resting scans of 30 minutes’ duration, for a total of 300 minutes of acquired data. ND also had 300 minutes of acquired data, but in the place of 2 of his 30-minute scans, he had several shorter scans collected. In one case, it was replaced with 2 scans, 8 and 22 minutes in length, while the other was replaced with 3 scans of 10 minutes’ duration each. In this latter case, the rest scans were also placed at intervals throughout his functional session, whereas in all other cases all resting-state data were collected prior to any other tasks being performed.

4.2.4 MRI data acquisition

Data were acquired as described in Chapter 2.

4.2.5 Task fMRI data preprocessing

fMRI task data were initially processed as described in Chapter 2. That is, data were corrected for within-scan movement using a rigid-body translation and rotation, aligned across scans, intensity-normalized to a common mode 1000, corrected for local field distortions, and transformed into a common atlas space.

4.2.6 Resting-state functional connectivity fMRI data preprocessing

Resting-state data initially underwent preprocessing steps similar to those described for the task data, but several additional steps were taken to reduce artifacts within the BOLD time series for each subject. Steps included nuisance regression, frame censoring, interpolation, and spectral filtering (Power et al., 2014a). Nuisance regressors included the global gray matter, white matter, and ventricular signals and their first derivatives, and 24 parameters derived from estimated subject motion (translational and rotation x,y,z and their polynomial expansions; Friston et al., 1996). Masks for global gray matter, white matter, and ventricles were defined using FreeSurfer. Frames were censored if their framewise displacement (FD) exceeded 0.2 mm. If fewer than 5
contiguous frames were present in the time series, these sections were also censored. Interpolation over censored epochs, which was necessary for subsequent bandpass filtering, was computed by a least-squares spectral estimation. Data were temporally filtered at $0.009 > f > 0.08$ Hz. Censored frames were not included in resting-state correlation calculations.

4.2.7 Sampling of fMRI data to the cortical surface

After preprocessing, resting-state data were sampled to the cortical surface, following the methods of Laumann et al. (submitted, see also Glasser et al., 2013; Laumann et al., 2015). Surfaces were generated from the subject’s mean MP-RAGE image using the FreeSurfer’s (version 5.3) `recon-all` processing pipeline (https://surfer.nmr.mgh.harvard.edu/). Steps included brain extraction, segmentation, generation of white matter and pial surfaces, inflation of the surfaces to a sphere, and registration of the spherical surface to the fsaverage surface (Dale et al., 1999; Fischl et al., 1999; Segonne et al., 2004). The two hemispheres were brought into common registration with one another via the “fs_LR” hybrid left-right fsaverage surface (Van Essen et al., 2012). Surfaces were initially resampled to a resolution of 164,000 vertices (164k fs_LR) using CARET software (Van Essen et al., 2001) and were then downsampled to a resolution of 32,492 vertices (fs_LR 32k). Transformation values from native surfaces to the fs_LR 32k surface were composed into a single deformation map. All steps involved in this surface sampling were implemented using a custom version of the Van Essen laboratory’s Freesurfer_to_fs_LR Pipeline (http://brainvis.wustl.edu) written by Timothy Laumann.

Following surface creation for each subject, their BOLD data were then sampled to their unique surface. The BOLD fMRI data were sampled to each subject’s native mid-thickness surface using the ribbon-constrained sampling procedure from the Connectome Workbench software package (Marcus et al., 2011). This sampled data from voxels located within the mid-
thickness surface ribbon (i.e., the space between the white and pial surfaces) and weighted each voxel by its location within the ribbon. Voxels were excluded if they had a coefficient of variation 0.5 standard deviations higher than the mean coefficient of neighboring voxels within a 5 mm Gaussian circle (Glasser et al., 2013). After being sampled to the native surface, time courses were deformed and resampled onto the 32k fs_LR surface using the subject-specific deformation map described above. After sampling to a common surface space, all data were geodesically smoothed using a Gaussian kernel ($\sigma = 2.55$ mm).

Surface data from each subject were then combined with data from subcortical structures and the cerebellum into a single CIFTI file using Connectome Workbench software. The resulting file thus contained all cortical and subcortical gray matter tissue for each participant. Volumetric data were smoothed using a 2.55 mm spherical Gaussian kernel to ensure consistency with the surface data.

### 4.2.8 Voxelwise resting-state network assignment

Resting-state network communities were defined in a data-driven manner using the Infomap algorithm (Rosvall & Bergstrom, 2008), following procedures used by Laumann et al. (2015). The BOLD time series data from each session were concatenated for each subject, and a cross-correlation matrix of edge connections was computed for all included nodes. Nodes included both surface vertices and subcortical voxels. Node connections within 10 mm of one another (geodesic distance for vertices, Euclidian distance for voxels) were removed to avoid spurious correlation values resulting from the applied spatial smoothing. System assignments were computed across 46 thresholds ranging from 0.05-5.0% edge densities (in steps of .01%). Network communities consisting of 400 or fewer nodes, and all subcortical or cerebellar voxels, were not further considered in this analysis. Network communities for each subject were labeled
according to a “consensus” assignment, previously described by Gordon et al. (2014) and more recently by Laumann et al. (2015). Network labels (e.g., visual, default) were assigned by minimizing all distance metrics across all communities.

For 7 of the 11 participants, the lowest possible edge density value (.05%) was used. For the remaining 4 subjects, the lowest edge densities possible that were devoid of obvious network labeling errors were selected manually by AWG (see Figures C.1-C.2 for two examples). For MSC04 and MSC08, the 4th lowest value was selected (.08); for MSC07, the 13th value was selected (.17); and for ND the 15th threshold was selected (.19). The spatial location and extent of the PMN was not strongly affected by this selection process, and the correlation of the .05 edge density map and the selected map for each individual’s PMN averaged \( r = .90 \) (range: .88-.93). This was also true for the DMN in 3 of these 4 subjects (MSC07, MSC08, ND; average \( r = .90 \), range: .82-.96), but appreciably changed the DMN estimate for MSC04 (\( r = -.075 \)). The FPCN measurements differed slightly more; ND had especially low agreement (\( r = .05 \)), and the remaining 3 subjects had an average \( r = .71 \) (range: .53-.93).

**4.2.9 Assessment of network size for each individual**

To decide whether to include ND alongside the MSC group, it was important to determine if gross differences existed between him and the MSC subjects that might impact later comparisons. The chosen approach measured the size of functional networks (specifically, the number of vertices associated with each network) in ND and the MSC controls. The three networks selected for this comparison were the PMN, DMN, and FPCN. The size of each

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7 An alternative strategy might have involved keeping the lowest edge density outputs and manually identifying each network label. Such an approach would leave more room for experimenter error than methods selected for use in this chapter.
network was estimated by the number of surface vertices associated with each network on the fs_LR 32k surface. For MSC subjects, a mean and 95% confidence interval surrounding the mean were calculated for the 3 networks being considered. ND’s vertex count was then compared to each of these ranges to determine if he significantly differed from the group. He did not differ in the size of any of the 3 networks, and so subsequent analyses were conducted using all 11 participants as a single group.

4.2.10 Converting surface network maps back into volume space

Comparison of task and RSFC data first required that all data be brought into a common space. The networks defined using RSFC methods were thus transformed into 711-2B volume space. This process was accomplished first by creating a vertexwise mask for each single network of interest (PMN, DMN, FPCN) on the surface, which resulted in 3 binary masks for each individual. This was performed in MATLAB with the FieldTrip Toolbox (Oostenveld et al., 2010). Mask vertices were output with an arbitrary value of 1 for each of the 3 masks. CIFTI files containing each mask were then converted to metric files for each hemisphere and then sampled into 711-2B volume space using Connectome Workbench software. The two volumes (each representing a single hemisphere) were then combined into a single volume file using FIDL (http://www.nil.wustl.edu/~fidl/). This resulted in a PMN, DMN, and FPN network mask for each subject. The transformation from surface to volume space slightly smoothed the mask, causing some blurring around the edges of clusters. To correct for this, the mask was redefined such that any voxels whose value had fallen below .95 were excluded. All voxels above this value were retained and reset to an arbitrary value of 1.

4.2.11 Calculating average repetition effects in the PMN, DMN, and FPCN

To better understand how the PMN, DMN, and FPCN responded in the IMT, we used the
masks derived from Infomap networks to designate each network as an ROI, and combined activity across all voxels within each network during Presentation 1 and Presentation 3 of Scene and Word stimuli (see Chapter 2). This analysis did not provide information about specific regions within a given network, but was meant to summarize the response of the network as a whole.

4.2.12 Comparing ROIs derived from resting-state analysis and those derived from the IMT

In addition to examining network-wide activity, activity within specific ROIs was compared between each network and the IMT-defined ROIs. This required a multi-step process to identify local centers of mass in the Infomap-defined network maps. First, the mask image representing each network was smoothed using a 3 mm blurring kernel, which allowed for identification of centers of mass within the mask image. The smoothed image was then analyzed using the same peak-detection algorithm used to identify peaks in the IMT statistical maps (peak_4dfp). As described in Chapter 2, peaks less than 10 mm apart were consolidated via coordinate averaging. Spherical ROIs (4 mm radius) were created around each identified peak within each subject, consistent with ROI creation in the IMT data as described in Chapter 2.

To compare regions as directly as possible, ROIs within the PMN, DMN, and FPCN were selected based on the same criteria used to identify putative PMN regions in Chapter 2. Briefly, this used a priori PMN coordinates for PMN PCU, MCC, and pIPL/dAG regions that were created by averaging meta-analytic retrieval success coordinates reported by McDermott et al. (2009) and Nelson et al. (2010). Right hemisphere PCU and pIPL/dAG regions were created by inverting the x-coordinate of left hemisphere regions. For each network in each subject, the ROI that fell closest to each a priori coordinate was selected. If no ROIs were located within 15
mm Euclidian distance of an *a priori* coordinate for a given network, then no ROI was associated with that region for a given individual. Time courses were extracted from each ROI by averaging activity across all included voxels, as described in Chapter 2.

Time courses were averaged across participants on a region-by-region basis, as was described previously. In addition, the time courses across all ROIs for all subjects were also averaged to produce network-level time courses. Each of the network-level time courses was correlated with the average of the IMT-defined ROI time courses. This provided a summary of the general agreement between the regions identified by the IMT and those within each individual network. After this demonstrated a clear dissociation between PMN/DMN time courses and FPCN time courses, a finer-grained approach was used to more closely investigate the DMN and the PMN ROIs.

In this alternative approach, the time series for each ROI was not initially averaged within each person, but rather was concatenated. This resulted in a time series that was fivefold longer but retained all information for each ROI. These longer time series were then averaged across individuals for PMN ROIs, DMN ROIs, and IMT-defined ROIs. After calculating the pairwise zero-order correlations, the difference between the PMN-IMT and the DMN-IMT correlations was tested using the Williams modification of the Hotelling *t*-test (Kenny, 1987). This test is designed for comparing correlated correlations between two variables (X₁ and X₂) and the same third variable (X₃), testing the null hypothesis that the correlation between X₁ and X₃ equals the correlation between X₂ and X₃. It takes the form:

\[ t_{n-3} = \frac{(r_{13} - r_{23})\sqrt{(n - 1)(1 + r_{12})}}{\sqrt{2K \left(\frac{n - 1}{n - 3}\right) + \frac{(r_{23} + r_{13})^2}{4}(1 - r_{12})^3}} \]

where *n* corresponds to degrees of freedom (in this case 120; 5 ROIs x 3 Presentations x 8 Time
Points), and where
\[ K = 1 - r_{12}^2 - r_{13}^2 - r_{23}^2 + 2r_{12}r_{13}r_{23} \]

4.2.13 Calculating agreement between IMT task data and Infomap network definitions

In addition to examining the similarity of time courses identified within ROIs taken from different resting state networks, we also examined the degree of overlap between the maps defined from IMT task data and the network maps defined using Infomap. This was performed in two ways. First, the proportion of significant IMT voxels that fell within the Infomap-defined PMN, DMN, and FPCN was assessed. This reflected the degree to which the IMT map consisted of each network. Secondly, the proportion of the PMN, DMN, and FPCN that was captured by significant IMT repetition enhancement voxels for both Stringent and Lenient thresholds was assessed. In other words, this second test measured the degree to which the task data encompassed the voxels within each network. Two task thresholds were used in these analyses, which correspond to the Strict and Lenient criteria applied in Chapter 2. Voxels surviving the Strict threshold exhibited a significant interaction of Presentation (3) and Time Point (8), and were subsequently found to show different activity between Presentation 3 and Presentation 1 at a \( |z| > 1.96 \). Voxels included in the Lenient threshold showed a difference in activity between Presentation 1 and Presentation 3 at \( |z| > 1.25 \). Refer to Chapter 2 for more specific methods on how these tests were conducted.
4.3 Results

4.3.1 The Infomap algorithm detected communities consistent with the PMN, DMN, and FPCN in all subjects.

Previous work has shown that the Infomap algorithm (Fortunato, 2010) can estimate the functional network architecture of large groups of subjects (e.g., Power et al., 2011), and more recently has been used to estimate the network organization of two highly-sampled individual subjects (Laumann et al., 2015). The present goal of assessing agreement between task-based and RSFC descriptions of networks required us to first characterize the 11 subjects in which IMT data had been collected. Figure 4.2 presents a subset of the networks for each individual. These consist of the PMN, and the adjacent DMN and FPCN, which were selected as comparison networks to characterize along the PMN. These three networks were used to conduct the comparisons that followed.

With respect to the PMN, all subjects possessed patches that fell in PCU and MCC regions. The pIPL/dAG component of the PMN was more variable, and was only observed in a subset of participants. Some participants also appeared to have aspects of the PMN near their anterior cingulate cortex and/or near their frontal pole on one or both hemispheres. DMN regions—particularly those close to PMN regions—were present in all subjects. Components of the FPCN were consistently present near pIPL/dAG and, with the exception of ND, were present near MCC as well. There were also numerous FPCN patches near PCU, but these were qualitatively more variable across subjects.

4.3.2 Networks sizes were somewhat variable across individual, but few statistical outliers were present

Recent reports suggest considerable variability in the systems-level organization of
Figure 4.2. Estimated networks within ND and MSC subjects. The parietal memory network (PMN), default mode network (DMN) and frontoparietal control network (FPCN) were defined at the single-subject level using the Infomap algorithm (Fortunato, 2010), and are presented in red, blue, and yellow, respectively.

individual subjects, at least when compared to results obtained from large-group averages (Gordon et al., 2015; Gordon et al., submitted; Laumann et al., 2015). Visual inspection of
Figure 4.2 is consistent with this observation, both for the size and placement of various network regions across the cortical surface. One means of assessing network variability within the current sample was to calculate each network’s size; to this end, the average number of surface vertices associated with the PMN, DMN, and FPCN was calculated for the MSC subjects. Furthermore, this was used an opportunity to determine if ND’s training may have altered the size of these networks compared to the MSC controls. As demonstrated in Figure 4.3, ND did not differ from the MSC group, who were themselves somewhat variable in the vertex count of each network. For both the PMN and DMN, a single MSC participant fell outside of the 95% confidence interval around the group mean (MSC08 and MSC03, respectively). Given that ND did not fall outside of the group in this analysis, subsequent analyses treated all 11 subjects as a single group.

Figure 4.3. Number of surface vertices identified within different functional networks, as defined by Infomap. A) Vertices identified in the parietal memory network. B) Vertices identified in the default mode and frontoparietal control networks. Error bars represent 95% confidence intervals around the MSC group mean. Outlier subjects are labeled.
4.3.3 Infomap-defined networks differ in the degree of activity during Presentation 1 and Presentation 3

If the networks defined by Infomap within each subject are accurately corresponding to different functional networks, then they should exhibit different patterns of activity during certain task states. Potential network differences for this specific task were tested by examining activity during Presentation 1 and Presentation 3 of the IMT (combining activity from the Scene and Word conditions across Time Points 3-5) in the PMN, DMN, and FPCN. Not only were differences in activity present across the three networks, but different networks responded differently across stimulus presentations. A 3 (Network: PMN, DMN, FPCN) x 2 (Presentation: 1, 3) repeated measures ANOVA revealed a main effect of Network ($F_{(2,20)} = 25.83, \eta_p^2 = .721, p < .001$), but no main effect of Presentation ($F_{(2,20)} = 1.80, \eta_p^2 = .153, p = .209$). This was qualified by a significant interaction of the Network and Presentation terms ($F_{(2,20)} = 2.36, \eta_p^2 = .349, p = .014$). As illustrated in Figure 4.4, both the PMN and DMN were numerically below zero and showed repetition enhancement effects across multiple presentations, whereas the FPCN was numerically above zero across item presentations and showed repetition priming effects. Responses for each network for each subject are presented in Figure C.3.

To determine if the PMN and DMN showed different degrees of repetition enhancement, a 2 (Network: PMN, DMN) x 2 (Presentation: 1, 3) repeated measures ANOVA was conducted. This analysis revealed that the DMN was more deactivated than the PMN overall, but the degree of repetition enhancement did not differ between the two networks. This was reflected statistically by a significant main effect of Network ($F_{(1,10)} = 16.08, \eta_p^2 = .617, p = .002$), and a main effect of Presentation ($F_{(1,10)} = 6.69, \eta_p^2 = .401, p = .027$), without a significant interaction ($F_{(1,10)} = 2.36, \eta_p^2 = .191, p = .155$).
The percent signal changes across each network were very low, and did not generally deviate significantly from baseline after correction for multiple comparisons. Prior to correcting for multiple comparisons, only the PMN did not significantly differ from baseline activity levels for Presentation 1 and Presentation 3. Following Bonferroni correction, only the whole-network activity within the DMN remained significantly below zero, and this was restricted to Presentation 1 only (Table 4.1).

4.3.4 Time courses from PMN and DMN ROIs correlate strongly with those from IMT ROIs

The previous comparisons were designed to assess network-wide activity, but offered only a gross description of each network’s response during the IMT. More specific information
Table 4.1. Whole network activity relative to baseline during IMT Presentations 1 and 3

<table>
<thead>
<tr>
<th>Network</th>
<th>Presentation</th>
<th>Response Magnitude</th>
<th>$t$-statistic</th>
<th>Uncorrected $p$</th>
<th>$p_{(corrected)}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>PMN</td>
<td>1</td>
<td>-.0021</td>
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<td>.061</td>
<td>.369</td>
</tr>
<tr>
<td></td>
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<td>-.0009</td>
<td>1.20</td>
<td>.258</td>
<td>&gt;1.0</td>
</tr>
<tr>
<td>DMN</td>
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<td>.006</td>
</tr>
<tr>
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<td>3</td>
<td>-.0044</td>
<td>2.83</td>
<td>.018</td>
<td>.108</td>
</tr>
<tr>
<td>FPCN</td>
<td>1</td>
<td>.0041</td>
<td>2.33</td>
<td>.042</td>
<td>.251</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>.0027</td>
<td>2.38</td>
<td>.039</td>
<td>.232</td>
</tr>
</tbody>
</table>

was obtained by extracting IMT time courses from specific ROIs in the Infomap-defined PMN, DMN, and FPCN. ROIs were identified using the same search criteria applied to task data in Chapter 2, but in this case the network membership was known for each (i.e., ROIs derived from the PMN mask were by definition considered members of the PMN, etc.). As in Chapter 2, ROIs were identified within individual subjects, and subsequent activity in corresponding ROIs was averaged across subjects.

The average response across all ROIs for each network, as well as the IMT region average from Chapter 2, is presented in Figure 4.5A. In comparison to the IMT-derived ROIs, both the DMN and PMN ROIs produced extremely similar time courses across all Presentations, while the FPCN behaved markedly different. A correlation analysis of this overall pattern revealed significant correlations between the original task-defined ROI time courses, and those of the PMN ($r = .85, p < .001$) and DMN ($r = .86, p < .001$) ROIs, but not a significant correlation between task-defined ROI time courses and FPCN ROI time courses ($r = .045, p = .83$).

Activity averaged across all network ROIs was a useful summary, but necessarily contained less information than would a comparison that retained time courses from each
Figure 4.5. BOLD response time courses across groups of ROIs. A) Time courses averaged across all ROIs defined in the implicit memory task, and from the parietal memory, default mode, and frontoparietal control networks, for Presentations 1-3 of the Scene and Word analysis described in Chapter 2. B) The average time series across all subjects after concatenating all ROIs from all presentations in the task-defined, PMN, and DMN ROIs.

A follow-up comparison was therefore conducted between the task-defined ROIs and the PMN and DMN ROIs. This demonstrated that both PMN and DMN ROIs were highly correlated with task-defined ROIs, but that the DMN was actually slightly more strongly correlated than the PMN. In this subsequent analysis, the time series from each ROI was
concatenated rather than averaged within each person, resulting in a single vector of 120 observations (3 Presentations x 5 ROIs x 8 Time Points) for each subject (Figure 4.5B). These were averaged across subjects and the resulting vectors were then correlated with one another. Correlations between the task-defined ROI time courses with each network ROI time course remained significant, as did the correlations between the two network ROIs time courses ($r_{\text{task-PMN}} = .64$, $r_{\text{task-DMN}} = .79$, $r_{\text{PMN-DMN}} = .59$, all $p < .001$). The difference between the obtained $r_{\text{task-PMN}}$ and $r_{\text{task-DMN}}$ values was directly compared, and the DMN ROI time courses were found to be significantly more similar to the task-defined ROI time courses than were PMN ROI time courses ($t_{117} = 3.06$, $p = .003$). DMN ROIs therefore corresponded better to the unknown-network ROIs defined from the task data.

### 4.3.5 IMT voxelwise maps consist of the DMN more than the PMN or FPCN

If the PMN was particularly sensitive to the number of item repetitions, then the voxels defined in the IMT should disproportionately fall within this network, as compared to the adjacent DMN or FPCN. However, this was not observed to be the case. Rather, for both the Strict and Lenient thresholdings of the IMT data, a larger proportion of IMT voxels fell within the DMN than the PMN or FPCN, (Figure 4.6A; see Figures C.4-C.5 for projections of task data over Infomap-defined networks at both Stringent and Lenient thresholds, respectively). This pattern was reflected in an ANOVA conducted using factors of Network (PMN, DMN, FPCN) and Threshold (Strict, Lenient). Main effects were observed for both Network ($F_{(2,20)} = 9.48$, $\eta^2_p = .487$, $p = .001$), and Threshold ($F_{(1,10)} = 7.23$, $\eta^2_p = .420$, $p = .023$), but these did not significantly interact ($F_{(1.34,13.39)} = 2.60$, $\eta^2_p = .206$, $p = .124$).
Figure 4.6. Spatial overlap of the voxels identified as significant in the implicit memory task, and voxels identified as being members of the parietal memory (PMN), default mode (DMN), and frontoparietal control (FPCN) networks. A) The IMT task map includes proportionally more DMN voxels than PMN or FPCN voxels, across multiple task map thresholds. B) The IMT task map covers proportionally more of the PMN than the DMN or FPCN across multiple task map thresholds. Error bars represent \( \text{SEM} \) and are based on data from all 11 subjects.

### 4.3.6 IMT voxelwise maps capture proportionally more of the PMN than the DMN or FPCN

After determining the degree to which the IMT task maps were made up of the PMN, DMN, and FPCN, we examined a complementary question—the degree to which the task maps encompassed the different networks. That is, we compared the total proportion of PMN, DMN, and FPCN voxels included in the IMT statistical maps using both the Strict and Lenient threshold criteria (Figure 4.6B). Across both thresholds, the PMN was most strongly captured by the IMT map. Comparatively little of the DMN or FPCN was captured in the Strict threshold
map, but more of the PMN than FPCN was captured under the Lenient threshold. These results were confirmed by an ANOVA with factors of Network (PMN, DMN, FPCN) and Threshold type (Strict, Lenient), which revealed a main effect of Network ($F_{(2,12)} = 15.39$, $\eta^2_p = .606$, $p < .001$, Greenhouse-Geisser corrected for nonsphericity), a main effect of Threshold ($F_{(1,10)} = 155.22$, $\eta^2_p = .939$, $p < .001$), and an interaction of Network and Threshold ($F_{(2,20)} = 15.20$, $\eta^2_p = .603$, $p < .001$).

4.4 Discussion

In the present chapter we compared the IMT-based statistical map—thought to capture the PMN—and various RSFC-derived networks as estimated by the Infomap algorithm. This led to several important observations. First, participants varied somewhat in the size of different networks, though no individual appears to be a clear outlier overall. With respect to the IMT data, both the PMN and DMN—as defined using RSFC data—show repetition enhancement effects, whereas the FPCN shows a degree of repetition priming. Furthermore, activity previously associated with the PMN was found to encompass both PMN and DMN regions, suggesting it was not specific to the PMN alone. Implications of these findings are now considered.

4.4.1 Network size varies across individuals

The data presented in this dissertation add to a growing number of reports concerned with assessing individual variability of functional network structure (Mueller et al., 2013; Gordon et al., 2014; Gordon et al., submitted; Laumann et al., 2015; see also Harrison et al., 2015). The purpose of the present experiment was not to examine inter-individual variability per se, but to
assess the agreement between a task-derived voxelwise map and a given individual’s estimated network structure. However, several notable observations can be made with respect to the network maps themselves.

First, there is a large degree of variability in the spatial extent of a given network across individuals. For instance, approximately 700 to 3,000 vertices were associated with the PMN in the 11 subjects examined here, with a similarly large range present in the DMN and FPCN (Figure 4.3). Adding to this variability was the presence (or absence) and location of certain network small “patches” (i.e., discrete portions of cortex associated with a given network; see Gordon et al., 2015). With respect to the PMN, only a subset of the current subjects possessed a detectable pIPL/dAG patch on either hemisphere; only one subject had these within 15 mm of the a priori PMN coordinates, whereas others had PMN patches in medial prefrontal cortex and the frontal poles (Figure 4.2). This is consistent with recent data reported by Gordon et al. (submitted), also agreeing to some extent with functional connectivity estimates of left pIPL/dAG as described by Nelson et al. (2010). Uniquely, ND possessed a patch of the PMN bilaterally in lateral temporal cortex. This was not present in any other participant, did not appear in Russ Poldrack’s MyConnectome dataset (Laumann et al., 2015), and has not been observed elsewhere to our knowledge. This patch was present across multiple Infomap edge density thresholds (e.g., Figure C.2), and was still detectable when a template-matching procedure (see Gordon et al., 2015) was used rather than Infomap. This suggests the lateral temporal patch was not an artifact of the specific analysis stream used here. ND also appeared unique in that he did not have a patch of FPCN near his MCC. Whether these features are idiosyncratic to ND, or perhaps are a result of his training as a memory athlete (which could presumably be observed in others), will need to be ascertained in future research.
4.4.2 Voxelwise analyses of task data across networks reflect basic differences in activity

As an admittedly coarse measure of comparing PMN, DMN, and FPCN responses in different IMT conditions, we compared activity across all voxels associated with each network. This revealed a clear dissociation between the FPCN and the other two networks, both in the direction of its activity relative to baseline, and how its activity differed between Presentations 1 and 3 (Figure 4.4). This dissociation was not unexpected; at a qualitative level, the IMT maps coincide with expanses of cortex that aligned with the PMN and DMN, but did not seem to capture the FPCN to any real degree.

The separation of the PMN from the FPCN in this context (as well as other dissociations observed elsewhere in this investigation, see Figures 4.5-4.6) is worthy of some emphasis. Depending on the specific analysis used, regions corresponding to those within the PMN have at times been associated with the FPCN, rather than identified as a separate network (Dosenbach et al., 2006; Dosenbach et al., 2007; Vincent et al., 2008; Spreng et al., 2010; Yeo et al., 2011). The data in this current experiment, which leverage the improved resolution offered by analyzing data at the single-subject level, favor a separation of the two networks. As most subjects’ Infomap solutions contained FPCN patches adjacent to PMN patches, prior studies may have lacked sufficient spatial specificity to resolve them.

4.4.3 PMN and DMN ROI time courses are both very similar to those derived from the IMT directly

The ROI selection procedure used in Chapter 2 was intended to identify subject-specific PMN regions. In the present chapter, the same selection procedure was able to identify PMN, DMN, and (to a lesser extent) FPCN regions—as defined using Infomap—that fit the selection criteria. When averaging activity in all 5 putative PMN ROIs (left and right pIPL/dAG, left and
right PCU, and MCC), we found PMN and DMN regions were both extremely similar ($r_s = .85$) to the time courses observed in task-defined ROIs (Figure 4.5A). It was only when the time series observed in each ROI were considered separately that the PMN and DMN appeared to differentially correlate with the task-defined ROIs, and at this point it became clear that the DMN ROIs were significantly more correlated with the task-defined ROIs with respect to activity time courses (Figure 4.5B). The similarity between PMN and IMT responses suggests that the conclusions reached in Chapter 2 are not unfounded, however the results also demonstrate that considering the PMN in isolation would misrepresent the current findings.

The similarity between DMN ROIs and the task ROIs was not a hypothesized outcome, but neither is it a complete surprise given the results described in Chapter 2 and contextualized briefly in the introduction to this chapter. Why might the DMN show robust repetition enhancement in the IMT? For one reason, DMN deactivation is correlated with task difficulty (McKiernan et al., 2003; Leech et al., 2011), and the faster RTs associated with repeat presentations in the IMT suggest that making a decision for stimuli during Presentation 2 or 3 was easier and/or less effortful than making the initial decision for a given stimulus. In other words, it was a reduction in task demands that likely led to reduced deactivation (and thus, repetition enhancement) in DMN regions.

This may explain why enhancement effects were observed in the DMN, but still fails to account for why more of the DMN was captured by the IMT than the PMN. We can only speculate as to why this occurred, but the simplest answer appears to be the nature of the IMT. If a task required more attention to be allocated to stimulus familiarity (as is done under explicit memory conditions), then we can hypothesize that the PMN would have responded more clearly with above-baseline activation. In turn, this would lead to a greater degree of enhancement, and
the PMN and DMN would have been more cleanly separated than they were in the IMT.

4.4.4 There are suggestions of PMN activation when we define ROIs from Infomap, even in the IMT

The putative PMN ROIs discussed in Chapter 2 (which may well be DMN ROIs, as determined in work described in this chapter) did not show above-baseline activations, and at a gross level, neither did the PMN ROIs as defined from Infomap (Figure 4.5A). However, there is a degree of nuance to this that suggests some above-baseline activity may have been present. As Figure C.6 illustrates, PMN PCU and MCC ROIs show time courses that numerically (but not significantly) activate above baseline for repeat presentations. It is only when averaged along with the pIPL/dAG PMN ROIs that activation is no longer evident. These findings should not be over-interpreted, especially given the lack of significance in above-baseline activation, but as an observation these benefit future PMN research.

4.4.5 Is it theoretically informative to compare resting-state network estimates to task maps?

In this chapter, we assumed that RSFC analyses were accurate in their identification of different functional networks, and leveraged that to make statements about PMN and DMN responses in the IMT. However, there was relatively poor correspondence between the IMT voxelwise maps produced for each subject (irrespective of which threshold was selected), and any of the networks to which the maps were compared. The DMN was best captured by the IMT maps, but still only covered less than 25% of the IMT maps' extent on average (Figure 4.6A). It was through a combination of time course comparisons and spatial overlap that we concluded a better correspondence between the DMN and IMT task than the PMN and IMT task maps. Only when ROIs were incorporated into the analysis could more specific claims be supported with the current data.

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The results noted above speak to a larger issue, which is establishing useful ways by which RSFC and task data can be used to localize specific functional networks (or components of networks). A similar question of correspondence between rest and task data was recently considered in the context of the MyConnectome project (Laumann et al., 2015). In this rich dataset, Laumann and colleagues demonstrated that task activations were more likely to occur within putative areal parcels than at areal boundaries, and that retinotopically-defined functional visual areas also respected putative boundaries. It must be stressed that the Infomap procedure does not define areal parcels, but supports the notion that network estimates from RSFC analyses should agree with task-defined map boundaries, given correct thresholding (which is nontrivial) and a well-designed task (which is more difficult still). The IMT was, in part, designed to create a situation in which the PMN might be particularly responsive. The data within this chapter clearly suggest this is not the case.

4.4.6 Shortcomings of the comparison between task and rest data made in the current chapter

The current chapter has several shortcomings that should be noted. For one, it relied on the Infomap procedure and did not compare this to other network estimates. This has several drawbacks, although it has proven useful previously when estimating the network structure of the human brain (e.g., Power et al., 2011). One shortcoming is that Infomap requires experimenter-selection of the proper output to use for each participant (which admittedly had minimal impact on the PMN across the 11 current subjects). Further, it is a non-linear algorithm that must assign a given vertex to a single network in a winner-take-all fashion. It also relies on a “random walk” approach to community detection; reproducing a map exactly is impossible, even within the same individual and using the same parameters, unless one records the original walk taken when
running the algorithm. Use of other algorithms in the future will be critical to establish the reliability of the current findings.

4.4.7 Conclusion

In this chapter we describe findings that the IMT results from Chapter 2 strongly correspond to both PMN and DMN regions, and actually show stronger association with the DMN. These data also show a clear dissociation between the FPCN, and the DMN and PMN, and provide preliminary evidence that more fine-grained distinctions can be observable even when neighboring networks behave highly similar under certain task conditions. This serves as a basis for future work to better understand the situations in which activity across PMN and DMN can diverge or converge as a function of task requirements.
4.5 References


Chapter 5: Conclusions and future directions

Abstract

The experiments in this dissertation examined the degree to which parietal memory network (PMN) regions exhibited effects under implicit memory task (IMT) conditions that were consistent with those hypothesized by Gilmore et al. (2015). By this account PMN regions deactivate in response to novel stimuli, show increased activity across multiple stimulus repetitions, and activate above baseline in response to familiar items.

In Chapter 2, putative PMN regions were identified in a group of 10 healthy subjects. These regions exhibited both initial deactivations and repetition enhancement, but did not activate above baseline. Data in this chapter suggested that a key difference between the IMT and explicit memory tasks is the degree to which one must orient to the familiarity dimension of a stimulus, which in turns implies a stronger role for attention in modulating PMN activity than was previously hypothesized.

In Chapter 3, the 10 subjects from Chapter 2 were compared to subject ND, a highly trained memory athlete. Although ND is capable of impressive memory feats, he did not appreciably differ from his control group. This suggests that training, even when it involves learning to very rapidly and effectively encode stimuli, does not appear to affect PMN (or whole-brain) activity in response to repeated stimulus presentations under IMT conditions (and has at best a negligible effect on overt behavior).

In Chapter 4, resting-state functional connectivity (RSFC) analysis was used to better determine whether regions of interest (ROIs) derived from the PMN or the neighboring default mode network (DMN) more closely corresponded to task-identified ROIs identified in Chapters
2 and 3. Results indicated that both networks behaved very similarly in the IMT, but that DMN ROIs appeared to show activity patterns that were more similar to those observed in task-defined ROIs. This suggests that the IMT does not selectively elicit PMN activity, but appears to affect multiple adjacent networks, thereby limiting its potential as a network localizer task.

In this final chapter, several key findings of this dissertation are discussed in a broader context. In addition, future directions of research that might solve outstanding issues in this dissertation are described.
5.1 Updating the novelty/familiarity hypothesis of PMN function based on implicit memory data

This dissertation was meant to test a straightforward set of predictions concerning functional response properties of a recently described cortical network. In particular, members of the McDermott laboratory have argued that activity within the parietal memory network (PMN) supports processes related to learning and memory, and more specifically reflects the degree to which a given stimulus is perceived to be novel or familiar (Gilmore et al., 2015). To the degree this account was true, the specifics of task conditions should have only a minor effect on PMN activity, with the bulk of the response being driven by item history. Familiarity, which is thought to automatically (and obligatorily) affect behavior (Jacoby, 1991), or its absence (i.e., novelty) should have led to patterns of activation or deactivation, even when these are not relevant to an ongoing task.

The aforementioned “straightforward” predictions were tested in a straightforward manner; subjects were placed in fairly basic implicit memory task (IMT) conditions. Here, they responded to semantic features of stimuli that were presented multiple times, without any need to attend to their prior experiences with these stimuli. Analyses indicated that only a subset of the proposed PMN response patterns were retained in the IMT, with no above-baseline activation observed. Further, interrogation of specific networks (discussed in Chapter 4) suggested that both the PMN and neighboring default mode network (DMN) respond every similarly in the IMT.

The lack of activation for familiar stimuli implies that the “hallmark” flip about baseline within PMN regions is not as universal as previously described. Rather, it suggests that task conditions can significantly affect the degree of activation far more than was previously
appreciated. This reduces the impact of familiarity _per se_ in leading to activations (although novelty and familiarity still appear to drive deactivation and repetition enhancement in PMN regions), and instead suggests that a separate process largely determines the degree of activation in response to familiarity. In the following section, I describe one such possibility, which appears to accommodate the findings of the IMT while minimally affecting other aspects of the novelty/familiarity hypothesis.

**5.1.1 Unexpectedness and the PMN**

It has been argued that parietal old/new effects are not attributable to the successful recovery of a memory trace, but rather reflect a violation of memory-guided expectations (O'Connor et al., 2010; Jaeger et al., 2013; for related evidence, see Waskom et al., 2016). Under this “Memory Orienting Model” it is the mismatch of expectation and retrieval success that modulates activity within certain parietal regions (a subset of which correspond quite well to the PMN; see O'Connor et al., 2010). The model does not account for initial deactivations observed within PMN regions (which behaved as we previously hypothesized), but may account for the lack of observed activation during Presentation 3 trials: the grouping of presentations in the IMT created a situation in which one rarely encountered novel stimuli in the context of familiar stimuli, or familiar stimuli in the context of novel stimuli, thereby reducing the “unexpectedness” associated with encountering familiar stimuli. This would then suggest that if the novel and familiar stimuli were intermixed rather than grouped (as is typically done in continuous recognition paradigms) one might continue to see the pattern of deactivation, repetition enhancement, and activation, as originally predicted by Gilmore et al. (2015). In an intermixed scenario, the relative familiarity of an item would not be strongly predicted by the items that
immediately preceded it, and therefore expectedness might again lead to above-baseline activation. This prediction can be tested easily in future research, and appears consistent with prior (explicit) continuous recognition tasks in the literature (Jessen et al., 2001).

The incorporation of unexpectedness into the novelty/familiarity account should be considered a refinement of the previous account forwarded by Gilmore et al. (2015). Whereas the previously hypothesized modulator of activation was a combination of familiarity (or perhaps “memory strength”) and “attentional capture” (a somewhat under-defined term), unexpectedness provides a specific means by which attentional capture may occur. It should be accompanied with a modification that attentional processes not only modulate the amount of above-baseline activation within the PMN, but also appear to be a major contributor to observing any above-baseline activity for familiar items.

5.2 Improving our neuroanatomical understanding of the PMN

The work contained in this dissertation served to improve our understanding of the PMN’s neuroanatomy, and along with a recent report by Gordon et al. (submitted), can address several outstanding issues in the literature. Of primary concern, data from Chapters 2 and 4 speak to the number of PMN regions, which varies somewhat depending on the specific methodology used when defining functional networks. After examining a combination of task and rest data, Gilmore et al. (2015) proposed a three-region network, consisting of left pIPL/dAG, left PCU, and MCC. However, both the present dataset and prior literature (Yeo et al., 2011; Gordon et al., 2014; Gordon et al., submitted; Laumann et al., 2015) suggest a
bilaterality to the PMN. This is not an altogether surprising point, but it does clearly answer one of several outstanding questions listed by Gilmore et al. (2015) at the end of a recent review. Namely, left and right hemisphere components of the network exist, but do not appear sensitive to the verbal or nonverbal nature of stimuli as might be observed in certain regions of frontal cortex (Kelley et al., 1998; McDermott et al., 1999).

Of perhaps greater interest are the patches of the PMN that appear to vary across individuals, most notably the pIPL/dAG patches. Whereas task results would lead one to conclude that pIPL/dAG is a critical component of the network, the current RSFC results indicate that only a portion of subjects have an identifiable PMN patch anywhere on lateral parietal cortex (see also Gordon et al., submitted). This is one area in which task and rest results still need to be reconciled. It may be the case that lateral components of the PMN, including pIPL/dAG as well as several frontal regions, can in certain circumstances break off from the PMN, whereas in other instances they remain a single network. Consider: in a recent parcellation scheme of left lateral parietal cortex, pIPL/dAG was associated not with PCU or MCC regions, but rather with a small network of predominantly frontal regions (Nelson et al., 2010). These seem to align with other “inconsistent” regions that emerge in some but not all subjects (see Figure 4.2). It is not clear how or why such differences develop across individuals, but an answer to this question would have important implications for our understanding of what functional networks identified in RSFC MRI represent.

One final point worth making on variability in PMN regions concerns the degree to which bilaterality is observed. Overall, it seems that the presence of an ROI in one hemisphere is strongly predictive of a homotopic ROI being identified, at least within the IMT data. That is,
identifying a pIPL/dAG ROI on one hemisphere meant an extremely high probability of
identifying a pIPL/dAG ROI on the other hemisphere, which was true also for PCU ROIs (Figure
2.9). Thus, this dissertation work serves, in part, to establish bilaterality as a property of the
PMN; while not altering functional understanding of the PMN, it can minimize the risk of a
small error propagating through the literature for an indeterminate period of time.

5.3 Combining task and resting-state data in the service of localizing cognitive processes

A driving force behind the decision to utilize a rather small number of subjects in this
dissertation work (at least in the context of current cognitive neuroscience research) was a desire
for anatomical precision in task and rest data. The more accurately function can be mapped to
structure, the more accurately our hypothesized accounts of different region or network functions
can be articulated (Posner et al., 1988; Devlin & Poldrack, 2007; Van Essen & Dierker, 2007).
This was discussed at some length in the Chapter 1, but is worth revisiting here—the
combination of task and rest data allowed far more precision than would otherwise have been
possible. Consider: in Chapter 2, putative PMN regions were defined in a reasonable and
principled manner at the single subject level. However, once resting-state data were
incorporated, it became clear that the activity patterns that were expected to capture the PMN
also captured a relatively large portion of DMN regions. In the case of the IMT task employed
within this dissertation, both the PMN and DMN behaved very similarly, but the incorporation of
multiple MRI techniques prevented an inaccurate portrayal of effects as exclusively falling
within a single network (and, indeed, suggests a certain sensitivity of the DMN to repetition
effects that are not frequently discussed in the literature).

Beyond the networks and task requirements specific to this dissertation, the use of converging methods is becoming increasingly necessary if we wish to use cognitive neuroscience to guide our understanding of human cognition. Incorporation of task and rest data can help determine if two investigators are discussing the same region, or two different regions, in their respective experiments. On a practical level, this would greatly improve inter-experimental results, and allow for more meaningful comparisons across datasets.

5.4 Future directions

Throughout this dissertation, I have made reference to knowledge gaps that should be addressed in future work. In this final section of this final chapter, I identify several important directions that are broad in scope, but that stand to greatly aid the field of cognitive neuroscience.

5.4.1 Improving techniques for single-subject analysis in the context of multi-subject experiments

The methods and analyses used to produce the data in this dissertation are a hybrid of single subject and group-level analysis. The focus was not on a single individual, but rather on how a small group of highly-sampled individuals performed a given task (and how a single individual compared to this reference group). The techniques and decisions used in the analyses of these data were informed by my history with group-level analysis of fMRI data. However, to properly leverage the utility of single subjects, methods need to be developed to facilitate inter-individual comparisons.

I noted in Chapter 2 that the degree to which a single subject’s statistical maps should be
thresholded was unclear, and to some degree arbitrary. A better solution should be identified in short order, as it will necessarily impact all downstream decisions. One recent approach has been to examine statistical maps across numerous thresholds, and describe results in terms of average relationships (Laumann et al., 2015). This approach has merit, though problems will emerge if different individuals have different distributions of statistical values (just as a typical average is more appropriate in relatively normal, as compared to heavily skewed, data). Alternatively, as was suggested in Chapter 2, one can attempt to utilize either the same proportion of voxels, or else the same number of voxels, across individuals. These latter approaches, however, still require a somewhat arbitrary decision to be made, and retain their weakness to differences in significant distributions across subjects.

One alternative approach is to utilize RSFC data as a means of determining the optimal threshold for each subject. For instance, one may be able to quickly collect basic “finger tapping” task data, in addition to the task of interest, and compare the finger-tapping activation map with a subject’s estimated “hand” motor system. One could determine a threshold for the motor data that maximally overlapped (or spatially correlated, etc.) with the rest data, and then apply this same threshold to data from an independent task.

Of course, RSFC data may or may not ultimately prove useful in determining how to modify thresholds across subjects; however, given that recent findings suggest rest data can parcellate the whole brain in a manner that leads to (relatively strong) functional homogeneity within a given parcel (e.g., Gordon et al., 2014), it appears this can be a particularly promising approach. Unfortunately, it was outside of the scope of the current dissertation work, and so remains an outstanding problem.
5.4.2 Developing localizer tasks for “higher order” functional networks

Functional localizers are relatively simple tasks that are thought to selectively (in a moderate, rather than strict, sense of the term) activate a single region or network of regions based on some known functional property (Huettel et al., 2009). For instance, one might compare images of faces to other types of visual stimuli to localize a fusiform face area (Kanwisher et al., 1997) or substitute scenes for faces to in order to localize a parahippocampal place area (Epstein & Kanwisher, 1998). The concept of a functional localizer is not without its flaws, which were discussed at some length in a series of commentaries and responses between Friston, Saxe, and others (Friston et al., 2006; Friston & Henson, 2006; Saxe et al., 2006). Perhaps most important is a recognition that no experimental task is “process pure,” and therefore clear limits must be placed on over-interpreting the functional role of a functionally-localized region.

It does appear, however, that certain tasks can strongly recapitulate functional networks as estimated by RSFC MRI. For example, finger tapping largely recapitulates the sensorimotor system (Biswal et al., 1995). In a more complex case, Bar and Aminoff (2003) identified what was termed a “contextual association network” by presenting objects that were either strongly associated with a single spatial context (e.g., a roulette wheel, associated with a casino), or objects that were weakly associated with numerous contexts (e.g., a roll of duct tape, which may appear in a truck, on a work bench, etc.). This contextual association network maps on very strongly to what some have referred to as the medial temporal lobe subsystem of the DMN (Andrews-Hanna et al., 2010; Gilmore et al., submitted), or has alternatively been labeled the parieto-occipital system (e.g., Laumann et al., 2015).

Here, I argue that the development of a network localizer task can be theoretically
informative. The IMT, used in the experiments detailed in this dissertation, was designed in part to potentially serve as a PMN localizer. If the functional account of the PMN offered by Gilmore et al. (2015) was correct, then one could have reasonably suspected a simple implicit memory task to elicit unique repetition enhancement effects within the PMN. This was not the case, but the experimental attempt to find a localizer has resulted in an improved understanding of PMN functional dynamics. If we assume that the network estimates produced in RSFC are largely accurate, then correspondence between potential localizer tasks and resting-state networks can be used to guide theory regarding network function. Experimenters can alter certain task parameters that are hypothesized to either strongly or weakly impact a given functional network, and changes in spatial overlap (and the specificity of that overlap) can be used to benchmark hypothesis accuracy.

5.5 Final thoughts

The various chapters within this dissertation all contain evidence that test the general accuracy of the novelty/familiarity account of PMN function (Gilmore et al., 2015). Within PMN regions, we expected to observe deactivation, repetition enhancement, and activation within the IMT. We found clear evidence for the first two predicted patterns of results, and I believe the lack of evidence for the third has improved our understanding of PMN function. As I conclude this dissertation, I wish to offer an informal assessment of the accuracy of our initial novelty/familiarity account. On this subject, I take the position of Jim Steinman (1977), which was disseminated to the public some 40 years ago by Michael Lee Aday under his stage name of Meat Loaf: “two out of three ain’t bad.”
5.6 References


Appendix A: Supplemental Materials for Chapter 2

Specific instructions for each task.

Face judgments:
In this next scan you’ll be viewing a series of faces. Some will be female, others will be male. Your task is to decide what the gender of each face is. You will see each face more than once. Regardless of how many times you have seen a face, please indicate whether it is male or female. You’ll make your responses with the button box, with either your left or right thumb. Press the [Right/Left] button to indicate that a face is female, and the [Left/Right] button to indicate that the face is male. [Button mappings were practiced until the subject was comfortable.] Do you have any questions?

Scene judgments:
In this next scan you’ll be viewing a series of scenes. Some will be indoor scenes, others will be outdoor scenes. Your task is to decide whether or not each picture you see is of an indoor or outdoor scene. You will see each picture more than once. Regardless of how many times you have seen a picture, please indicate whether it is an indoor or outdoor scene. You’ll make your responses with the button box, with either your left or right thumb. Press the [Right/Left] button to indicate that a scene is indoors, and the [Left/Right] button to indicate that the scene is outdoors. [Button mappings were practiced until the subject was comfortable.] Do you have any questions?

Word judgments:
In this next scan you’ll be viewing a series of nouns. Some will be abstract, others will be concrete. Abstract words refer to ideas that do not have a physical or set form. Concrete words are words for which a physical or set form exists. Your task is to decide whether each noun is abstract or concrete. You will see each noun more than once. Regardless of how many times you have seen a noun, please indicate whether it is abstract or concrete. You’ll make your responses with the button box, with either your left or right thumb. Press the [Right/Left] button to indicate that a word is abstract, and the [Left/Right] button to indicate that the word is concrete. [Button mappings were practiced until the subject was comfortable.] Do you have any questions?
Supplemental Figures

Voxelwise results for all stimuli combined

MSC01

MSC02

MSC03

MSC04

MSC05

MSC06

MSC07

MSC08

MSC09

MSC10

-4.0 -1.96 / 1.96 4.0
z-statistic

Figure A.1. Voxelwise results for each subject when averaging activity across all judgment tasks. Regions exhibiting repetition enhancement are shown in warm colors, and repetition suppression in cool colors.
Voxelwise and time course results for all stimuli combined

Figure A.2. Time courses of BOLD activity when averaging across all judgment tasks. ROIs show individual subject and average group activity during Presentation 1, Presentation 2, and Presentation 3. *p < .05 (Bonferroni corrected) vs. 0
Figure A.3. Results for the MSC group when performing Face judgments only. Top: Voxelwise statistical maps reflect regions that show repetition enhancement (warm colors) and repetition suppression (cool colors). Bottom: Time courses for each group-defined ROI.

*p < .05 (Bonferroni corrected) vs. 0
Figure A.4. Results for the MSC group when performing Scene judgments only. Top: Voxelwise statistical maps reflecting regions that show repetition enhancement (warm colors) and repetition suppression (cool colors). Bottom: Time courses for each group-defined ROI.

*p < .05 (Bonferroni corrected) vs. 0
Figure A.5. Results for the MSC group when performing Word judgments only. Top: Voxelwise statistical maps reflection regions that show repetition enhancement (warm colors) and repetition suppression (cool colors). Bottom: Time courses for each group-defined ROI.
*p < .05 (Bonferroni corrected) vs. 0
Figure A.6. Results for the MSC group when combining Scene and Word judgments (averaging activity across tasks). Top: Voxelwise statistical maps reflecting regions that show repetition enhancement (warm colors) and repetition suppression (cool colors). Bottom: Time courses for each group-defined ROI. *p < .05 (Bonferroni corrected) vs. 0
Figure A.7. Difference image of Presentation 3 and Presentation 1 for Face judgments only, at a more lenient threshold than shown in Figure 2.6.
Figure A.8. Difference image of Presentation 3 and Presentation 1 for Scene judgments only, at a more lenient threshold than shown in Figure 2.7.
Figure A.9. Difference image of Presentation 3 and Presentation 1 for Word judgments only, at a more lenient threshold than shown in Figure 2.8.
Figure A.10. Difference image of Presentation 3 and Presentation 1 for Scene and Word judgments, at a more lenient threshold than shown in Figure 2.9.
## Supplemental Tables

Table A.1. Lexical properties of words used in the IMT

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<td>3, -40, 33</td>
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MNI152 coordinates for each subject-specific ROI

<table>
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<tr>
<th>Subject</th>
<th>Euclidian distance from reference coordinates</th>
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<td>MSC02</td>
<td>8.2 8.5 9.9 6.0 7.7</td>
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<td>8.8 7.3 8.1 7.3 12.8</td>
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<tr>
<td>MSC08</td>
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<td>MSC10</td>
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</tbody>
</table>
Appendix B: Supplemental Materials for Chapter 3

Supplemental Figures

Figure B.1. Voxelwise statistical results for Face, Scene, and Word stimuli, separated by stimulus type. Significant voxels were first identified by a Presentation x Time Point ANOVA ($z > 3; k \geq 3$), which were then tested for Presentation 3 – Presentation 1 activity differences using a paired-samples t-test ($|z| > 1.96$).
Figure B.2. Difference image of Presentation 3 and Presentation 1 for Face, Scene, Word, and Scenes and Words combined. Images are analogous to those presented in Figure 3.3 and B.1, but at a more lenient threshold (requiring $|z| > 1.25$ for a paired-samples, two-tailed $t$-test between Presentation 3 and Presentation 1).
Appendix C: Supplemental Materials for Chapter 4

Specific instructions for resting-state scans

*During this first scan, a plus sign will be presented on the screen. All you need to do is simply relax and look at the plus sign. Please keep your eyes open the entire time, and be as still as possible. It's extremely important that you stay awake for the entire duration of this scan. This scan will last ~30 minutes.*
Supplemental Figures

Figure C.1. Visualization of lowest possible and selected edge density maps within MSC04, as compared to the brain’s network structure as defined from a large group of subjects. Top data adapted from Power, et al. (2011), other network map colors follow this convention, which differs from the color scheme used in Figure 4.2 and Supplemental Figures 4.4 and 4.5.
Figure C.2. Visualization of lowest possible and selected edge density maps within ND, as compared to the brain’s network structure as defined from a large group of subjects. Top data adapted from Power, et al. (2011), other network map colors follow this convention, which differs from the color scheme used in Figure 4.2 and Supplemental Figures 4.4 and 4.5.
Figure C.3. Single subject network response magnitudes from all voxels contained within the parietal memory (PMN), default mode (DMN), and frontoparietal control (FPCN) networks.
Figure C.4. Statistical maps taken from the “Stringent” implicit memory task (IMT) threshold, overlaid on subject-specific network maps. Voxels that displayed a significant Presentation x Time Point interaction ($z > 3$), and also displayed repetition enhancement effects ($z > 1.96$), are presented in magenta. Green circles highlight small IMT enhancement clusters.
Figure C.5. Supplemental Figure 4.5. Statistical maps taken from the “Lenient” implicit memory task threshold, overlaid on subject-specific network maps. Voxels that displayed greater activity during Presentation 3 than Presentation 1, at an uncorrected $z > 1.25$, are presented in magenta.