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The dynamic self: exploring the critical role of the default mode network in self-referential processing

Carissa Louise Philippi
University of Iowa

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THE DYNAMIC SELF:
EXPLORING THE CRITICAL ROLE OF THE DEFAULT MODE NETWORK
IN SELF-REFERENTIAL PROCESSING

by

Carissa Louise Philippi

An Abstract

Of a thesis submitted in partial fulfillment
of the requirements for the Doctor of
Philosophy degree in Neuroscience
in the Graduate College of
The University of Iowa

July 2011

Thesis Supervisors: Assistant Professor David Rudrauf
Professor Daniel Tranel

ABSTRACT

Investigation of the neural correlates of the self has implicated a network of brain regions including the medial prefrontal cortex (MPFC), posterior cingulate (PCC), precuneus (pC), and inferior parietal lobule (IPL). At the same time, recent neuroimaging work has identified the Default Mode Network (DMN), a network of brain regions that are highly active at 'rest' (without an active cognitive task). While the functional significance of the DMN remains unknown, converging evidence suggests that the DMN might be *critical* for self-referential processing (e.g., introspection). In this dissertation, I tested this hypothesis using a lesion approach. In the first experiment, I examined the critical role of the DMN hubs (MPFC, IPL) in autobiographical memory (AM) retrieval. I predicted that if the DMN hubs were critical for AM, then lesions to either the MPFC or IPL should result in AM retrieval impairments. I tested this prediction using the Iowa Autobiographical Memory Questionnaire (IAMQ), a questionnaire that assessed retrograde AM retrieval. In support of the prediction, lesions to the MPFC and IPL were associated with significant AM retrieval impairments. While not predicted, AM retrieval deficits were also associated with lesions in medial and lateral temporal cortices, regions also considered part of the DMN. In the second experiment, I tested the critical role of the DMN hubs in the self-reference effect (SRE), a well-known memory advantage conferred by self-related processing. I predicted that if the DMN hubs were critical for the SRE, then damage to the MPFC or IPL should diminish the effect. I used a standard personality trait judgment paradigm to test this prediction. In partial support of the prediction, I found that damage to the MPFC abolished the SRE with a "self" specific deficit. While IPL damage was associated with a diminished SRE, the effects were not significant. In the

third experiment, I tested the hypothesis that the DMN is critical for accurate knowledge of one's personality. I predicted that if the DMN hubs are critical for accurate self-knowledge, then damage to either the MPFC or IPL should be associated with less accurate personality reports. In partial support of the prediction, MPFC and IPL groups demonstrated less accurate personality ratings. However, performance for all lesion groups was comparable and not significantly different from healthy subjects. In the fourth experiment, I sought to test the hypothesis that the DMN is critical for mind wandering (MW). I predicted that if the DMN hubs are critical for MW, then damage to the MPFC and IPL should result in decreased MW. To test this prediction, I used two approaches: 1) an experience sampling method (Sustained Attention to Response Task), and 2) a self-report measure (Imaginal Processes Inventory scale of MW). Contrary to my prediction, IPL lesions were associated with increased MW on the SART. By contrast, in support of the prediction, both MPFC and IPL lesions were associated with significant self-reported decreases in MW. Together, these experiments provide some evidence to support the hypothesis that the DMN is critical for self-referential processing. Future work might investigate the impact of DMN lesions on other self-processes (e.g., self-agency).

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Graduate College
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CERTIFICATE OF APPROVAL

PH.D. THESIS

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To My Grandfather, Eugene Smalley.

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ABSTRACT

Investigation of the neural correlates of the self has implicated a network of brain regions including the medial prefrontal cortex (MPFC), posterior cingulate (PCC), precuneus (pC), and inferior parietal lobule (IPL). At the same time, recent neuroimaging work has identified the Default Mode Network (DMN), a network of brain regions that are highly active at 'rest' (without an active cognitive task). While the functional significance of the DMN remains unknown, converging evidence suggests that the DMN might be *critical* for self-referential processing (e.g., introspection). In this dissertation, I tested this hypothesis using a lesion approach. In the first experiment, I examined the critical role of the DMN hubs (MPFC, IPL) in autobiographical memory (AM) retrieval. I predicted that if the DMN hubs were critical for AM, then lesions to either the MPFC or IPL should result in AM retrieval impairments. I tested this prediction using the Iowa Autobiographical Memory Questionnaire (IAMQ), a questionnaire that assessed retrograde AM retrieval. In support of the prediction, lesions to the MPFC and IPL were associated with significant AM retrieval impairments. While not predicted, AM retrieval deficits were also associated with lesions in medial and lateral temporal cortices, regions also considered part of the DMN. In the second experiment, I tested the critical role of the DMN hubs in the self-reference effect (SRE), a well-known memory advantage conferred by self-related processing. I predicted that if the DMN hubs were critical for the SRE, then damage to the MPFC or IPL should diminish the effect. I used a standard personality trait judgment paradigm to test this prediction. In partial support of the prediction, I found that damage to the MPFC abolished the SRE with a "self" specific deficit. While IPL

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CHAPTER 1

INTRODUCTION

1.1 Self and Self-Referential Processing

A sense of self is central to human experience. The self lies at the affective heart of our lives, and serves as an object of continual evaluation by ourselves and by others. Not only is it difficult to imagine human experience devoid of a self representation, it may be impossible to be conscious without it (Damasio, 1999). As Damasio suggests, “If ‘self-consciousness’ is taken to mean ‘consciousness with a sense of self,’ then all human consciousness is necessarily covered by the term—there is just no other kind of consciousness as far as I can see” (Damasio 1999, p19). Phenomenologically the self may be an essential part of human life, but such subjective experience does not address the potential phylogenetic and ontological origins of a self.

1.1.1 The Self and Its Origins

While some argue that a self is uniquely human, recent neuroscientific theories (based in ethology and comparative psychology) suggest that a core or proto-self is likely present at least in other mammalian species (Panksepp & Northoff, 2009; Damasio, 2010). From this standpoint, the self may be an adaptation, evolved very early on to promote survival and reproductive success. With a developed sense of self, an organism could represent a perspective, or an image of oneself spatially situated in an environmental context. In this way, the organism may be constantly informed of its own well being in the struggle for preservation. The development of a self may have become evolutionarily central as the co-evolution of cognitive systems in nature put pressure on

awareness. Moreover, the storage of internal representations in memory may also be critical for modeling past, present, and anticipating future outcomes. Taken together, a self representation may have developed to integrate internal information about the state of the body with external information about the state of the environment to maximize the chances of survival.

1.1.2 Theoretical Perspectives on the Self

The concept of the self has been fervently debated by philosophers, psychologists, anthropologists, sociologists, and biologists for centuries. Conceptually, the self can often seem vague, as it has been used to refer to different processes and abilities across many disciplines (e.g., self-image, social-self, self-awareness, self-verification, self-recognition). While these terms can be descriptively useful and relevant, the empirical investigation of the self could benefit from a more unified theoretical framework. In the following sections, I will provide a brief overview of different theoretical perspectives on the *self* from classical philosophy, psychology, and neuroscience. I will discuss the relevant theories, scientific research, and definitions of *self* within these fields as classified under either specific or integrated perspectives.

1.1.2.1 Specific Domains of Self

In classical philosophical traditions, there are two basic distinctions for the self that can be helpful for interpreting different theoretical frameworks for self across fields: self as a *subject*, and self as an *object* (for others or for self-awareness). The subjective or experiential self, represents the for-me-ness quality of experience, or what it is like to be imbued with a self-concept and perspective. Furthermore, subjective experience includes an implicit sense of ownership (i.e., “This thought I have is mine”) and agency (i.e.,

“This action I perform is caused by me”) (Levine, 2001; Nagel, 1974). Whereas the objective self requires metacognitive, reflective mechanisms applied to a somewhat reified “image” of the self becoming an object of representation (e.g., I see myself in the mirror, or imagine myself delivering a lecture). Besides the distinctions between subject and object, these definitions also distinguish between different types of processing responsible for the generation of each. The “subjective” self, under a certain view (e.g. Sartre and the Phenomenological tradition), is considered to be a pre-attentive (pre-conscious), reflexive, or pre-reflective phenomenon. It is something that does not require overt reflection or introspection to appear but is yet given. In other words it would be an ongoing process of self-representation associated with a core self-awareness, which constitutes the foundation of all subjective experience. By contrast, the “objective” self would require a process of reflection, involving controlled attention and constituting a higher-order form of meta-consciousness potentially embedded into a narrative.

Building from philosophical notions of the self, in psychology and neuroscience, self-specific processes have been distinguished into at least two domains including physical and psychological processes (Gillihan & Farah, 2005). A physical or bodily self-process is characterized by an ability to perform basic self-other distinctions, often through the integration of information from different sensory (i.e., visual, somatosensory) and motor domains (Blakemore & Frith, 2003; Daprati et al., 2010; Decety, 1999; Jeannerod, 2003). In other words, physical self-processes enable individuals to differentiate themselves (*self*) from *other* objects, people, and stimuli in the environment. An extensive research literature, from animals to humans, has investigated various types of bodily self-processes such as interoceptive awareness (e.g., heartbeat sensation)

(Craig, 2002; 2004; 2009; Critchley, 2004), body ownership (Botvinick & Cohen, 1998; Ehrsson et al., 2004; Tsakiris et al., 2007), self-face recognition (Gallup, 1970, Kircher et al., 2000; Keenan et al., 2001; Platek et al., 2008; Povinelli et al., 1993, Reiss and Marino, 2001), and an implicit sense of self-agency (Jeannerod, 2003; van den Bos & Jeannerod, 2002; David et al., 2008). In many instances, elaborate and innovative paradigms have been used to explore the mechanisms underlying these processes. For example, in a well-known body ownership task, simultaneous tactile stimulation is applied to both the hand of a participant (which is out of view), and to a rubber hand placed in front of the participant (e.g., Botvinick & Cohen, 1998). Intriguingly, in this so-called rubber hand illusion, the participant begins to feel that the rubber hand is their *own* hand (Botvinick & Cohen, 1998). The fact that this manipulation of ownership can occur suggests that different types of sensory information (visual, tactile, and proprioceptive) are integrated (spatially and temporally) in order to facilitate the self-recognition of one's body. It seems that the spatial and temporal coincidence of such multimodal sensory information is a key factor mediating the difference between attributing ownership to yourself versus to another person.

The mechanisms underlying ownership seem to apply also to the domain of self-agency, or the ability to recognize one's actions (or thoughts) as one's own. The predominant theory explaining the mechanisms of self-agency in action is the comparator model (Blakemore et al., 2001). This model proposes a type of discrepancy feedback loop where intended or predicted actions are compared with actual outcomes to decipher the agent. When the self is an agent, the discrepancy (predicted – actual) is small. However, if the discrepancy is large enough the action will be attributed to an external agent.

Research suggests that recognition of the discrepancy occurs only if the perceived discrepancy is large enough (Blakemore & Frith, 2003). These findings suggest that self-agency discrepancies are only consciously detected if the action is not one's own action.

Besides self-recognition in action, self-recognition in faces (i.e., mirror self-recognition) has been an active and fascinating area of research in both humans and animals. In fact, visual recognition of one's self in a mirror has been a gold-standard probe for assessing self-awareness in animals (Gallup, 1970, Povinelli et al., 1993, Reiss and Marino, 2001). In his pioneering work, Gallup developed a paradigm to test whether chimpanzees could learn to recognize themselves in a mirror (Gallup, 1970). In this study, chimpanzees were given prolonged exposure to mirror over a period of two days. Early on, the animals displayed species-typical behaviors indicating no self-recognition or self-awareness (e.g., signs of aggression directed at their reflection). However, after some time the chimpanzees began to exhibit self-focused grooming behaviors in the mirror including attempting to get food out of their teeth and picking their noses (Gallup, 1970, p 86). Following this prolonged exposure, red marks were placed between their eyebrows while the chimpanzees were anesthetized. When placed back in front of the mirror, the chimpanzees spent more time in front of the mirror and importantly displayed behavior directed toward the red marks. These results provided support for the presence of self-recognition abilities, or self-awareness, in chimpanzees and suggested that this may not be a uniquely human ability. Beyond animals, research in humans suggests this ability is not present at birth, although it does appear to develop fairly early on. For example, most infants exhibit mirror recognition, and learn to identify their reflection at around 18 months of age (Amsterdam, 1972). As this ability appears early in

development, it can be difficult to empirically investigate these processes in adults. Thus, research on self-face recognition has also used pictorial stimuli, such as in tasks that require the recognition of one's face in a photograph or digital image (see Platek et al., 2008 for review).

In humans, in addition to physical self-processes, extensive empirical research on psychological self-processes has been conducted. Psychological self-processes are those that primarily involve conscious processes, often requiring self-reflection and introspection. In other words, these processes may be said to constitute one's personal narrative (e.g., Gallagher, 2000). Such psychological self-processes include as episodic and semantic autobiographical memories (e.g., Tulving, 1983; 2005; Klein et al., 1996), the collection of personality traits or self-concept (e.g., Craik et al., 1999; Demo, 1992; Markus, 1977; Rogers et al., 1977), and self-reflection, self-referential processing, and introspection (e.g., Andreasen et al., 1995; Andrews-Hanna et al., 2011; Antrobus et al., 1970; Amodio & Frith, 2006; Kelley et al., 2002; Northoff et al., 2006). Each of these examples of psychological self-processes will be the main focus of the experiments (1a-1c, 2) in this dissertation. Therefore, I will reserve a detailed discussion of the relevant conceptual, theoretical, and empirical background research for these psychological self-processes for chapters 2 and 3.

Beyond physical and psychological self-processes, various theoretical frameworks have been proposed that separate different domains of self-processing into putative levels (James, 1890; Damasio, 1999; 2010; Stuss & Benson, 1986; Stuss, 1991). The levels within these frameworks often seem to be classified based on the types of self-processing required. For example, as described above, the "lower" levels seem to include non-

conscious bodily processes (i.e., interoceptive awareness), whereas the “higher-order” levels include psychological and meta-cognitive processes (e.g., introspection). Many of these hierarchical frameworks of self have also been applied to neuroanatomical structures (e.g., Damasio, 1999; 2010). For example, Damasio proposed a tripartite framework that separated self-consciousness or self-processing into three putative levels (Damasio, 1999; 2010). At the primary level, there is a basic protoself self that consists of the basic primordial feelings of the body (Damasio, 1999, p 199; 2010, p 181). This protoself can be described as a reflexive self, or subjective self, and would include bodily or sensory representations of oneself (e.g., interoception). At the secondary level, is the core self, which includes an interaction with the protoself. The core self processes involve the conscious, non-verbal, integration of the current state of the organism (i.e., sensory processes) with external information, putting the organism in context (“embodied”). At a tertiary level, is the “autobiographical self” (Damasio, 1999; 2010) which would consist of the collection of our self knowledge, or the memories from our past, and the representation of a self-concept or self-schema embedded in a biographical narrative.

In summary, specific domains of self seem to have been studied and classified into different categories based primarily on three criteria: 1) the type of processing (i.e., subjective, objective), 2) the content (i.e., physical, psychological), and 3) the level of processing (i.e., conscious/unconscious). In the next section, I will describe two theoretical perspectives of self that have incorporated at least a few of these specific domains to describe integrated self-referential processing frameworks. Note: Although Damasio’s tripartite framework could be considered a hybrid of specific and integrated

perspectives, it was discussed under this section based on the description of levels of self-processing in the framework. This theoretical perspective provided a complement to the background on specific domains of self.

1.1.2.2 Integrated Perspectives of Self

In an effort to integrate self research across fields (e.g., philosophy and psychology), and to consider these *self* processes from an evolutionary perspective, Panksepp and Northoff have proposed a self-relational theory (Panksepp & Northoff, 2008). The relational theory of the self proposes that instead of focusing on content-based definitions of self (e.g., self-face recognition, self-agency), the self can instead be described as a *process* that functions to integrate emotional, interoceptive, and sensory-motor information to facilitate goal-directed actions (Northoff & Panksepp, 2009; Panksepp & Northoff, 2008). Based on this self-relational framework, Panksepp and Northoff (2008) further suggest that there is a common, transpecies core self that could exist across different species. This core self would function in animals as well as humans to relate information within the organism (e.g., emotional, interoceptive) to information in the environment (e.g., predator, food source, conspecific). In this way, self-relational processing would facilitate the valuation of stimuli for the organisms (self-relatedness) based on the association (or temporal coincidence) between internal states (e.g., emotional, interoceptive) and external stimuli. The transpecies self is similar functionally Damasio's proto and core self (1999; 2010) described above. The self-relational processing framework has also been applied to the neural substrate, which will be discussed in the sections below.

A similar theoretical framework developed by Schmitz & Johnson (2007) attempts to provide a unified account of various findings from neuroscience research (neuroimaging and neuropsychological) primarily on the self and emotion (See section 1.2.2.2 below). The appraisal of self-relevance theory proposes that there are two types of processes that interact to identify and appraise self-relevant information. In the first process, pre-attentive (bottom-up) mechanisms operate to facilitate orienting the organism to salient self-relevant information (Schmitz & Johnson, 2007, p 586). It can also be described as constituting the subjective experience of self-relevance (e.g., feeling fearful when seeing a bear outside of your cabin window). In the second process, higher-order (top-down), meta-cognitive processes initiate self-reflection and introspection. Under this framework, top-down self-reflective processes might operate in conjunction with subjective bottom-up processing to enhance self-relevant information processing. In this way, such interactions could function to enhance encoding of self-relevant information.

Taken together, both specific and integrative perspectives incorporate at least three types of processes: 1) a subjective, reflexive, experience of self (e.g., bodily processes); 2) the autobiographical self, developed through self-referential processing (e.g., psychological processes); 3) self-reflective, metacognitive capacities. In contrast to the majority of the research on specific domains of self which might focus on one self-process (e.g. self-agency), the integrative perspectives provide frameworks where self-processing can occur across modalities. Thus, integrative frameworks are particularly appealing from a network perspective.

Similar to conceptual perspectives of self reviewed above, in next section I will describe relevant research on the neural correlates of self based on both specific and integrated (network) perspectives.

1.2 Neural Correlates of Self

1.2.1 Neural Correlates of Specific Domains of Self

The neural correlates of self have been studied extensively in both neuroscience and neuropsychology by focusing on specific domains of self-processing. In this section, I will provide a brief overview of relevant neuroimaging and complementary lesion work for the following seven specific domains of self: interoceptive awareness and emotional experience, self-recognition (in faces), self-agency, autobiographical memory, self-reflection and self-referential processing.

Interoceptive awareness is the knowledge of one's of own internal bodily sensations or the visceral state of the body (e.g., Craig, 2009; Critchley et al., 2004). For example, types of interoceptive processes include heartbeat sensation, itch, bowel distention, and tickle sensation (Craig, 2002). Converging evidence from functional neuroimaging work suggests that interoceptive awareness relies critically on the anterior insular cortex and anterior cingulate cortex (e.g., Craig, 2004; Craig, 2009; Goldstein et al., 2009; Singer et al., 2009). However, a recent human lesion study measuring awareness of heart beat sensations, showed that the insula and ACC were not the only cortical substrates to play a causal role in interoceptive awareness (Khalsa et al., 2009). Instead, somatosensory afferents from the skin also appeared to play an independent role in carrying sensory information about cardiovascular responses. These results validated

functional neuroimaging research on interoceptive awareness reporting somatosensory cortical activation (in addition to insula and ACC).

Emotional experience can be defined as the conscious experience of a subjective feeling state that arises in an organism in response to a stimulus (internal or external) and entails a physiological response, and a behavioral or bodily response (cf. Damasio, 2003). Thus, emotional experience can be considered a self-related process, in that it entails a *personal* experience and awareness of emotional feelings that may include both conscious and unconscious processes. Experimental tasks of emotional experience often involve subjective ratings of emotions following presentation of emotion-evoking stimuli during experimental settings (Lane et al., 1998). Similar to the neural correlates of interoceptive awareness, the emotional experience and emotional awareness (e.g., Lane et al., 1998) are also consistently associated with activity in the ACC and insular cortices (e.g., Bartels & Zeki, 2004; Critchley et al., 2004; Craig, 2009 for review in context of interoception).

Self-face recognition involves the ability to recognize one's own face, either in a mirror or in photographs (as mentioned in the previous section). Investigation of the neural correlates of self-face recognition in functional imaging has implicated a network of brain regions including lateral regions of the middle and inferior frontal gyrus, temporal, and ventral temporal-occipital regions (e.g., Keenan et al., 2000; Kircher et al., 2001; Platek et al., 2008). Moreover, both functional imaging (e.g., Keenan et al., 2001; Platek et al., 2008) and lesion work in split-brain patients (e.g., Sperry et al., 1979) provides converging evidence to suggest that the right hemisphere may play a critical role.

Self-agency constitutes the ability to recognize oneself as the agent of one's thoughts and actions (Gallagher, 2000). Self-agency can be divided into two different levels of self-related processing: 1) the sense of self-agency, and the 2) judgment of self-agency (Synofzik et al., 2008). These conceptual distinctions are important to consider when examining the neural correlates of self-agency (see David et al., 2008 for a review). As David et al. (2008) point out in their review, the sense of self-agency has been shown to activate a distributed network of brain regions (i.e., premotor and somatosensory cortices) with little consensus about which regions are critical. On the other hand, the judgment of self-agency seems to be more consistently associated with the insula and inferior parietal lobule (e.g., Farrer & Frith, 2002; Farrer et al., 2003), and the prefrontal cortex (e.g., Slachevsky et al., 2001).

Autobiographical memory can be described as the collection of personal memories that can include both episodic (context-specific) and semantic (context-free) components (Tulving, 1983; 2005). Autobiographical memory retrieval involves the integration of different types of information across modalities (e.g., visual, olfactory, auditory), and as such has been associated with a network of brain regions including the medial prefrontal cortex (MPFC), medial and lateral temporal cortices, and medial and lateral parietal regions (precuneus, posterior cingulate, retrosplenial cortex, and inferior parietal lobule) (Cabeza & St. Jacques, 2007; Svoboda et al., 2006; Tranel & Jones, 2006; Kroll et al., 1997; Thaiss & Petrides, 2008). Note: autobiographical memory will be discussed in more detail as it will be the focus of experiment 1a in the next chapter.

Self-referential processing can be defined as the cognitive process of contemplating information in relation to oneself. For example, when evaluating whether a particular personality trait (e.g., productive) is descriptive of you. Self-referential processing has been associated with a network of structures including cortical midline structures (e.g., medial prefrontal cortex, precuneus, posterior cingulate), and lateral parietal cortices (e.g., inferior parietal lobule) (e.g., Amodio & Frith, 2006; Craik et al., 1999; Kelley et al., 2002; see Northoff et al., 2006 for a meta-analysis). Interestingly, though perhaps not surprisingly, there is significant overlap between this self-referential processing network and the network implicated in autobiographical memory.

In summary, neuroimaging and lesion research on the neural correlates of specific domains of self-processing has implicated a network of brain regions, both distinct and similar. Intriguingly, the neuroanatomical overlap across different types of self-processes has led researchers to speculate about the existence of a supramodal network responsible for self-processing in general. In the following section, I will discuss the two integrated theories mentioned earlier as applied to different neural network perspectives for self.

1.2.2 Neural Network Perspectives of Self

1.2.2.1 Subcortical-Cortical Midline Structures (SCMS)

The self-relational theory (as mentioned above), suggests that self-related processing is instantiated in a subcortical-cortical network (SCMS) (Panksepp & Northoff, 2008). The theory purports that the dynamic interaction between cortical and subcortical substrates in the SCMS network is responsible for enabling self processing. Whereas the subcortical structures are involved in emotional (i.e., amygdala) and motivational (i.e., striatum, PAG) processes, the cortical brain regions (i.e., MPFC, IPL,

PCC) may be more critical for the representation, monitoring, evaluation and integration of self-related information. Moreover, this framework suggests that the higher order reflective self-processes (e.g., introspection) build on a more basic preexisting core-self. Thus, more abstract and complex self-related information (e.g., personality characteristics) is processed within the SCMS network, predominantly in the cortical midline components of the network (cf. Northoff et al., 2006; Panksepp & Northoff, 2008). This SCMS network seems like a plausible candidate for a supramodal self-referential network that could support various types of self processing including physical self-processes (i.e., interoceptive awareness), the recollection of autobiographical memories, and self-referential processing and self-reflection.

1.2.2.2 Appraisal of Self-Relevance (ASR) Network

Similar to the SCMS, Schmitz & Johnson (2007) propose a neural network responsible for orienting to, identifying, and evaluating self-relevant information from the environment. In this appraisal of self-relevance network (ASR), there are two subsystems in the brain that are involved: 1) ventromedial prefrontal (VMPFC) –subcortical network, and 2) dorsomedial (DMPFC) – posterior cingulate (PCC) network. In the first system, the ventral cortical–subcortical structures are responsible for the locating and maintaining information for subsequent appraisal of self-relevance. Moreover, Schmitz and Johnson (2007) also suggest that the VMPFC in particular may be critical as a “self-relevance detector”. In the second system, the dorsal-ventral MPFC, dorsorostral ACC and PCC structures are considered important for introspection, self-reflection, and evaluation of self-relevant stimuli. The authors provide evidence from neuroimaging and lesion studies of emotional and cognitive processing (e.g., emotional fear response) to suggest that this

network is a supramodal processing network for self-relevance. Taken together, this ASR network is capable of binding introspective processing with ongoing awareness of one's environment. In line with the SCMS, this network accounts for the interaction between subjective experience of a self, and the self-reflective processes in a unified network perspective. Moreover, the ASR network provides a neural framework that can subserve different types of self-processing.

Together, the SCMS and ASR neural network perspectives provide unified accounts of self-processing across modalities and domains of self-processing. In the following section, I will discuss relevant empirical research on the default mode network (DMN) and its proposed link to self-referential processing. In the context of this dissertation, the discovery that brain activity correlated with internal thought processes at rest has invited researchers to study self-related processing and subjectivity in a new way (Andreasen et al., 1995; Raichle et al., 2001; Buckner et al., 2008).

1.3 Default Mode Network (DMN) And Self-Referential Processing

1.3.1 “Discovery” of the DMN

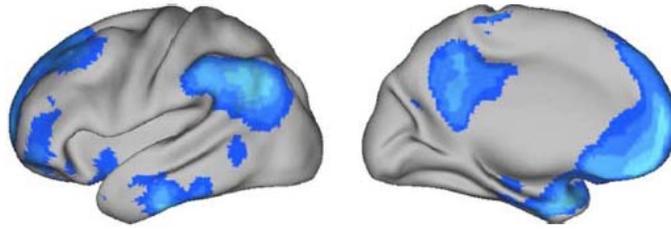
Recent research has stimulated interest in the brain mechanisms underlying wakeful resting states (without an active cognitive task), by revealing a “default” mode network (DMN) of brain regions with high baseline metabolic rates at rest (Raichle et al., 2001). The brain regions included most consistently in the DMN are the medial prefrontal cortex (MPFC), posterior cingulate (PCC)/precuneus (pC)/retrosplenial cortex (RsP), and the inferior parietal lobule (IPL) (Figure 1; Buckner et al., 2008). These brain regions have been described as the putative “hubs” or core regions of the network (a term that

will be described in more detail in section 1.3.4 below) (Buckner et al., 2008, p. 5-11).

Note, other regions besides the putative hubs, such as the medial and lateral temporal cortices, are also considered part of the DMN (e.g., Buckner et al., 2008). Observations of consistent relative decreases in activity in the same set of brain regions during active tasks, regardless of task modality (task-independent decreases), suggested that higher activity 'at rest' may be related to specific ongoing internal processes (Shulman et al., 1997; Mazoyer et al., 2001). Raichle and colleagues (2001) proposed that these brain regions constituted a tonically active network, deactivated during active tasks.

Neuroimaging findings from analysis of resting-state functional connectivity and low frequency fluctuations of the BOLD signal in fMRI suggested that the DMN was a dynamic and functionally connected network (Greicius et al., 2003; Fox et al., 2005; Fransson et al., 2005). Evidence from neuroanatomical tracing studies in animals and diffusion tensor imaging (DTI) in humans suggests that various white matter tracts (e.g., cingulum bundle) provide structural connections between the hub regions of the DMN (e.g., Greicius et al., 2009; Buckner et al., 2008 for review). While converging evidence has indicated that the DMN is highly metabolically active during rest, and functionally and structurally connected, this does not address the potential functional significance of the DMN.

Figure 1. Lateral and midsagittal views of the brain with functional activations in the Default Mode Network (DMN) during rest conditions.



*This figure was published previously in Buckner et al., 2008.

1.3.2 Functional Significance of the DMN

Following the discovery of the DMN, researchers began to speculate about the processes subserved by the network, including internal mental processes, spontaneous thought, or the stream of consciousness (Raichle et al., 2001, in reference to James, 1890). The association between the DMN and internally directed mentation or self-related processes was based primarily on two lines of evidence: 1) retrospective self-reports, and 2) converging evidence from functional imaging work on the neural correlates of self. For example, in a study by Andreasen and colleagues (1995) found that subjects reported that during rest they were thinking about themselves, and their past memories and future goals. More recent studies have corroborated these findings, with the use of structured questionnaires administered after scanning to assess thought content during rest periods (e.g., Andrews-Hanna et al., 2010). Moreover, in the second line of evidence, as opposed to other cognitive tasks (i.e., visual search) that have been shown to relatively “deactivate” or decrease activity in the DMN, a variety of self-referential tasks tend to activate the same network of brain regions (Andreasen et al., 1995; Buckner et al., 2008 for review). For instance, activity in the DMN (in particular the MPFC, pC/PCC/Rsp, and IPL) has been shown in tasks involving mind wandering or

spontaneous thought (Andrew-Hanna et al., 2010; Christoff et al., 2009; see Gruberger et al., 2011 for review; Mason et al., 2007), autobiographical memory retrieval (Andreasen et al., 1995; Svoboda et al., 2006), emotional processing of pictures (Gusnard et al., 2001), future thinking (Buckner and Carroll, 2007), and self-referential processing in general (e.g., Northoff et al., 2006). Moreover, a quantitative meta-analysis of the brain networks common across functional imaging studies found consistent involvement of the DMN for theory of mind (ToM), autobiographical memory, and prospection (i.e. imagining ourselves in the future) (Spreng et al., 2008).

Thus, based on the aforementioned evidence, Buckner and colleagues (2008) suggest that the DMN constitutes a system by which individuals may perform mental simulation of behavior in activating past episodic memories, present thoughts, and simulating future events. Similar hypotheses suggest that the DMN is critical for spontaneous self-related thought (e.g., Andrews-Hanna et al., 2010), or self-processing in general (e.g., Wicker et al., 2003; see Legrand & Ruby, 2009 for opposing view). Alternative hypotheses have been proposed, such as that the DMN is crucial for attending to the external environment (e.g., Gilbert et al., 2007). However, in this dissertation I will focus on the first two hypotheses, as the main objective was to examine the role of the DMN in self-referential processing.

To date most of the research investigating DMN has relied on functional imaging and focused on descriptive correlations between functional activity and behavioral measures, while complementary neuropsychological and lesion methodologies have not yet been used to assess the critical and causal role of the DMN and its hubs in these processes (cf. Buckner et al., 2008). In this dissertation, in line with other theories (e.g.,

Gusnard, 2005; Lou et al., 2004; 2010), I suggest that the building of an adaptive self-concept could be what unites the different findings about the processes underlying the default mode and the DMN. Note, the term “critical” will be used throughout this dissertation as it is used in neuropsychological studies, to indicate when a brain structure (e.g., MPFC), is *necessary* for a particular function (i.e., self-processing).

1.3.3 DMN and Mental Health Disorders

Understanding the critical role of the default mode network in internal mental processes and self-referential processing is highly relevant to mental health as the disturbance of the sense of self, self-awareness, and insight is at the center of several mental health disorders (cf. Broyd et al., 2009). Furthermore, impairments in introspection and alterations in internal cognitions can hinder rehabilitation and treatment for many patients suffering from mental health illnesses. Studies investigating DMN activity in mental health disorders are steadily increasing in prevalence. Aberrant default mode network (DMN) activity and altered functional connectivity has been reported in anxiety disorder (Zhao et al., 2007), depression (Greicius et al., 2007), schizophrenia (Garrity et al., 2007), autism (Kennedy et al., 2006), and attention deficit/hyperactivity disorder (Uddin et al., 2008). Of note, this research is also germane to other neurological diseases as the neuritic plaques and neurofibrillary tangles characteristic of Alzheimer’s disease (AD) preferentially aggregate in structures of the DMN (i.e., PCC/pC), and these regions show decreased metabolic activity in AD (Buckner et al., 2008; Buckner et al., 2005). Thus understanding the psychological processes underlying default mode network activity could have significant implications for identification, prevention, therapy and rehabilitation for patients with these devastating disorders.

1.3.4 Putative Hub and Network Properties of the DMN

In the following section, I will provide a brief overview of basic definitions of networks and hubs. These network concepts will be important for understanding the experimental design, aims, and predictions for the studies presented in this dissertation (see 1.4 Chapter Conclusions). Although the precise network properties of the DMN remain unknown, I will also offer a putative proposal for how information is processed within the network in terms of the *content* and *order* (serial/parallel) of processing.

Neural networks can be defined as “sets of nodes linked by connections” (Sporns et al., 2004, p 418). Brain regions or nodes within a network can be connected either directly (e.g., a white matter tract linking two brain regions) or indirectly (e.g., interneurons or multiple synaptic connections). Whereas the nodes constitute the individual components of the network in general, the “hubs” are the most highly interconnected regions within the network (Sporns et al., 2004). This suggests that an individual hub, with numerous afferent and efferent connections, is integral to the normal functioning of the network. Such network or hub properties are particularly relevant for human neurologic disease. For example, network hubs can be functionally and/or structurally disconnected due to brain injury (e.g., stroke). In this case, damage to a single hub could lead to significant dysfunction in the network and in the specific processes subserved by the network (e.g., cognitive, affective, or perceptual). Similarly, in the context of this dissertation, it is possible that damage to the hubs of the DMN (MPFC and IPL) could result in network dysfunction and measurable deficits in self-referential processing. In partial support of this claim, recent neuroimaging studies found that patients with Alzheimer’s disease (AD) had atrophy in DMN structures and corresponding decreases in functional connectivity with the same network (Seeley et al.,

2009; Zhou et al., 2010). It will be important in future studies to investigate this further, using the lesion method to examine the consequences of focal DMN hub damage on functional connectivity within the network and corresponding behavioral impairments (e.g., autobiographical memory, self-reflection/self-awareness).

Beyond definitions of networks and hubs, below I will discuss how information processing might occur within the DMN in terms of content (self-referential processing) and circuitry (serial/parallel). I would like to acknowledge that although the DMN is currently an active topic of research (e.g., Andrews-Hanna, 2011), the network properties and content of processing subserved by the DMN remain largely unknown. Thus, the following proposal is meant to be tentative and is to be used (in the context of this dissertation) to inform predictions about the effects of lesions to the MPFC and IPL hubs of the DMN.

In terms of the content of processing within the DMN, as mentioned earlier, functional imaging work suggests that this network supports self-referential processing (e.g., Buckner et al., 2008; Gusnard et al., 2001; Lou et al., 2010; Northoff et al., 2006). However, these findings do not address the role of the individual hubs of the DMN in self-processing. Neuroimaging and lesion studies suggest that the MPFC and IPL hubs of the DMN are involved in both unique and overlapping self-processes.

Functional neuroimaging research has implicated the *MPFC* across a variety of tasks requiring self-processing including the self-evaluation of one's own personality traits (e.g., Craik et al., 1999; Kelley et al., 2002), subjective experience of emotion (e.g., Gusnard et al., 2001), and ratings of pictures and traits for self-relatedness (e.g., D'Argembeau et al., 2005; Moran et al., 2006). Similarly, lesion work suggests that the

MPFC (in particular the ventromedial prefrontal cortex [vMPFC]) is critical for self-awareness and the maintenance of a stable personality (e.g., Anderson et al., 2006; Barrash et al., 2000; in press; Damasio et al., 1994; Eslinger & Damasio, 1986; Harlow, 1868; Prigatano, 1996; Stuss, 1991). Taken together, the MPFC could contribute to the representation and monitoring of self-relevant information (e.g., Northoff and Panksepp, 2008; Schmitz and Johnson, 2007).

Neuroimaging and neuropsychological studies provide evidence for the role of the *IPL* in body representation, feelings of ownership, agency, and action (e.g., Berlucchi & Aglioti, 1997; Daprati et al., 2010; Farrer & Frith, 2002; Farrer et al., 2003; Spengler et al., 2009). In an intriguing proposal for the contribution of the parietal lobes to consciousness, Daprati and colleagues (2010) proposed a model in which the *IPL* is critical for bodily awareness and the integration of bodily representations to enable the conscious awareness of the body in action. Neuropsychological studies support this claim, for example in the case of alien hand syndrome which can result from damage to the *IPL* (e.g., Bundick and Spinella, 2000; Martí-Fàbregas et al., 2000). This syndrome is associated with an alteration in the sense of ownership and agency. Specifically, alien hand syndrome is described as the perception that one is not under voluntary control of their own hand (see Scepkowski and Cronin-Golomb, 2003 for review). Besides bodily representation, lesion studies have also suggested that the *IPL* could contribute to episodic memory. In sum, the *IPL* may contribute to self-awareness by enabling the continuous recognition of the body in space, in a moment-to-moment monitoring and integration of the body in action (Daprati et al., 2010).

Together the MPFC and IPL hubs of the DMN might be critical for the conscious awareness of oneself (see Gusnard and Raichle, 2001), with the MPFC contributing to the representation and knowledge of one's memories and emotions, and the IPL involved in the awareness of one's bodily representation. While the MPFC and IPL contribute to distinct types of self-processes, as part of the DMN the IPL may also be involved in episodic memory retrieval. Together, self-processing in the MPFC and IPL hubs of the DMN may be both distinct and similar.

While the order of information processing (serial/parallel) within the DMN remains unknown, results from functional connectivity analysis in fMRI provide support for a model of parallel processing. Specifically, the hubs of the DMN (MPFC, IPL, and the PCC) exhibit functionally correlated activity at rest (e.g., Greicius et al., 2003). This suggests that the DMN hubs are active at the same time, and could process information in parallel. If information processing within the DMN occurs in parallel, then damage to the DMN hubs would be expected to result in more subtle deficits in self-processing as the processing in one region (e.g., MPFC) would not depend upon the processing in another region (e.g., IPL). However, given limitations in the temporal resolution of the fMRI (on the order of second), it is possible that more fine grained temporal analysis with high-density electroencephalography (HD-EEG) or intracranial EEG methods could provide support for an alternative account of information processing (e.g., serial). In a serial processing account, in contrast to the parallel processing prediction, damage to the DMN hubs would be expected to result in significant deficits in self-processing. However, it is important to note that this order of processing framework (e.g., parallel/serial) may be an oversimplification of the dynamics occurring within the DMN. For example, the

dynamics within the network could entail a complex combination of both types of processing.

1.3.5 Considerations for Using the Lesion Method to Test Network Hypotheses

The lesion method is used to examine brain-behavior relationships; and to assess the necessary or critical role of a specific brain region to a particular function (e.g., cognitive, affective, or sensory). By comparison, functional neuroimaging methods are used to identify the neural substrates and systems that contribute to certain functions. While it has been suggested that the lesion method is well suited to test network or systems hypotheses (Damasio, 2000), potential limitations should be considered. First, it is difficult to know precisely how lesions to individual hubs will affect network connectivity and functioning. Depending upon the role of the region within the network, the effects of damage could differ. In support of this claim, computer simulated modeling of the impact of lesions to resting state activity found that lesions to midline cortical regions (e.g., PCC) resulted in global alterations in functional connectivity whereas lesions to primary sensory cortices had more local effects (Alstott et al., 2009). Second, it is also possible that lesions could have indirect effects on the network, known as diaschisis (see Feeney and Baron, 1986 for review). Arguably, one way to address these concerns is to test network hypotheses that are well characterized (Damasio, 2000). Another way to overcome such limitations is to combine functional neuroimaging and lesion methodologies to assess the effects of injury to single hubs on functional connectivity within spared regions of the network. These analyses could also be compared with effects simulated lesions predicted by computational modeling of functional connectivity within a network (e.g., Alstott et al., 2009). Together, while

beyond the scope of this dissertation, future research using these complementary methods is warranted to explore brain-behavior relationships from a more dynamic network perspective. Despite these limitations, it is still possible and valuable to test network or systems hypotheses with the lesion method. Specifically, if the DMN does indeed constitute a network, with the MPFC, PCC, and IPL hubs, it is reasonable to assume that damage to any of the hubs will result in measurable impairments in self-referential processing putatively subserved by the network.

1.4 Chapter Conclusions

The self is a multifaceted, multilayered, dynamic and adaptive system. Moreover, the self is maintained and modified across the lifespan based on experience within a social and environmental context. Until recently, investigations of the neural correlates of the self have focused predominantly on specific domains of self-related processes (e.g., self-recognition, interoceptive awareness) associated with particular brain regions (e.g., MPFC, insula) and hemispheres (Craig, 2009; Keenan et al., 2001). While these findings have been crucial for understanding the neural correlates of different aspects of self and self-awareness in isolation, these studies do not explain how different domains of self might be integrated from a systems perspective. In other words, is there a neural network responsible for self-related information processing across modalities?

With the recent discovery of the DMN in functional neuroimaging, it is possible to test the provocative hypothesis that the multifaceted self is instantiated in a supramodal self-referential processing neural network, the Default Mode Network (DMN). If the DMN is indeed critical as a *network* for self-referential processing across modalities, then damage to any of the hubs of the network (MPFC and IPL) might be expected to result in

similar impairments. If, on the other hand, certain regions within the DMN are more crucial for self-referential processing (e.g., self-concept), then damage to a single hub (e.g., the MPFC) might result in a deficit. For example, patients with MPFC damage might have an impaired self-reference effect in memory, while patients with IPL damage may be unimpaired. These results would suggest that the DMN may not operate as a supramodal self-referential processing network, but instead particular brain regions might be more critical for the instantiation of a self. Although not testable in this dissertation, it is also possible that particular hubs are necessary for certain types of self-related processing. For instance, the MPFC might be critical for the representation of personality and self knowledge, while the IPL might be crucial for the bodily representation and bodily sensations (i.e., feeling that you are the owner of your limb). Note, this dissertation is limited by the availability of patients with brain lesions affecting the Precuneus/Posterior Cingulate Cortex (pC/PCC) hub of the DMN. Consistent with reports that damage to the pC/PCC region is relatively uncommon (Cavanna & Trimble, 2006), there are few patients in the Iowa Lesion Registry with focal damage to the pc/PCC. Therefore, it is somewhat impractical to use the lesion approach to test the critical role of this hub of the DMN in self-referential processing. Instead, I will focus on the MPFC and IPL, as there are sufficient subject numbers for both of these lesion groups to test the proposed hypothesis.

Despite these limitations, the principal goal for my dissertation is to assess whether two of the hubs of the DMN (MPFC and IPL) are crucial as a supramodal network for self-referential processing. I will utilize the lesion method to address this goal. In a series of three experiments in Chapter 2, I will examine whether two hubs of

the DMN (MPFC and IPL) are *critical* for 1) the retrieval of past self-knowledge (autobiographical memory retrieval), 2) self-referential processing and encoding of new self-related information in memory (self-reference effect), and 3) the accuracy of self-knowledge (personality trait ratings). In Chapter 3, I will investigate the critical role of two hubs of the DMN in spontaneous self-referential processing or mind wandering using two complementary “online” objective (Sustained Attention to Response Task) and “offline” subjective (mind wandering questionnaire) measures. These lesion studies will include brain-damaged comparison participants, who will have lesions outside the DMN, in order to establish the specificity of the brain-behavior relationships.

CHAPTER 2

SELF REPRESENTATION: THE CRITICAL ROLE OF THE DMN IN RETRIEVAL, ENCODING, AND ACCURACY OF SELF-RELEVANT INFORMATION

2.1 Background

Converging lines of evidence from functional imaging work on the self and the DMN have led researchers to hypothesize that the DMN is *critical* for self-referential processing (e.g., Andreasen et al., 1995; Andrews-Hanna et al., 2010; Buckner et al., 2008; Wicker et al., 2003). However, no lesion study has yet investigated whether the DMN or the hubs of the DMN are necessary for self-processing. In this chapter, I sought to test this hypothesis using both group-level (Experiment 1a) and targeted (Experiment 1b-1c) lesion approaches. I used a variety of paradigms to investigate the critical role of two of the DMN hubs (MPFC and IPL) in self-knowledge and the retrieval, encoding, and accuracy of self-relevant information. Importantly, many of the paradigms used in this chapter are the same as those that have been used in previous studies which have provided evidence for this hypothesis (e.g., Andreasen et al., 1995; Spreng et al., 2008). Specifically, I examined autobiographical memory retrieval (Experiment 1a), the self-reference effect (SRE) in memory (Experiment 1b), and the accuracy of one's knowledge of their own personality traits (Experiment 1c).

2.2 Specific Aim and Hypotheses

2.2.1 Specific Aim

To assess the critical role of the MPFC and IPL hubs of the DMN in the retrieval, encoding, and accuracy of self-knowledge.

2.2.1.1 Hypothesis 1a

The MPFC and IPL hubs of the DMN are *critical* for the retrieval of self-knowledge. In experiment 1a, I predict that patients with lesions to the MPFC or IPL will have impairments in episodic autobiographical memory (AM) retrieval. If both MPFC and IPL patients are impaired in episodic AM retrieval, this will provide support for H1a. On the contrary, if neither MPFC nor IPL lesions impair episodic AM retrieval, H1a will be falsified.

2.2.1.2 Hypothesis 1b

The MPFC and IPL hubs of the DMN are *critical* for the encoding and retrieval of self-knowledge. In experiment 1b, I predict that patients with lesions to the MPFC or IPL will have a reduced self-reference effect (SRE). If both MPFC and IPL patients have a reduced SRE, this will provide support for H1b. On the other hand, if neither MPFC nor IPL lesions reduce the SRE, H1b will be falsified.

2.2.1.3 Hypothesis 1c

The MPFC and IPL hubs of the DMN are *critical* for the retrieval and accuracy of self-knowledge. In experiment 1c I predict that damage to the MPFC or IPL will be associated with reduced accuracy in self-rated personality traits. If both MPFC and IPL patients have reduced accuracy in self-reported personality this will provide support for H1c. However, the hypothesis (H1c) will be falsified if neither MPFC nor IPL groups have reduced accuracy in rating their personality traits.

2.3 Experiment 1a: DMN and Autobiographical Memory

2.3.1 Introduction (1a)

The ability to recollect and re-experience personal events from the past is essential for the development and maintenance of our unique personal narrative. Autobiographical memory (AM) is characterized as personal episodic memory, or the process of mentally traveling back in time (Tulving, 1983; 2005) to relive an event from our past (e.g. remembering your college graduation, including where you were and how you felt). AM has classically been described as episodic (e.g. temporally and spatially specific), however autobiographical memories also incorporate temporally independent information, or personal semantic memories (e.g. your address, name of your high school). Thus, the process of AM retrieval and formation often requires both semantic (context-free general knowledge) and episodic (multisensory, and context-specific) memory and relies on the integration of perceptual, affective, and cognitive processes. For example, vivid recollection of a personal event may include visualization of the scene, association of smells, sounds, emotion, and executive functions to monitor and update the ongoing process.

The integration of multimodal and multisensory processes during autobiographical memory retrieval requires large scale coordination of a network of brain regions. Neuroimaging and lesion studies have implicated multiple brain regions in AM retrieval including prefrontal (MPFC, vMPFC, dMPFC), temporal, and parietal (PCC/RSP, pC, IPL) cortices (Cabeza & St. Jacques, 2007; Svoboda et al., 2006; Tranel & Jones, 2006; Kroll et al., 1997; Thaiss & Petrides, 2008). AM recollection incorporates both general personal (semantic) facts and context-specific (episodic) information (Tulving, 2002); however, few studies have directly compared these aspects of AM within the same study (for exceptions see Levine et al., 2004).

While the neural correlates of AM have been studied independently, recent research on the default mode network (DMN) suggests there may be a *common* network underlying various types of self-related processing (Andreasen et al., 1995; Buckner and Carroll, 2007; Northoff & Panksepp, 2008; Raichle et al., 2001). Consequently, if activity in the DMN is required for all types of self-relevant information processing, it follows that the DMN might also be required for the retrieval of knowledge about oneself, or AM. In support of this claim, Andreasen and colleagues (1995) found similar recruitment of the MPFC and precuneus (pC) (hubs of the DMN) during resting state (without an active cognitive task) and an episodic memory retrieval task. While the overlap between autobiographical memory and the DMN has been identified in functional imaging (Andreasen et al., 1995; Spreng et al., 2008), no large-scale lesion study has investigated the unique contribution of the default mode network hubs to AM retrieval.

In experiment 1a, I sought to address these unanswered questions. I performed a group-level and targeted lesion study to 1) determine whether the DMN regions are *critical* for AM retrieval, 2) examine the neural basis of the retrieval of autobiographical memories, and 3) explore the brain regions critical for semantic and episodic components of autobiographical memory. I tested subjects with stable focal brain lesions acquired prior to brain damage on the Iowa Autobiographical Memory Questionnaire (IAMQ) (Jones et al., 1998), and performed a standard voxelwise lesion-deficit analysis (Rudrauf et al., 2008). If the DMN is *critical* as a network for the retrieval of self-knowledge, then damage to the MPFC and IPL should be associated with impaired AM retrieval on the IAMQ. These results would also provide support for the hypothesized role of the DMN as a supramodal self-referential processing network. On the contrary, if one hub of the

DMN (e.g., MPFC) is critical for AM, then damage to a single hub should be associated with AM retrieval deficits. For example, damage to the MPFC might impair AM retrieval while IPL damage would not. This would suggest that the DMN is not critical for self-knowledge. Based on the hypothesized role of the DMN in AM retrieval, I predicted that damage to the MPFC and IPL (hubs of the DMN) would impair the retrieval of AM acquired prior to brain damage. The pC/PCC/RSP was not included in the above prediction as there were very few patients in the sample with lesions specific to this DMN hub region (N=2). I acknowledge the limitations in recruitment of patients with brain injury to the pc/PCC/RSP, as there are only a handful of subjects with lesions specific to this region in the Iowa Patient Registry.

2.3.2 Methods

2.3.2.1 Participants

The sample consisted of two groups: a brain damaged group (N=93), and a neurologically normal, healthy comparison group (N=34) (See Table 1 for demographic information). For the brain damaged group, 93 subjects (Mean age 53.5 ± 13.5) with stable focal brain lesions were selected from the Cognitive Neuroscience Patient Registry of the University of Iowa's Department of Neurology. Patients with various lesion etiologies were included (hemorrhage [9L/3R/5B], infarct [18L/17R/4B], surgical resection of focal lesions (tumor [3L/3R/7B], surgical treatment for epilepsy [5L/6R/4B]), and head trauma (1B). Patients were initially selected based on a group level approach with two criteria: 1) patients lesions were mapped in standard anatomical coordinates (P.C.), and 2) patients that had completed the IAMQ. To directly address

Hypothesis 1a, patients were also selected if their lesions were restricted to the DMN hubs of interest (the MPFC or IPL regions). See Figure 2 for lesion distribution.

All patients were selected using standard inclusion criteria for the Registry: stable (non-progressive), circumscribed brain lesions. All subjects were characterized neuropsychologically and neuroanatomically in the chronic epoch (> three months post onset of lesion), according to the standard protocols of the Benton Neuropsychology Laboratory (Tranel, 2007) and the Laboratory of Human Neuroanatomy and Neuroimaging (Damasio and Damasio, 1989; Damasio, 1995; Frank et al., 1997). As part of the standard protocol, I also excluded all subjects with any psychiatric disorders or other neurological illnesses.

For the healthy comparison group, data from 34 neurologically normal subjects (Mean age = 43 ± 13.5) were used; 33 of the healthy comparison subjects had participated in an earlier study (Tranel & Jones, 2006), 1 subject was tested for this dissertation.

All participants gave informed consent according to a protocol approved by the Institutional Review Board of the University of Iowa.

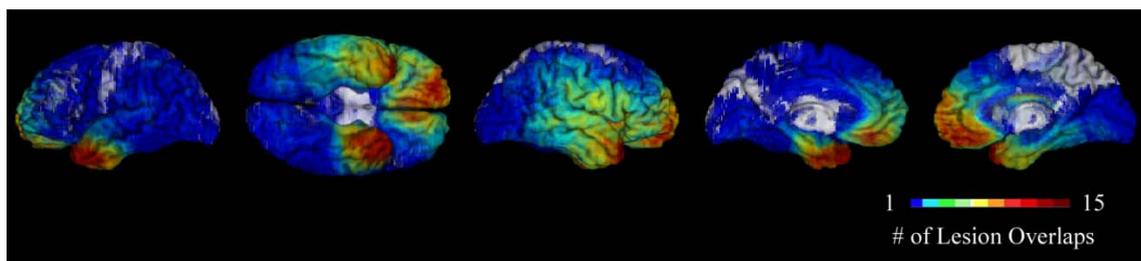
Table 1. Demographic information is reported for all subjects.

Group	Age (yrs)	Education (yrs)	Sex	Handedness	Chronicity (yrs)	Laterality
BD (N=93)	53.5 (13.5)	13.6 (2.8)	52M/41F	78R/2L/13M	9.2 (6.3)	35L/35R/23B
NC (N=34)	43.2 (13.4)	N/A	N/A	N/A	N/A	N/A

Abbreviations: BD, Brain damaged; NC, Normal comparison; Age and education are reported in group means with standard deviations in parentheses; M, Male; F, Female; R, Right handed; Handedness: L, Left handed; M, Mixed handedness; Chronicity is the time between lesion onset and experimental testing; Laterality indicates the hemispheric location of the lesion: L, Left hemisphere; R, Right hemisphere; B, Bilateral.

*Additional demographic information was not available for the healthy comparison group as the data from these subjects were collected as part of a previous study (Tranel & Jones, 2006).

Figure 2. Lesion overlap map (NMap) for all brain damaged subjects (N=93).



Overlap maps are displayed on standard reference brain (P.C.) (See *Lesion Mapping Procedures*). Images from left to right: lateral left, ventral, lateral right, midsagittal (right, left). Color code indicates total number of overlapping lesions at each voxel.

2.3.2.2 Lesion Mapping Procedures

All subjects underwent structural scanning procedures. Magnetic resonance (MR) images were acquired in a 1.5 Tesla General Electric Sigma scanner with a 3D SPGR sequence yielding 1.5 mm contiguous T1 weighted coronal cuts. If subjects were unable to undergo MR scanning, computerized axial tomography (CT) data was collected. Lesion maps were generated using the MAP-3 method (Frank et al., 1997; Fiez et al., 2000; Damasio et al., 2004), in which the boundaries of the lesions of a given subject are visually identified on MR or CT scans and manually transferred onto a normal reference brain (P.C. local standard space; resolution, 0.94 x 0.94 x 1.6 mm) based on the delineation of homologous anatomical landmarks. This procedure requires anatomical expertise but circumvents the problems of interindividual registration encountered with lesion data and the problems of combining subjects scanned with different imaging modalities. Lesion delineation and transfer were done using Brainvox (Frank et al., 1997). The general procedure is the following: (1) a normal template brain MRI scan is reconstructed in three dimensions from thin contiguous MR slices; (2) major sulci are identified and color coded in the template brain and the lesion brain; (3) the slices in the template brain are matched in orientation and thickness to those of the lesioned brain (MRI or CT) taking into consideration the intersection of the slices with the color-coded sulci; (4) the lesion contour on each slice is manually traced by an expert on the template brain (H.D.), taking into consideration the distance of the lesion contour to identifiable landmarks, such as sulci and subcortical structures, and respecting the gray and white matter components of the lesion; and (5) the collection of transferred traces defines a volume that can be saved as a binary mask of the lesion. One advantage of this time

consuming approach is that it preserves anatomical boundaries and tissue compartments in the mapping of the lesions onto the reference brain, enabling group-level analysis. Lesion overlap maps (NMaps) were created by summing the 3-dimensional MAP-3 binary lesion mask for all subjects.

2.3.2.3 Iowa Autobiographical Memory Questionnaire

All subjects completed the Iowa Autobiographical Memory Questionnaire (IAMQ) (Jones et al., 1998). The IAMQ is a comprehensive self-report inventory that assesses autobiographical memory across the life span. In particular there are five IAMQ temporal epochs including: Early Childhood and Adolescence (birth-18yr), Young Adulthood (19-39yrs), Middle Adulthood (40-59yrs), Late Adulthood (60+yrs), Recent Life (past yr). I focused on retrieval of AM related to information acquired prior to lesion onset (retrograde memory). I also subdivided the IAMQ into “semantic” and “episodic” components based upon the type of autobiographical memory required for each question (see *Memory Components* for more detail).

2.3.2.4 Behavioral Data Analysis

In order to perform the lesion analysis (Rudrauf et al., 2008), subject performance was dichotomized into two groups, impaired and unimpaired. First, I selected a unique retrieval epoch (out of the scores for the 4 retrograde time periods) for each subject based on the time before lesion onset (see *Retrieval Epoch* below). Next, I divided the composite scores (percent correct recognition/total possible) into semantic and episodic memory components (see *Memory Components* below). All scores were then Z-transformed for normalization. Subjects were defined as impaired based on comparison to the normal healthy comparison group (1.65 SD below the mean; < 5th percentile). See

Tables 5 for mean Z-scores and total numbers of impaired/unimpaired subjects in each memory type (Composite, Semantic, Episodic).

2.3.2.4.1 Retrieval Epoch

Retrograde retrieval epoch was calculated by subtracting 5 years from age of lesion onset. I then used the time period before the current time period for the resulting age (e.g. If age at lesion onset = 55; Time period = Young adulthood).

2.3.1.4.2 Memory Components

As mentioned above, I decomposed the IAMQ into “semantic” (e.g. What was your street address in high school?) and “episodic” (e.g. Recall an incident when you were in high school.) aspects.

2.3.2.5 Neuropsychological Variables

All patients were tested on various neuropsychological measures including: intelligence (Wechsler Adult Intelligence Scale – III: Verbal IQ), general and working memory (Wechsler Memory Scale – III; General Memory Index, Working Memory Index), verbal memory (Rey Auditory – Verbal Learning Test; Trial 5 and 30-minute delayed recall), visuospatial memory (Complex Figure Test; 30-minute delayed recall), language (Token Test from the Multilingual Aphasia Examination), reading ability (Wide Range Achievement Test – Revised: Reading Standard Score) and general mood (Beck Depression Inventory – II). These neuropsychological variables were measured to investigate potential group differences in intelligence, general memory, language, reading ability, or mood (see Tables 2 – 4) that account for differences in autobiographical memory retrieval scores.

Table 2. Demographic and neuropsychological variables reported for composite memory groups.

	Unimpaired Composite AM (N=63)	Impaired Composite AM (N=30)
Age (yrs)	50.8 (13.7)	59.2 (11.1)
Education (yrs)	14.2 (2.8)	12.2 (2.5)*
Sex	38M / 25F	14M / 16F
Handedness	55R / 1L / 7M	23R / 1L / 6M
Chronicity (yrs)	10.1 (6.1)	7.3 (6.5)
Laterality	17B / 17L / 29R	6B / 18L / 6R
WAIS – III: VIQ	106.1 (16.4)	94.5 (12.5)
WMS – III: GMI	103.0 (17.1)	85.7 (13.8)
WMS – III: WMI	101.5 (13.1)	100.5 (14.9)
Rey AVLT: T5/30 recall	11.7(2.6) / 9.3(3.9)	10.1(3.3) / 8.0(3.8)
CFT: 30 recall	19.1 (6.3)	14.9 (7.6)
Token Test	42.7 (4.3)	42.1 (2.3)
WRAT-R: Reading SS	101.7 (13.7)	92.8 (10.4)
BDI - II	6.2 (5.3)	6.6 (5.1)

Abbreviations: Number of subjects (N); Autobiographical Memory (AM); Wechsler Adult Intelligence Scale – III Verbal IQ (WAIS-III VIQ); Wechsler Memory Scale – III: General Memory Index (WMS-III GMI); Wechsler Memory Scale – III: Working Memory Index (WAIS-III WMI); Rey Auditory-Verbal Learning Test: Trial 5/30-min recall (Rey AVLT: T5/30 recall); Complex Figure Test: 30-min recall (CFT: 30 recall); Wide Range Achievement Test – Revised: Reading Standard Score (WRAT-R: Reading SS); Beck Depression Inventory (BDI - II).

Note: Means and standard deviations (SD) are reported based on analysis of composite retrograde memory scores. Specifically, patients were classified as impaired in composite AM based on reference to a healthy comparison group (<1.65 SD below the mean). Mann-Whitney U test, *significant at $p < 0.05$, two-tailed, Bonferroni's corrected for multiple comparisons, $p = 0.002$.

Table 3. Demographic and neuropsychological variables reported for semantic memory groups.

	Unimpaired Semantic AM (N=62)	Impaired Semantic AM (N=31)
Age (yrs)	51.0 (13.8)	58.5 (11.4)
Education (yrs)	14.1 (3.0)	12.5 (2.2)
Sex	38M / 24F	14M / 17F
Handedness	54R / 1L / 7M	24R / 1L / 6M
Chronicity (yrs)	10.4 (6.6)	6.9 (5.1)
Laterality	16B / 20L / 26R	7B / 15L / 9R
WAIS – III: VIQ	106.9 (16.2)	93.9 (12.5)
WMS – III: GMI	103.5 (15.7)	89.1 (18.8)
WMS – III: WMI	102.2 (13.5)	99.4 (13.3)
Rey-AVLT: T5/30 recall	11.7 (2.6) / 9.6 (3.8)	10.1 (3.2) / 7.6 (3.8)
CFT: 30 recall	19.2 (6.5)	14.8 (7.0)*
Token Test	42.4 (4.4)	42.5 (2.1)
WRAT-R: Reading SS	101.0 (14.6)	95.0 (9.4)
BDI - II	6.6 (5.6)	5.7 (4.3)

Abbreviations: Number of subjects (N); Autobiographical Memory (AM); Wechsler Adult Intelligence Scale – III Verbal IQ (WAIS-III VIQ); Wechsler Memory Scale – III: General Memory Index (WMS-III GMI); Wechsler Memory Scale – III: Working Memory Index (WMS-III WMI); Rey Auditory-Verbal Learning Test: Trial 5/30-min recall (Rey AVLT: T5/30 recall); Complex Figure Test: 30-min recall (CFT: 30 recall); Wide Range Achievement Test – Revised: Reading Standard Score (WRAT-R: Reading SS); Beck Depression Inventory (BDI - II).

Note: Means and standard deviations (SD) are reported based on analysis of semantic retrograde memory scores. Specifically, patients were classified as impaired in semantic AM based on reference to a healthy comparison group (<1.65 SD below the mean). Mann-Whitney U test, *significant at $p < 0.05$, two-tailed, Bonferroni's corrected for multiple comparisons, $p = 0.002$.

Table 4. Demographic and neuropsychological variables reported for episodic memory groups.

	Unimpaired Episodic AM (N=82)	Impaired Episodic AM (N=11)
Age (yrs)	53.4 (13.6)	54.2 (12.8)
Education (yrs)	13.8 (2.8)	11.8 (2.1)
Sex	47M / 35F	5M / 6F
Handedness	69R / 1L / 12M	9R / 1L / 1M
Chronicity (yrs)	9.0 (6.2)	10.6 (7.5)
Laterality	20B / 29L / 33R	3B / 6L / 2R
WAIS – III: VIQ	103.5 (15.2)	99.5 (22.9)
WMS – III: GMI	97.8 (17.4)	109.0 (20.2)
WMS – III: WMI	101.4 (13.5)	100.6 (13.7)
Rey AVLT: T5/30 recall	11.1 (3.0) / 8.8 (4.0)	11.4 (2.5) / 9.5 (2.6)
CFT: 30 recall	17.8 (6.9)	18.1 (7.6)
Token Test	42.6 (4.0)	41.6 (2.3)
WRAT-R: Reading SS	99.8 (13.4)	92.9 (12.9)
BDI - II	6.1 (5.0)	7.6 (6.7)

Abbreviations: Number of subjects (N); Autobiographical Memory (AM); Wechsler Adult Intelligence Scale – III Verbal IQ (WAIS-III VIQ); Wechsler Memory Scale – III: General Memory Index (WMS-III GMI); Wechsler Memory Scale – III: Working Memory Index (WMS-III WMI); Rey Auditory-Verbal Learning Test: Trial 5/30-min recall (Rey AVLT: T5/30 recall); Complex Figure Test: 30-min recall (CFT: 30 recall); Wide Range Achievement Test – Revised: Reading Standard Score (WRAT-R: Reading SS); Beck Depression Inventory (BDI - II).

Note: Means and standard deviations (SD) are reported based on analysis of episodic retrograde memory scores. Specifically, patients were classified as impaired in episodic AM based on reference to a healthy comparison group (<1.65 SD below the mean). There were no significant differences between groups. Mann-Whitney U test, two-tailed, Bonferroni's corrected for multiple comparisons, $p = 0.002$.

2.3.2.6 *Voxelwise Proportional MAP3 (PM3) Lesion-Deficit Analysis*

Lesion-deficit relationships and statistical power were estimated using voxelwise proportional difference maps (PM3) (Rudrauf et al, 2008). PM3 expresses, for every voxel, the proportion of subjects whose lesion includes the voxel and who have a deficit (MLD) relative to the total number of subjects with a deficit (ND), minus the proportion of subjects with a lesion at the voxel and no deficit (MLnD) relative to the total number of subjects with no deficit (NnD). The formula can be expressed with the equation $\text{Prob}(L | D) - \text{Prob}(L | nD)$, the conditional probability of a lesion (L) given a deficit (D) minus the conditional probability of a lesion given no deficit (nD). For example, at a given voxel, if all patients with a lesion have a deficit, the $\text{PM3} = 1$, whereas $\text{PM3} = 0$ when half the patients have a lesion and a deficit, and the remainder have a lesion and no deficit. The PM3 maps were thresholded using exact statistics from permutation tests (Rudrauf et al., 2008). The statistical thresholds for the PM3 analysis were determined based on preliminary power analyses, i.e., “effective coverage maps” (ECMs) (Rudrauf et al., 2008). Effective coverage is defined as the voxel map in which effects can be detected at a given significance threshold, assuming there is the maximal lesion – deficit relationship permitted by the sample. A satisfactory effective coverage implies the ability to detect effects over a large percentage of the brain, especially within regions for which hypotheses have been formulated. I selected the one-tailed, uncorrected threshold of $p < 0.05$ as the main threshold for the PM3 analysis. *Note: the lesion-deficit results from the PM3 analysis were not corrected for multiple comparisons.

2.3.3 Results (1a)

2.3.3.1 Behavioral Results

As mentioned above, subjects were dichotomized for lesion-deficit analysis into impaired and unimpaired groups for each of the AM components (*composite*, *semantic*, *episodic*) (See Table 5 for Ns, and average memory scores). For each memory type, “impaired” groups had mean AM scores that were significantly lower than “unimpaired” groups (Mann-Whitney U test, each $p < 0.001$).

There were no significant differences between *episodic* AM groups for any demographic or neuropsychological variables (Mann-Whitney U Test, $P > 0.05$). However, there were significant differences between *composite* AM groups for education (Mann-Whitney U Test, $p = 0.002$), and between *semantic* AM groups for the Complex Figure Test 30-minute recall (Mann-Whitney U Test, $p = 0.002$) (See Table 2-3). Importantly, after controlling for these variables in a follow-up analysis, significant differences between “impaired” and “unimpaired” groups remained for both *composite* and *semantic* AM (ANOVA, each $p < 0.001$).

Table 5. Z-transformed scores reported.

Group	N	Composite AM Score	Semantic AM Score	Episodic AM Score
Unimpaired Composite	63	0.1 (0.8)	-0.0 (0.8)	0.1 (1.0)
Impaired Composite	3	-3.1 (1.2)	-3.4 (1.9)	-1.0 (1.2)
Unimpaired Semantic	62	0.1 (0.8)	0.1 (0.7)	-0.0 (1.2)
Impaired Semantic	31	-2.9 (1.3)	-3.4 (1.7)	-0.6 (1.1)
Unimpaired Episodic	82	-0.8 (1.8)	-1.1 (2.1)	0.1 (0.9)
Impaired Episodic	11	-1.6 (1.3)	-0.7 (1.5)	-2.4 (0.5)
NC	34	0.0 (1.0)	0.0 (1.0)	0.0 (1.0)

Abbreviations: Number of subjects (N), Autobiographical Memory (AM), Normal Comparison (NC).

*Means and standard deviations for the Z-transformed AM scores are reported for all memory types (Composite, Semantic, and Episodic).

2.3.3.2 Lesion-Deficit Analysis Results

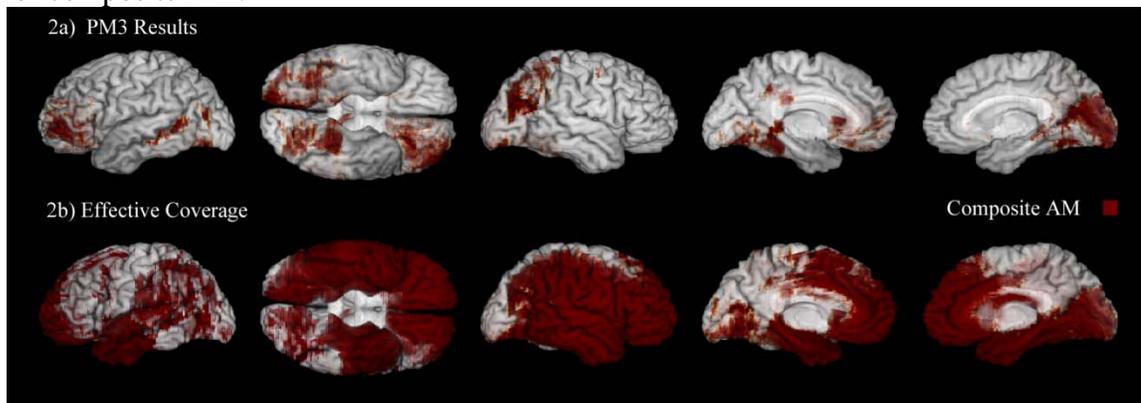
In support of hypothesis 1a, deficits in composite retrograde AM were significantly associated with damage to the MPFC and IPL (Figure 3). Effects were present in portions of the left MPFC, including the ventromedial prefrontal cortices (vMPFC) and extending to frontopolar regions. While prefrontal effects were primarily localized in the left hemisphere, a few significant voxels were found in the right posterior orbitofrontal cortices. The IPL was implicated in the right hemisphere only. While no hypotheses were made for the pC/PCC/RSP hub of the DMN (due to lower numbers of subjects with lesions specific to this region), significant effects were found in regions of the PCC and RSP in the left hemisphere. The pC was not implicated in either hemisphere.

Besides the hubs of the DMN, damage to temporal, parietal, and occipital regions was also associated impaired composite retrograde AM. Significant effects in superior lateral parietal and occipital cortices were present in the right hemisphere. Effects were also found bilaterally in the ventral temporal and occipital regions including the fusiform gyrus. In the left hemisphere, effects were found along the superior temporal sulcus.

When breaking down the IAMQ into semantic and episodic components, distinct ventral and dorsal prefrontal regions were implicated (Figure 4). For semantic memory, MPFC effects were similar to those for composite memory, including left vMPFC and frontopolar regions. Whereas for episodic memory, significant effects were found in primarily right dorsal MPFC and anterior cingulate (ACC) regions, encompassing Brodmann areas 8, 9, and 32. Both episodic and semantic memory AM deficits were associated with damage to the right IPL, with more extensive effects for episodic AM. Significant effects for episodic AM were also present in the PCC bilaterally, and effects extended to include portions of the retrosplenial cortex (RSP). There were also significant effects for episodic AM extending along right mesial temporal regions (parahippocampal and hippocampal cortices).

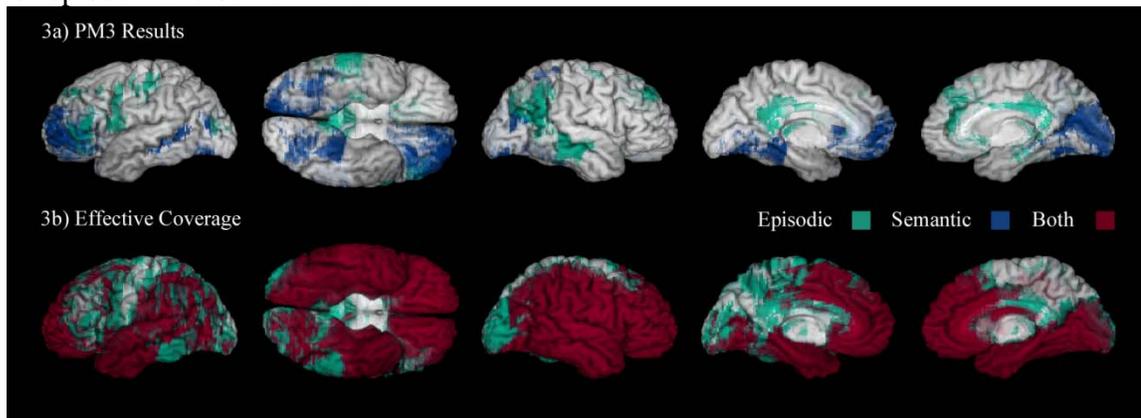
Semantic memory deficits were also associated with damage to the ventral temporal and occipital cortices bilaterally (including the fusiform gyrus), right superior parietal, parahippocampal gyrus, and primary visual cortices. Analyses for episodic memory implicated the left inferior frontal gyrus, primary motor and premotor cortex, and the right superior parietal cortices and inferior temporal gyrus. Effective coverage for all conditions was sufficient in both hemispheres in these PF regions, as well as in the posterior parietal regions (IPL and SPL) (Figure 2 and Figure 3).

Figure 3. Lesion proportion difference maps (PM3) and effective coverage maps (ECM) for composite AM.



2a) Thresholded PM3 results for composite AM (red indicates lesion-deficit effects significant at $p < 0.05$, uncorrected). 2b) Effective coverage map (red indicates effective coverage at $p < 0.05$). PM3 maps are displayed on standard reference brain (P.C.). Images for each row (2a and 2b) appear as follows: left lateral, ventral, right lateral, midsagittal (left, right).

Figure 4. Lesion proportion difference maps (PM3) and effective coverage maps (ECM) for episodic and semantic AM.



3a) Thresholded PM3 results for episodic and semantic AM are represented on the same brain (Color codes: GREEN = episodic AM, BLUE = semantic AM, RED = both; effects for both memory types are significant at $p < 0.05$, uncorrected). 3b) Effective coverage map (Color codes: GREEN = effective coverage based on episodic AM; BLUE = effective coverage based on semantic AM; RED = effective coverage for episodic and semantic; ECM maps are significant at $p < 0.05$). PM3 maps are displayed on standard reference brain (P.C.). Images for each row (3a and 3b) appear as follows: left lateral, ventral, right lateral, midsagittal (left, right).

2.3.4 Discussion (1a)

These findings support the hypothesis that the DMN is *critical* as a network for the retrieval of autobiographical memory (Hypothesis 1a), since damage to the MPFC and IPL hubs were associated with deficits in AM retrieval. These results are convergent with recent functional imaging literature on the default network (Raichle et al., 2001; Greicius et al., 2003) and its implication in AM (Andreasen et al., 1995; Buckner et al., 2008; Spreng et al., 2008). Consistent with theoretical and neuroanatomical distinctions between episodic and semantic AM (Tulving, 1983; 2005), the findings also suggest that AM relies on distinct prefrontal components, depending upon declarative type (semantic vs episodic). Whereas semantic memory retrieval deficits were associated with damage to ventromedial regions of the MPFC, episodic retrieval impairments were associated with more dorsal MPFC lesions.

While brain damage to the DMN hubs (MPFC, IPL, and PCC/Rsp) was significantly associated with impairments in AM retrieval, effects were also found in other brain regions (e.g., superior temporal cortices, occipital cortex). Intriguingly, a significant proportion of these regions (i.e., parahippocampal gyrus [PHG], lateral superior temporal cortices [LTC]) have also been identified as structures belonging to the DMN (Buckner et al., 2008). This suggests that AM retrieval could require a more extended DMN (beyond the hubs), including the PHG and LTC. Notably, this would be consistent with the core AM network identified in a meta-analysis of 24 functional imaging studies of AM (Svoboda et al., 2006). However, there were still some effects present in regions outside the DMN, such as those in ventral temporo-occipital cortices.

Taken together, the present results provide support for the hypothesis that DMN is critical for autobiographical memory retrieval.

Despite the fact that temporal polar (TP) cortices have been consistently implicated in a number of functional imaging and lesion studies of AM (e.g., Svoboda et al., 2006; Maguire, 2001; Wheeler and McMillan, 2001) there were no significant effects present in the TP for semantic, episodic, or composite AM measures. In order to explore this further, I selected from the total sample (N=93) all patients with lesions to the temporal lobe (TL) (N=46). I also subdivided the TL patients into impaired (N=18) and unimpaired (N=28) groups based on their IAMQ scores (semantic, episodic, and composite). Interestingly, the maximum lesion overlap for both impaired and unimpaired groups was found in temporal polar cortices. Thus, it is possible that TP regions were not implicated in the current study because of the greater proportion of unimpaired subjects that had TP lesions. Differences in lesion etiology and age at onset could partially explain these effects. For example, in the case of patients who underwent temporal lobectomies to treat epilepsy, considerable reorganization could have occurred as a result of a long standing seizure disorder. Thus, AM retrieval could be performed by other brain regions in these patients. Alternatively, it could be the case that patients in the unimpaired group with TP lesions had AM scores that were just below the cutoff for impairment. In this way, patients could have been classified as unimpaired despite having some difficulties in AM retrieval. In support of this claim, one subject with a lesion to the TP in the right hemisphere had an episodic AM retrieval score just above the cutoff (-1.5).

There are some limitations to this study that should be considered, both in terms of the IAMQ and the lesion distribution in the sample. First, the IAMQ was not originally

designed to measure episodic and semantic AM separately. Therefore, the total number of episodic and semantic AM questions was not equivalent; there were more semantic questions. This was reflected in the PM3 results (See Figures 3 and 4), as the lesion-deficit effects for the composite and semantic AM were almost identical. While not the primary focus of the present experiment, future lesion studies could investigate potential neuroanatomical dissociations between episodic and semantic AM (e.g., effects of laterality for semantic vs episodic AM) by using tasks designed to assess episodic and semantic AM independently. Second, the lesion-deficit effects found in the PCC and Rsp should be interpreted with caution. These effects were the result of 1 subject with a bilateral lesion to the PCC and extending to the Rsp, who had a significant impairment in episodic AM (-1.9). As noted in the introduction, there are few patients in the Iowa Patient Registry with lesions to the pC/PCC/Rsp. This is primarily because the PCC/Rsp is a region that is rarely damaged in stroke, as it is located in a watershed region with tributaries from the middle cerebral artery and posterior cerebral artery. The cases that are in the registry (N = 2) are lesions that were caused by tumor resections. Thus, it might be possible to test the role of the pC/PCC/Rsp in AM and other self-related processes by recruiting individuals with tumors resections to this region.

The findings from this study (1a) provide some evidence for the crucial role of the DMN in AM retrieval of past memories, a type of self-referential processing. However, this does not directly address whether the DMN is necessary for various types of self-referential processing across modalities. Therefore, under Experiment 1b, I examined whether the DMN is critical for the encoding and retrieval of self-relevant information (self-knowledge).

2.4 Experiment 1b: DMN and the Self-Reference Effect

2.4.1 Introduction (1b)

When individuals contemplate information in relation to themselves, e.g., daydream about future successes or reflect on a negative event that transpired at work, they engage a cognitive process of self-reference. Several psychological studies suggest that the process of self-reference, associated with the building of a self-concept, is valuable and may be evolutionarily adaptive. Self-reference plays a role in the consolidation of memory (Rogers et al., 1977), the perception of social cues (Lombardo et al., 2010; Eisenberger & Lieberman, 2004), and is more generally integral to emotional control, reappraisal, and effective psychotherapeutic interventions (Mansell, 2010). The ability to evaluate whether information is self-relevant is especially crucial in the social realm where deficiencies can have significant consequences for normal social interaction. For example, individuals with autism have a variety of self-referential processing deficits (i.e., self-other distinctions) that are thought to contribute to impairments in interpersonal functioning (Lombardo et al., 2010).

Neuroimaging research has implicated a network of brain regions, including the medial prefrontal cortex (MPFC), posterior cingulate (PCC), precuneus (pC), and the inferior parietal lobule (IPL) across a variety of self-referential processing paradigms from tasks engaging mind wandering to tasks requiring personality trait evaluation (Christoff et al., 2009; Kelley et al., 2002; Mason et al., 2007; Moran et al., 2006; Northoff et al., 2006; Schmitz et al., 2004). These same brain regions comprise the central hubs of the default mode network (DMN), a network (as described in section 1.3

of Chapter 1) which has been associated with similar self-related processes (i.e., mind wandering, autobiographical memory retrieval) (Andreasen et al., 1995; Christoff et al., 2009; Buckner et al., 2008; Gusnard et al., 2001; Spreng et al., 2008). Together, this apparent functional overlap between self processing and DM networks has led researchers to speculate that the DMN may constitute the neural basis for self (e.g., Gusnard et al., 2001; Gusnard, 2005; Lou et al., 2010; Schilbach et al., 2008; Wicker et al., 2003; see Legrand & Ruby, 2009 for an alternative hypothesis). For example, Gusnard et al. (2001) found that increased activity in the dorsal MPFC when subjects were contemplating how pictures made them feel versus evaluating the superficial qualities of the picture (e.g., was it taken indoors). This was interpreted as evidence that the MPFC, as part of the DMN, is involved in internally directed thought processes. More recently, converging functional imaging research has found activity in the hubs of the DMN during mind wandering (e.g., Mason et al., 2007; Christoff et al., 2009; Andrew-Hanna et al., 2010). Together, these findings have provided further support for the role of the DMN in self-referential processing.

Self-referential processing confers a special memory advantage, a phenomenon known as the self-reference effect (SRE) (Symons and Johnson, 1997). For example, personality traits processed for self-relevance—i.e., in relation to oneself (e.g., “Am I a generous person?”) are better remembered than traits processed for other-relevance (e.g., “Is Sally a generous person?”) (Rogers et al., 1977). Neuroimaging research has shown that the MPFC is active during this type of self-referential processing, viz., judging personality traits (Kelley et al., 2002; Macrae et al., 2004; Schmitz et al., 2004). Moreover, MPFC activity is parametrically modulated by self-relevance (Moran et al.,

2006), and its activity is predictive of subsequent memory for self-relevant traits (Macrae et al., 2004). Together, these findings have led to the hypothesis that the MPFC might play a critical role in the representation of self-relevance (Schmitz and Johnson, 2007; Northoff and Panksepp, 2008).

Although research on the SRE has consistently implicated the MPFC in self-specific processing, the PCC and IPL also appear to be involved (e.g., Lou et al., 2004; 2010). In fact, recent research using transcranial magnetic stimulation (TMS) suggests that the IPL, but not the MPFC, may be important for self-referential processing and the SRE. In a study by Lou et al. (2010), single-pulse TMS applied to the IPL during a trait judgment task was found to suppress the SRE. By contrast, TMS targeting the MPFC did not result in similar SRE disruption. However, there were some notable methodological limitations to this study. Specifically, the MPFC regions are difficult to target using TMS, and a subset of subjects asked to discontinue the TMS to this region due to considerable discomfort (Lou et al., 2010). Therefore, the necessary contribution of the MPFC to the SRE is still unclear.

While previous work has established a correlation between self-referential processing and the hubs of the DMN (MPFC, IPL), it remains an open question whether the DMN hubs are *critical* for such processing. In regard to the self-reference effect (SRE) in particular, I predicted that if the DMN as a network is critical for this effect, then patients with MPFC and IPL damage should fail to show it. Alternatively, if the DMN as a network is not necessary for the SRE, then damage to the MPFC and/or IPL may not disrupt the effect (Hypothesis 1b). I tested these predictions in the current study (Experiment 1b).

2.4.2 Methods (1b)

2.4.2.1 Participants (1b)

Medial Prefrontal Cortex (MPFC) group: Thirteen patients with lesions to the MPFC (11 bilateral, 2 unilateral right) were selected from the Cognitive Neuroscience Patient Registry of the University of Iowa's Department of Neurology (see Table 6 for demographic information for all participant groups). Patient groups were defined based on functional neuroanatomical criteria. Specifically, the MPFC group was chosen based on a previous study using a similar version of the self-referential processing task used in this study (Kelley et al., 2002). In the previous study, functional imaging results revealed activity in the medial prefrontal cortex (MPFC) in the right hemisphere with Montreal Neurological Institute (MNI) coordinates ($x = 10, y = 52, z = 2$) (putatively corresponding to Brodmann's area 10). Note: 1 of the patients in the MPFC group was not mapped. The patient had a bilateral MPFC lesion, and their MRI scan was visually inspected to verify that their lesion overlapped with this right MPFC region of interest (ROI). All remaining 12 mapped subjects included in the MPFC group had lesions that overlapped with this right MPFC ROI (See Figure 5).

Inferior Parietal Lobule (IPL) group: Eight patients with brain injury (3 left, 5 right) were selected from the Cognitive Neuroscience Patient Registry of the University of Iowa's Department of Neurology. All patients in the IPL group had lesions that encompassed the angular gyrus (see Figure 6 for the lesion overlap maps for all patient groups).

Brain Damaged Comparison (BDC) group: Ten patients with brain damage were selected; their lesions involved cortices outside of the putative self-referential processing

networks, e.g., Default Mode Network or Cortical Midline Structures (Buckner et al., 2008; Northoff et al., 2006). The BDC group was chosen to match the MPFC group on average age and education. The lesions were bilateral in 4 cases (with damage primarily to medial and lateral occipital, temporal, and parietal regions) and unilateral in 6 cases (with damage to medial and lateral occipital, temporal and insular regions).

General Inclusion Criteria: The inclusion criteria were the same as those described in Experiment 1a under section 2.3.2.1.

Detailed neuroanatomical description of MPFC group: The functional imaging literature (e.g. Kelley et al., 2002) has revealed an anatomo-functional entity that corresponds broadly to the MPFC as a topographic ensemble (that is both ventral "V" and dorsal "D" components of the medial prefrontal cortex). Accordingly, the patients selected for this dissertation had damage that encompassed MPFC (see Figure 5). Many of these patients have damage that extends into the ventromedial prefrontal cortex (VMPFC). Notably, the ROI from Kelley et al. (2002) (see Figure 5) is really at the boundary between VMPFC and DMPFC, in a location maximally covered by the sample. Thus the MPFC patient sample was appropriate for testing the hypothesis derived from the functional imaging literature—and the fact that the maximal overlap in the MPFC lesions was centered right on the coordinates published by Kelley et al. (2002) provides definitive support for this claim.

Healthy Comparison (NC) group: 15 healthy adults with no history of psychiatric or neurological illnesses were studied. Subjects were recruited from the Registry of healthy subjects in the Department of Neurology (Table 6).

All participants gave informed consent according to a protocol approved by the Institutional Review Board of the University of Iowa.

Table 6. Demographic and neuropsychological variables for all groups.

	MPFC (N=13)	IPL (N=8)	BDC (N=10)	NC * (N=12)
Age (yrs)	63.1 (9.8)	60.6 (10.0)	59.2 (14.3)	70.1 (10.8)
Education (yrs)	13.5 (2.3)	13.0 (2.3)	16.4 (2.3)	15.5 (3.0)
Sex	6M/7F	6M/2F	5M/5F	7M/5F
Handedness	11R/1L/ 1M	7R/0L/ 1M	10R/0L/ 0M	12R/0L/ 0M
Chronicity (yrs)	14.4 (8.4)	16.0 (10.6)	11.6 (5.7)	N/A
Laterality	11B/0L/ 2R	0B/3L/ 5R	4B/5L/ 1R	N/A
WAIS – III: VIQ	105.6 (15.0)	93.2 (11.0)	113.1 (10.6)	118.8* (12.2)
WMS – III: GMI	106.5 (14.3)	99.1 (19.0)	103.1 (15.0)	N/A
WMS – III: WMI	106.4 (14.5)	92.2 (15.7)	103.7 (13.8)	110.4 (6.7)
Rey AVLT: T5/30 recall	11.2(2.6) /8.7 (2.8)	12.3(2.1) /10.7(3.0)	12.2(2.3) /8.0(3.7)	13.2(1.4)/ 9.7(3.3)
CFT: 30 recall	19.9 (6.5)	20.7 (7.4)	16.3 (6.5)	21.1 (5.3)
Token Test	43.8 (0.4)	41.3 (3.7)	41.9 (3.0)	N/A
WRAT-R: Reading SS	100.5 (9.9)	99.6 (18.2)	105.8 (9.7)	N/A
BDI - II	4.6 (4.5)	7.4 (6.3)	5.8 (5.4)	3.1 (3.1)

Abbreviations: Group; Number of subjects (N), Medial Prefrontal Cortex

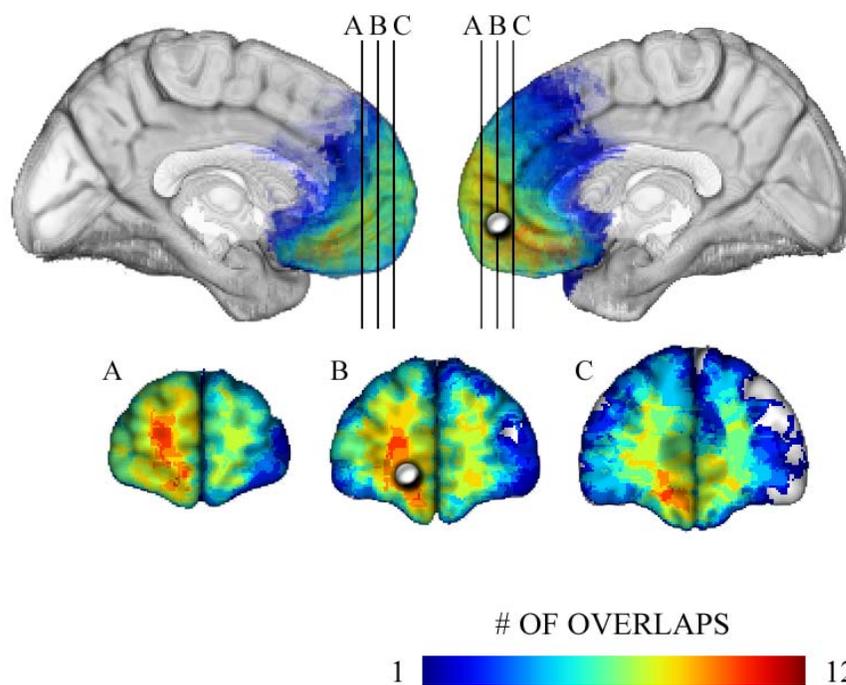
Table 6 – Continued

(MPFC), Inferior Parietal Lobule (IPL), Brain Damaged Comparison (BDC), Normal Comparison (NC); Sex; Male (M); Female (F); Handedness; Right (R); Left (L); Mixed, (M); Chronicity is the time between lesion onset and experimental testing; Laterality indicates the hemispheric location of the lesion: Left hemisphere (L); Right hemisphere (R); Bilateral (B); Wechsler Adult Intelligence Scale – III Verbal IQ (WAIS-III VIQ); Wechsler Memory Scale – III: General Memory Index (WMS-III GMI); Wechsler Memory Scale – III: Working Memory Index (WAIS-III WMI); Rey Auditory-Verbal Learning Test: Trial 5/30-min recall (Rey AVLT: T5/30 recall); Complex Figure Test: 30-min recall (CFT: 30 recall); Wide Range Achievement Test – Revised: Reading Standard Score (WRAT-R: Reading SS); Beck Depression Inventory (BDI - II).

Note: Means and standard deviations in parentheses are provided. Lesion specific measures are only reported for the patient groups (laterality, chronicity). There were no significant differences between groups for education, chronicity, or most of the neuropsychological measures (ANOVA, Bonferroni corrected significance level of $p = 0.005$). However, there was a significant difference between groups for WAIS-III Verbal IQ ($p < 0.005$; see [2.4.3 Results](#)).

*Neuropsychological measures were unavailable for 3 participants of the 15 participants in the NC group. Means and standard deviations are reported for the remaining subjects ($N = 12$).

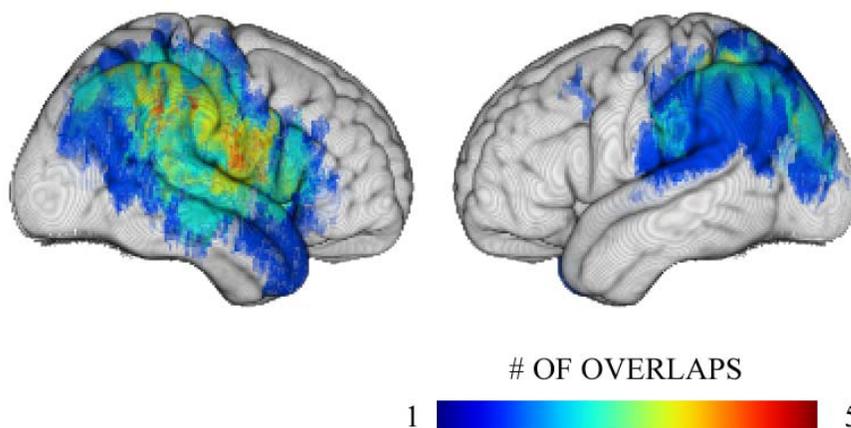
Figure 5. Lesion overlap map (NMap) for the MPFC group.



Note: Lesion overlap map for the MPFC group (*N = 12), displayed on the Montreal Neurological Institute template (MNI-152). The maximum overlap is 12 (see color scale). Midsagittal views are presented for both hemispheres. Coronal slices are in radiologic convention (left on the right). A gray dot is plotted in the right hemisphere at the location of the ROI from Kelley et al. (2002) where neural activity was associated with encoding during *self* trials ($x = 10, y = 52, z = 2$). The ROI overlies the region of maximum lesion overlap for the MPFC group.

*Note: One subject in the MPFC group (out of 13) was not included as the lesion map was unavailable (See Methods section 2.4.2.1).

Figure 6. Lesion overlap map (NMap) for the IPL group.



Note: Lesion overlap map for the IPL group ($N = 8$) is displayed on the Montreal Neurological Institute template (MNI-152). The maximum overlap is 5 (see color scale). Lateral views are presented for both hemispheres. All subjects in the IPL group had lesions that encompassed the angular gyrus (either in the right or left hemisphere).

2.4.2.2 Personality Trait Judgment Paradigm (SRE Task) Procedure

A set of 270 trait adjectives (normed from Anderson, 1968) were selected and counterbalanced for syllable number, word length, and valence (135 negative traits, 135 positive traits). I used a slightly modified version of the trait judgment task used in Kelley et al. (2002) (e.g., changed the person used for the other condition). There were three different conditions in which participants were asked to make trait judgments: 1) *self* (e.g. Does this trait describe you?), 2) *other* (e.g. Does this trait describe Oprah Winfrey?), and 3) *case* (e.g. Is this trait capitalized?). On each trial, a fixation cross was presented for 500 ms followed by simultaneous presentation of a cue denoting the condition (e.g., *self*) and a trait adjective. Subjects made yes/no responses for each trial. Response time was not collected as reaction times in brain damaged participants tend to be highly variable and not reliably informative. Detailed instructions and practice blocks were given before

the experimental task in order to assure that the subjects understood and were comfortable with the task. Two blocks consisting of 45 trials each (15 *self*, 15 *other*, 15 *case*) were given. The order of the trials was randomized, and the traits adjectives for each condition were counterbalanced. To assess the self-reference effect, subjects performed an unexpected recognition memory task completed after a 15-minute retention interval. In the recognition task, subjects were presented with 180 trait adjectives including 90 “old” (from the encoding trials) and 90 “new” traits. A fixation was presented before each word for 500 ms. Next, subjects were presented with the trait adjectives, one at a time, for 2000 ms each. Subjects were instructed to make “yes” or “no” responses based on whether they remembered the word from before.

2.4.2.3 Lesion Mapping Procedures

The lesion mapping procedures were the same as those described in Experiment 1a under section 2.3.2.2. In addition, in order to display the lesion maps in Montreal Neurological Institute (MNI) space, linear warping algorithms were used to transfer the lesion masks for all subjects from the P.C. space (standard for the MAP3 method) to standard MNI space (MNI-152).

2.4.2.4 Neuropsychological Variables

Neuropsychological measures were the same as those described in Experiment 1a under section 2.3.2.5. Note, there was complete neuropsychological data available for all patient groups. However, for the NC group neuropsychological measures were only available for 12 out of the 15 subjects (Table 6).

2.4.3 Results (1b)

2.4.3.1 SRE Analysis

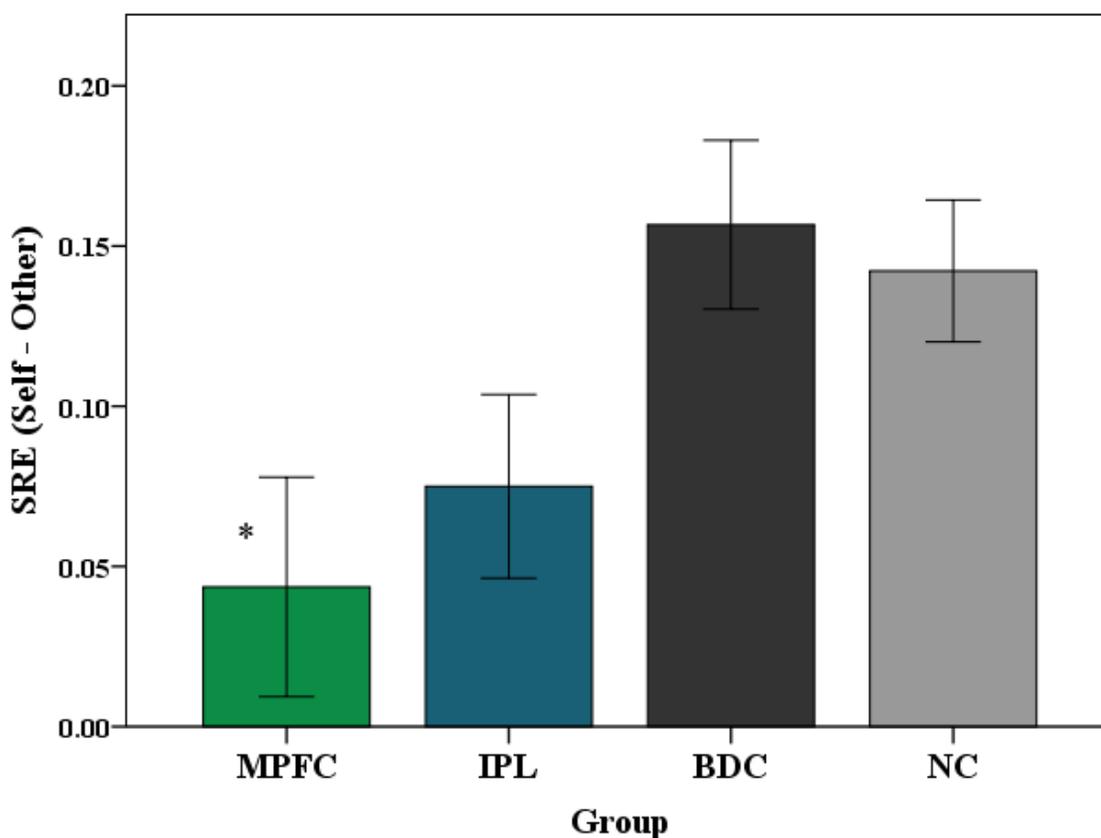
In support of the main prediction (Hypothesis 1b), there was a significant effect of Group for the SRE ($F_{3,44} = 3.68$, $p < 0.05$, $r = .46$). *Post hoc* analyses revealed that the MPFC group showed a significantly lower SRE than both the BDC ($U = 26.5$, $p < 0.01$, $r = -0.50$, 1-tailed) and NC ($U = 48.5$, $p < .05$, $r = -0.43$, 1-tailed) groups (Figure 7). These effects could be specifically attributed to recognition deficits in the *self* condition for the MPFC group (MPFC $M = 0.16$; IPL $M = 0.32$; BDC $M = 0.33$; NC $M = 0.30$), as recognition performance was approximately equivalent as compared with BDC and NC control groups in both *other* (MPFC $M = 0.12$; BDC $M = 0.17$; NC $M = 0.16$) and *case* (MPFC $M = 0.01$; BDC $M = -0.02$; NC $M = 0.04$) conditions (Figure 8). In fact, the SRE was virtually abolished in the MPFC group, as the patients recognized virtually the same numbers of traits for the *self* versus *other* conditions.

Similar to the MPFC group, the IPL group appeared to have a lower SRE ($M = .07$) than the BDC ($M = .16$) and NC ($M = .14$) groups (Figure 7). Intriguingly, in contrast to the MPFC group, the lower SRE for the IPL group could be attributed to a greater recognition of traits in the *other* condition (IPL $M = 0.25$; MPFC $M = 0.11$; BDC $M = 0.16$; NC $M = 0.14$) (Figure 8). However, despite having a lower mean SRE, there was only a trend toward a significant difference between the IPL group as compared with either control groups (BDC, $U = 25$, $r = -0.32$; NC, $U = 38$, $r = -0.30$; each $p = 0.08$, 1-tailed).

There were no significant group differences in demographic variables (age, education, or chronicity; Bonferroni corrected significance level of $p = 0.005$) that could have accounted for these results. While there were no differences in the majority of neuropsychological factors such as general memory, language, and mood (Bonferroni

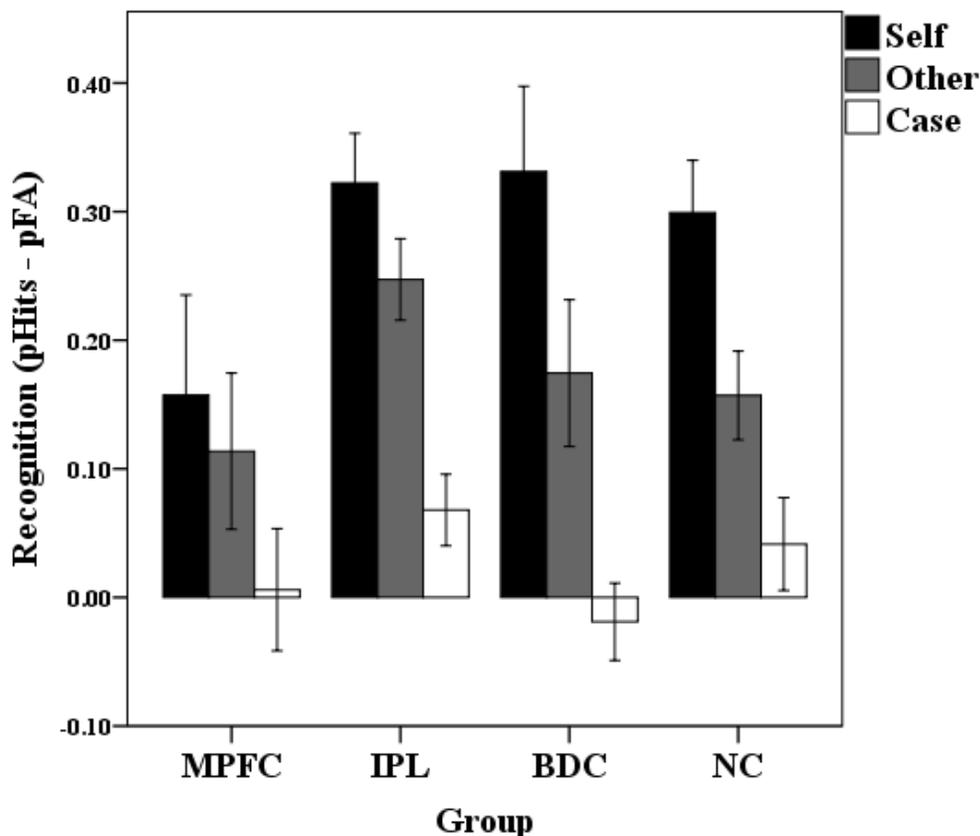
corrected significance level of $p = 0.005$, for all contrasts), there was a significant difference between groups for verbal intelligence (WAIS-III Verbal IQ; see Table 6). However, the significant effect of Group for the SRE remained even after controlling for Verbal IQ ($F_{3,41} = 2.80$, $p < 0.05$), suggesting that these results were not due to differences in verbal intelligence.

Figure 7. Self Reference Effect (SRE) group averages.



Note: The average SRE was significantly lower in the MPFC group than in both the brain damaged comparison (BDC) and normal comparison (NC) groups. There was a trend toward a lower SRE for the IPL group. * $P < 0.05$, ANOVA; $P < 0.01$ (MPFC v BDC), $P < 0.05$ (MPFC v NC), pairwise comparisons, 1-tailed. Error bars correspond to 1 standard error of the mean.

Figure 8. Mean recognition scores for all conditions.



Note: Mean recognition scores are reported for all conditions (*self*, *other*, *case*) for each participant group. Recognition scores for each condition are reported in standard format (pHits – pFA). Error bars correspond to 1 standard error of the mean.

2.4.4 Discussion (1b)

The results provide partial support for the hypothesis that the DMN plays a critical role in mediating the self-reference advantage in memory, as MPFC damage was found to abolish the SRE. Intriguingly, these SRE decrements appeared to be somewhat “self” specific. The MPFC group remembered 50% fewer traits from the *self* condition as compared with all other groups (IPL, BDC and NC). By contrast, the *other* trait recognition for the MPFC group was relatively unaffected (similar across groups). These findings are consistent with neuroimaging studies that have pointed to the importance of

the MPFC in the SRE (Macrae et al., 2004; Moran et al., 2006; Kelley et al., 2002; Northoff et al., 2006; Schmitz et al., 2004). They are also compatible with the claim that the MPFC may facilitate the representation and detection of self-relevance (Schmitz & Johnson, 2007; Northoff and Panksepp, 2008).

While the MPFC has been the focus of numerous studies on the self, debate remains regarding the unique role of the MPFC in self-processing (Legrand & Ruby, 2009; Lou et al., 2010). The PCC, pC, and IPL are also consistently active during self-processing tasks (e.g., Northoff & Bermpohl, 2004; Northoff et al., 2006), and might be necessary such functions (Dastjerdi et al., 2011; Lou et al., 2004; 2010). For example, as mentioned previously, TMS applied to the IPL was found to diminish the SRE (Lou et al., 2010). As part of the DMN, the IPL might mediate self processing in conjunction with the MPFC (Lou et al., 2010; Northoff et al., 2006). In partial support of this hypothesis (1b), in the present study, patients with IPL damage demonstrated a diminished SRE. However, the effect for this group only trended toward significance. Although the SRE was lower for the IPL group, the pattern of “impairment” was different from the MPFC group. Specifically, it appeared that the IPL group was remembering *more* traits from the *other* condition. Interestingly, this is consistent with the results from the TMS study mentioned above (Lou et al., 2010), where subjects with TMS applied to the IPL demonstrated better performance for the *other* condition than the *self* condition. It will be interesting in future research to explore these dissociations and the neural mechanisms underlying these differences in SRE performance. In terms of the limitations in the interpretation of these findings for the IPL group, it is possible that the small sample size and variability in the lesion etiology or lesion laterality for this group could

have contributed to the variance. In fact, 2 out of 3 of the patients with the lowest SRE scores (at or below 0) had IPL lesions in the left hemisphere. This was likely not due to language impairments, as measures of language functioning were similar across groups. Thus, it could be that left but not right IPL damage disrupts the normal SRE. Future lesion studies could investigate this claim, with larger sample sizes, to explore whether laterality of lesion differentially modulates this effect.

The ability to detect and encode information for self-relevance might contribute not only to the formation of a self concept, but also more broadly to psychological and social functioning. Across a variety of psychopathological conditions and personality disorders, self-referential processing appears to be dysfunctional, making it a major target for psychotherapy (Mansell, 2010). Recent research in patients with autism provides evidence for an association between aberrant MPFC activity and both self-referential processing deficits and impaired social functioning (Lombardo et al., 2010). Besides the MPFC, results from resting-state fMRI studies suggest abnormal DMN activity is associated with a variety of neurologic and psychiatric illnesses (see Buckner et al., 2008 and Broyd et al., 2009 for reviews). Thus, understanding the neural substrates of self-referential processing could prove to be particularly beneficial for the treatment of both neurologic and psychiatric illnesses (e.g., deep brain stimulation [DBS] for major depression).

The results from this study (1b) provide evidence for the role of DMN in the encoding and retrieval of self-knowledge. However, these findings do not address whether the DMN is necessary for accurate knowledge of one's own personality. I addressed this topic in the next experiment (1c).

2.5 Experiment 1c: DMN and the Accuracy of Self-Knowledge

2.5.1 Introduction (1c)

The understanding that we have of ourselves, what we are like (e.g., meditative, productive, athletic), our attitudes, beliefs, goals, and accomplishments, are all elements of our self-knowledge. Similar to theoretical perspectives on autobiographical memory (Tulving, 1983), self-knowledge can be separated into two components: *episodic* (e.g., “I gave \$100 to my local National Public Radio station”) and *semantic* (e.g., “I am a generous person”) (e.g., Klein et al., 1996; Tulving, 1983; 2005). Thus, episodic self-knowledge is a personal memory associated with a specific event occurring at a specific time and place (context-specific). Whereas semantic self-knowledge entails personal information or facts that an individual has about oneself not linked to a specific context (context-free). Research on self-knowledge, personality, and self-concept has focused extensively on the semantic type of self-knowledge (e.g., Bower & Gilligan, 1979; Higgins et al., 1988; Klein et al., 1996; Markus, 1977). Semantic self-knowledge is often assessed with trait judgment paradigms in which participants are asked to rate traits for self-descriptiveness (e.g., Klein et al., 1996; Klein & Gangi, 2010). Evidence from neuropsychological studies suggests that semantic knowledge of one’s personality is fairly robust and can function even when episodic memory is impaired (e.g., Klein et al., 1996; Klein & Gangi, 2010). For example, Klein and colleagues (1996) found that a patient with retrograde amnesia following a traumatic brain injury retained the ability to accurately report her own knowledge of her personality traits both before and after the injury. Accuracy of personality trait ratings was assessed by comparing her own ratings

to those of her boyfriend. Similar maintenance of accurate semantic self-knowledge has been found in individuals with amnesia due to traumatic brain injury and in children with autism (Klein et al., 1999; see Klein & Gangi, 2010 for review). These neuropsychological studies have been useful in demonstrating the functional independence of episodic and semantic autobiographical self-knowledge (i.e., when semantic knowledge is intact). However, it is still unclear what brain regions might be critical for accurate self-knowledge of one's personality traits.

Functional neuroimaging research on self-referential processing provides some clue as to the regions that would be involved in accurate semantic self-knowledge. Specifically, functional imaging work (as mentioned earlier) has reliably implicated the MPFC, PCC/pC, and IPL, hubs of the DMN, in self-referential processing during the evaluation of traits for self-relevance (e.g., Craik et al., 1999; Kelley et al., 2002; Macrae et al., 2004; Moran et al., 2006; Northoff et al., 2006). However, no targeted lesion study has yet investigated the critical role of these regions in the accurate retrieval of self-knowledge. In the present study, I aimed to test the hypothesis that the DMN is *critical* for the ability to accurately report one's own personality traits (a type of semantic self-knowledge).

2.5.2 Methods

2.5.2.1 Participants (1c)

Medial Prefrontal Cortex (MPFC) group: Four patients with bilateral lesions to the MPFC were selected from the Cognitive Neuroscience Patient Registry of the University of Iowa's Department of Neurology (see Table 7 for demographic information for all participant groups).

Inferior Parietal Lobule (IPL) group: Five patients with brain injury (2 left, 3 right) were selected from the Cognitive Neuroscience Patient Registry of the University of Iowa's Department of Neurology. All patients in the IPL group had lesions that encompassed, and were relatively restricted to the angular gyrus.

Brain Damaged Comparison (BDC) group: Four patients with lesions (3 left, 1 bilateral) were selected from the Cognitive Neuroscience Patient Registry of the University of Iowa's Department of Neurology. BDC patients were selected if the lesion damaged cortices outside of the default mode hubs (e.g. ventral occipito-temporal).

General Inclusion Criteria: Inclusion criteria for the patient groups were the same as in Experiment 1b (see section 2.4.2.1 *Participants*).

Healthy comparison group (NC; non-brain injured group): Twenty healthy participants (Mean age 63.9 ± 7.9) with no history of psychiatric or neurological illnesses were studied. Subjects were recruited from the Registry of healthy subjects in the Department of Neurology (see Table 7 for complete demographic information).

Exclusion criteria: All healthy subjects were screened over the phone prior to induction in the study. Based on the phone interview, healthy subjects with any history of psychiatric disorder, previous neurological illness or stroke were excluded from the study.

All participants gave informed consent according to a protocol approved by the Institutional Review Board of the University of Iowa.

2.5.2.2 *Lesion Mapping Procedures*

The lesion mapping procedures were the same as those described in Experiment 1a under section 2.3.1.2.

Table 7. Demographic information is reported for all participants.

Group	Age (yrs)	Education (yrs)	Sex	Handedness	Chronicity (yrs)	Laterality
MPFC (N=4)	67.5 (3.9)	13.0 (0.8)	1M/3F	3R/0L/1M	11.0 (3.4)	0L/0R/4B
IPL (N=5)	57.8 (11.4)	14.0 (2.3)	2M/3F	5R/0L/0M	16.4 (12.3)	2L/3R/0B
BDC (N=4)	65.5 (9.6)	17.0 (1.2)	3M/1F	3R/0L/1M	8.8 (2.1)	3L/0R/1B
NC (N=20)	63.9 (7.9)	14.7 (2.2)	7M/13F	20R/0L/0M	N/A	N/A

Abbreviations: Group; Number of subjects (N), Medial Prefrontal Cortex (MPFC), Inferior Parietal Lobule (IPL), Brain Damaged Comparison (BDC), Normal Comparison (NC); Sex; Male (M); Female (F); Handedness; Right (R); Left (L); Mixed, (M); Chronicity is the time between lesion onset and experimental testing; Laterality indicates the hemispheric location of the lesion: Left hemisphere (L); Right hemisphere (R); Bilateral (B).

Note: There were no significant differences between groups for age, education, or chronicity (Bonferroni corrected significance level of $p = 0.016$).

2.5.2.3 Neuropsychological Measures

Neuropsychological measures were the same as those described in Experiment 1a under section 2.3.2.5. Note: neuropsychological measures were not available for the NC group in this study (1c). There were no significant differences between patient groups in any of the neuropsychological measures (Kruskal-Wallis, Bonferroni corrected significance level of $p = 0.005$).

2.5.2.4 Personality Trait Accuracy Procedure

Personality trait accuracy was assessed by comparing the patient's self-reported ratings of personality traits with those from a collateral (i.e., a close friend or spouse). A set of 40 trait adjectives (normed from Anderson, 1968) were selected based on valence, with an equal number of negative and positive traits (20 negative, 20 positive). In this task, all traits were presented on a sheet of paper. Subjects were asked to rate each trait for self-relevance on a scale of 1 to 4 (1 = "Not at all like me", 4 = "Extremely like me") (see Appendix A1 for complete list of stimuli). To collect accuracy measurements, a collateral rated the subject on the exact same set of traits on the same rating scale. This trait verification was conducted either over the phone (N=30) or in person (N=3).

2.5.2.5 Data Analysis Procedures

2.5.2.5.1 Accuracy Scores

Trait accuracy scores were generated for each participant based on the correlation between self-reported trait ratings of relevance and the collateral ratings. This is a measure, based on Pearson product-moment correlation, that has been used previously to assess accuracy of self-reported trait knowledge in amnesic patients (Klein, Loftus, and Kihlstrom, 1996). With this analysis, I aimed to assess whether the DMN was necessary for accurate self-knowledge of personality traits.

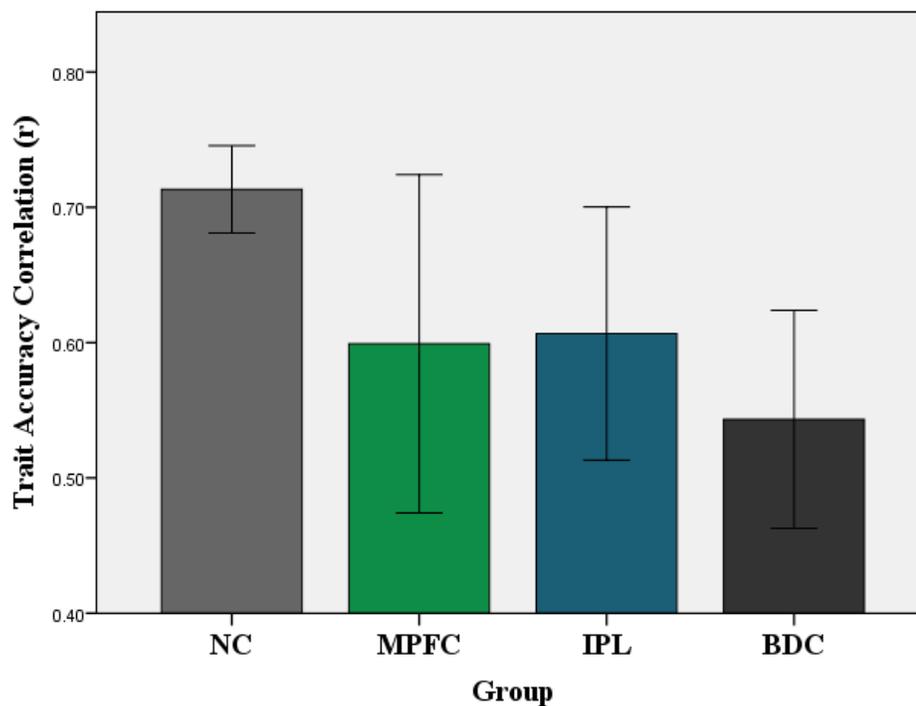
2.5.2.5.2 Group-Level Statistical Analysis

Non-parametric Kruskal-Wallis statistical analysis was used for group comparisons. I compared differences between groups in trait accuracy, or the correlation between participant trait ratings (*self*) and collateral ratings (*other*).

2.5.3 Results (1c)

In support of the main prediction, the MPFC and IPL groups were less accurate in their personality trait ratings (MPFC: $M = 0.60$; IPL: $M = 0.61$) than the NC group ($M = 0.71$). In fact, one patient with MPFC damage had the lowest personality trait accuracy correlation out of all patients tested ($r = .28$, $p > 0.05$). Moreover, 3 out of 5 of the patients from the IPL group had personality trait accuracy correlations that were well below the mean of the NC group ($r < 0.55$). However, despite these behavioral results, there was no significant effect of Group for the accuracy measure ($H(3) = 3.77$, $p > 0.05$). These nonsignificant effects could be attributed, in part, to the similarity in performance across all patient groups (MPFC, IPL, and BDC), as each group each had lower trait accuracy correlations than the NC group (Figure 9).

Figure 9. Mean trait accuracy correlations for all groups.



Note: Trait accuracy ratings represent the correlation between the subject's own ratings of a set of 40 personality traits (*self*) and the ratings of a collateral (i.e., friend, spouse). Each trait was rated on a scale of 1 ("Not at all like me") to 4 ("Extremely like me"). Mean trait accuracy is reported for all groups.

2.5.4 Discussion (1c)

In the present study, damage to the MPFC and IPL was associated with less accurate self-knowledge of personality traits. These findings are consistent with functional neuroimaging research implicating the DMN hubs in self-referential processing during personality trait judgment tasks (e.g., Craik et al., 1999; Kelley et al., 2002; Macrae et al., 2004; Moran et al., 2006; Northoff et al., 2006). The results are also in line with neuropsychological studies of patients with deficits in self-awareness following brain injury (i.e., in anosognosia), in particular when frontal and parietal

regions are involved. For example, accurate self-reports of everyday behaviors and functions can be significantly impaired after brain damage to the MPFC and IPL (e.g., Damasio, 1994; Heilman et al., 2003; Orfei et al., 2006; Prigatano & Altman, 1990; Stuss & Benson, 1986).

However, these results did not provide strong support for the main prediction as all patient groups had lower personality trait accuracy correlations than the NC group. Thus, the neuroanatomical specificity of these findings remains unclear and should be interpreted with caution. Despite the fact the MPFC and IPL groups had lower trait accuracy correlations than the NC group, there were no significant group differences in this measure. These results could be attributed in part to limitations in the patient sample and the experimental task. First, there was variability within each of the patient groups. Although individual cases within the MPFC and IPL groups demonstrated considerably low personality accuracy correlations, the performance for the groups as a whole did not necessarily follow the same pattern. The variability in the patient group performance could have been due to a variety of factors including: small sample sizes, chronicity, lesion etiology, and the reliability of the collateral. In future studies it will be important to study larger sample sizes and control for potential confounding factors (e.g., reliability of the collateral). It is also possible that accuracy of semantic self-knowledge could be modulated by the degree or severity of personality change after brain injury. Specifically, if there were no changes in personality after brain injury, patients may be able to retrieve the intact and accurate semantic knowledge of their personality from before brain injury. On the other hand, if personality change did occur after brain injury, patients might be unable to update their personal semantic knowledge with the new information about their

personality. Therefore, it might be interesting in future research to investigate this claim by examining the relationship between accuracy of self-knowledge in patients with and without acquired personality change after brain injury to the DMN hubs.

Second, in terms of the trait rating task, it is possible that lower accuracy of personality ratings across all subjects could have been attributed to a floor effect. Psychology studies of personality trait accuracy suggest that trait accuracy is fairly low (e.g., .70), even in healthy individuals with no neurologic or psychiatric illnesses, (e.g., John and Robins, 1994). Thus, it may have been difficult to find a significant effect in the present study given the decreased range of potential scores for personality trait accuracy. Another limitation in the present task was that a relatively small number of traits were used (N=40). Therefore, it is possible that the types of traits included were not those that would demonstrate differences between groups. For example, if traits with higher positive or negative valence were used there might be group differences in the accuracy of positive traits versus negative traits. In support of this claim, research suggests that patients with lesions to the orbitofrontal cortex tend to have overly positive views of their social behavior (Beer et al., 2006). In this view, it is possible that lesions to the same region would result in overly positive ratings of their personality. In terms of the DMN and self-referential processing network perspectives, this claim would be consistent with the hypothesis that the VMPFC is involved in the affective coloring, or valuation of stimuli for self-relevance, in particular for one's personality (e.g., Northoff & Panksepp, 2008; Schmitz & Johnson, 2007).

2.6 Chapter Conclusions

In conclusion, the results from all three experiments in this chapter (1a-1c) provided partial support for the main hypotheses. In Experiment 1a, while damage to the DMN hubs (MPFC, IPL, and PCC) was associated with impairments in AM retrieval, other regions within the DMN (i.e., medial and lateral temporal cortices) were also implicated. These findings suggest that a more “extended” or distributed DMN (including the medial temporal subsystem) might interact to facilitate the retrieval of past memories (see Buckner et al., 2008). In Experiment 2b, damage to the MPFC was associated with a “*self*” specific impairment in the SRE. Interestingly, patients with IPL damage showed a trend toward a lower SRE that appeared to be due to an “*other*” specific advantage. Together the results from Experiment 2b suggest that the DMN hubs (MPFC and IPL) may contribute to self-processing, but in different ways. In Experiment 1c, lesions to the DMN hubs were associated with decrements in the ability to accurately report one’s personality traits. These results provide partial support for the hypothesis that the DMN is critical for accurate reports of personality traits. However, there was no significant effect of Group, as the BDC group also showed lower personality trait accuracy ratings. Thus, questions remain regarding the specificity of the findings. Future work is warranted to examine the correlation between acquired personality change after DMN damage and accuracy of semantic memory.

CHAPTER 3

SPONTANEOUS SELF-REFERENTIAL PROCESSING: THE CRITICAL ROLE OF THE DMN IN MIND WANDERING

3.1 Introduction

The internal workings of the human mind are silent to the external world, yet the mind is often resonant, with a continuous flow of thoughts, realistic (i.e., planning), ruminative (i.e., fears), and hopeful (i.e., dreams, loves). Such mind wandering can be characterized as a type of self-referential processing, often involving the reflection on one's life from daily events, problems to be solved, to plans for the future. Arguably, mind wandering, introspection, and self-reflection are integral to self-awareness and to our daily lives in general. Moreover, in the field of psychiatry, introspection and self-awareness are essential for therapeutic progress (e.g., Freud, 1940; Beck, 1963).

Empirical investigation of mind wandering in psychology grew in favor in the late 1960s, and various researchers used different terms to describe these unprovoked thoughts including: daydreaming (Singer, 1974), stimulus independent thoughts (SITs) (Antrobus et al., 1970), and task unrelated thoughts (TUTs) (Giambra, 1995). While rigorous experimental examination of mind wandering may seem challenging, a number of paradigms have been developed to assess the frequency of stimulus independent thought either online, in retrospective reports, or in experience sampling methods (Smallwood & Schooler, 2006; see also Gruberger et al., 2011 for a review). Based on the premise that mind wandering increases during mundane, well-practiced, or boring tasks (e.g., low cognitive load, reading), such studies have employed a host of paradigms

including reading and attentional tasks (e.g., sustained attention to response task [SART]). In the majority of mind wandering paradigms, performance errors are used as objective measures of mind wandering (e.g., Christoff et al., 2009; Robertson et al., 1997; Smallwood et al., 2004; 2008). Such sustained attention tasks (i.e., SART) have been used in combination with intermittent thought probes to assess both the frequency and content of mind wandering (Christoff et al., 2009; Giambra, 1995).

While in our daily lives mind wandering seems to occupy a significant proportion of our thoughts (e.g., planning a meal while in line at the grocery store, or thinking over an incident that happened at work when driving home), the precise function of these spontaneous thoughts remains unknown. Different hypotheses have been proposed to account for the functional significance of mind wandering. One hypothesis suggests that mind wandering serves an important and adaptive role in the mental simulation of future events (e.g., Klinger, 1971; Singer, 1966; Buckner et al., 2008). A similar hypothesis emphasizes the advantages afforded by mind wandering in the facilitation of learning and problem solving (e.g., Baars, 2010). On the other hand, it is also possible that mind wandering is an epiphenomenon, with such spontaneous thoughts generated as a by-product of a cognitive system designed to shift attention to the external environment (Gilbert et al., 2007).

Functional neuroimaging work on the DMN has begun to shed light on the neural systems underlying mind wandering. The DMN, a network of brain regions with high metabolic activity at 'rest' (without an active cognitive task), has been consistently implicated in spontaneous cognition (Andreasen et al., 1995; Andrews-Hanna et al., 2010; Buckner et al., 2008; Christoff et al., 2009; Mason et al., 2007; Raichle et al., 2001;

see also Gruberger et al., 2011; Andrews-Hanna, 2011 for a reviews). Early evidence for this connection was based primarily on retrospective reports of thoughts that had occurred during “rest” periods in functional imaging (e.g., Andreasen et al., 1995). For example, in a Positron Emission Tomography (PET) study by Andreasen and colleagues (1995) the majority of subjects reported thinking about the past and planning for future events during the rest conditions. More recent research has applied experience sampling methods using attention tasks (i.e., SART) to examine modulation of DMN activity “online” during mind wandering (Andrews-Hanna et al., 2010; Christoff et al., 2009; Mason et al., 2007). These findings provide support for the hypothesis that the DMN is critical for mind wandering. However, some researchers suggest alternative explanations for the functional significance of the DMN. Notably, Gilbert et al. (2007) argue that the DMN functions to enable attention to the external environment, or what is referred to as “stimulus oriented thought” (SOT).

While functional imaging studies have suggested a link between the DMN and mind wandering, debate remains regarding the *critical* role of the DMN in the generation of these spontaneous cognitions. In the present study, I sought to test the hypothesis that the MPFC and IPL hubs of the DMN are critical for mind wandering by using a targeted lesion approach. I used two complementary methods to assess mind wandering frequency (as a measure of self-referential processing): 1) an “online”, experience sampling approach in the SART, and 2) an “offline” or retrospective self-report measure based on the Imaginal Processes Inventory (IPI) mind wandering scale.

3.2 Specific Aim and Hypothesis

3.2.1 Specific Aim

To examine the critical role of the MPFC and IPL hubs of the DMN in self-referential processing and mind wandering.

3.2.1.1 Hypothesis

The MPFC and IPL hubs of the DMN are *critical* for self-referential processing and mind wandering. I predict that the MPFC and IPL patients will show a reduction in mind wandering frequency. In particular, both MPFC and IPL groups will have a lower frequency of mind wandering as measured objectively by number of errors on the mind wandering computer task. If both MPFC and IPL groups have lower frequencies scores of mind wandering, then the hypothesis will be supported. Alternatively, if neither MPFC nor IPL groups have lower frequencies scores of mind wandering, then the hypothesis will be falsified.

3.3 Methods

3.3.1. Participants

Medial Prefrontal Cortex (MPFC) and Brain Damaged Comparison (BDC)

group: were the same as those that participated in experiment 1c. See section 2.5.2.1 for a description, and Table 7 (from Chapter 2) for demographic information.

Inferior Parietal Lobule (IPL) group: Six patients (3 male, 3 female; all right handed) with brain injury (3 left, 3 right; Mean chronicity = 16.5 yrs, SD = 11.3) were selected from the Cognitive Neuroscience Patient Registry of the University of Iowa's Department of Neurology. The IPL group was younger on average age than the other groups (M = 59.7 yrs, SD = 11.1), but this difference was not significant (Kruskal-Wallis, $H(3) = 1.94, p > 0.05$). The IPL group was matched in average education to the MPFC group (M = 13.7 yrs, SD = 2.3). All patients in the IPL group had lesions that

encompassed, and were relatively restricted to the angular gyrus. Note: Five of the six patients in this study were the same as those that participated in experiment 1c.

General Inclusion Criteria: Inclusion criteria for the patient groups were the same as in Experiment 1b (see section 2.3.1.1 Participants).

Healthy comparison group (NC; non-brain injured group): Sixteen healthy participants without brain damage were tested on the SART task (Mean age = 64.9 yrs, SD = 6.9; 4 male, 12 female; Mean education = 14.6 yrs, SD = 2.2). These 16 subjects were a subset of the same participants used in experiment 1c. See section 2.5.2.2 for a description. The mind wandering data from four of the original twenty subjects could not be used due to computer malfunctions during the task. Note: The IPI mind wandering frequency scale was administered to all twenty subjects, so all 20 NC subjects were included in the IPI results (see section 3.4.2).

Exclusion criteria: Exclusion criteria for the NC group was the same as in Experiment 1c (see section 2.5.2.2 *Participants*).

All participants gave informed consent according to a protocol approved by the Institutional Review Board of the University of Iowa.

3.3.2 Lesion Mapping Procedures

The lesion mapping procedures were the same as those described in Experiment 1a under section 2.3.2.2.

3.3.3 Neuropsychological Measures

All the same neuropsychological measures described in Experiment 1a under section 2.3.2.5, were also used in this study. To address potential confounds in mind wandering performance due to group differences in processing speed, I also included

Trails A and WMS-III processing speed index. There were no significant differences between groups for any of the neuropsychological factors, including Trails A and WMS-III processing speed index (Kruskal-Wallis, Bonferroni correction was applied for a significance level of $p = 0.004$, each $p > 0.004$).

3.3.4 Mind Wandering Task Procedures

3.3.4.1 Sustained Attention to Response Task (SART)

Mind wandering frequency was assessed using a modified version of the sustained attention to response task (SART) used in a prior functional imaging study (Christoff et al., 2009). In this SART task, numbers between 0 and 9 were presented sequentially in the center of the computer screen for two seconds each. Participants were instructed to press the spacebar for each number (0 to 9), and to withhold their response for the number 3 (not to press the spacebar). The number 3 was the *target* number, and all other numbers between 0 and 9 were *nontargets*. One block was administered, with 329 trials total. There were 33 trials for each of the nine *nontarget* numbers and 16 trials for the *target* number (~5% of trials). *Targets* numbers were fairly infrequent and constituted about 5% of the total trials.

Thought probes were used to assess subjective reports of mind wandering during the experiment. The thought probes appeared pseudorandomly (~1 per minute) throughout the experiment (16 total). For each thought probe, the subject was presented with two questions. In the first question the subject was asked, “Where was your attention focused just before the probe?”. The subjects used a continuous rating scale to rate their attentional focus from 0 (*Completely On-task*) to 100 (*Completely Off-task*). The second question asked subjects, “How aware were you of where your attention was focused”.

The subjects used a similar continuous rating scale to rate their awareness from 0 (*Completely Aware*) to 100 (*Completely Unaware*). For both continuous ratings, subjects used a mouse to move a red bar along the scale (left to right), and pressed the spacebar to submit their response.

All subjects received detailed instructions and practice blocks (N = 15 trials/block) prior to beginning the experiment. Note, one practice block was usually sufficient for subjects to understand and perform the task.

3.3.4.2 Classification of Mind Wandering Frequency on the SART

There were three measures of mind wandering frequency calculated based on SART task performance: 1) Total number of errors on the SART (targets and nontargets) was used as an “objective” measure of mind wandering frequency. In order to analyze the subjective ratings, participant answers to thought probes were divided based on their ratings into “off-task” (0 – 50) and “on-task” (51-100); 2) The total percentage of “on-task” and “off-task” thought probes was used as a subjective measure of mind wandering frequency for each subject; 3) I also calculated the number of errors in 10-second intervals prior to both “on-task” and “off-task” thought probes to investigate differences in performance based on subjective ratings of mind wandering (on-task errors/off-task errors).

3.3.4.3 Imaginal Processes Inventory

To measure “offline” or retrospective self-reports of mind wandering frequency, the daydreaming scale from the Imaginal Processes Inventory (IPI) was administered. The daydreaming scale from the IPI is a 12-item questionnaire that was developed and previously used to assess daydreaming (Singer & Antrobus, 1972). All questions require

multiple choice answers, with five possible answers for each question. For example, one question states, “*Recalling things from my past, thinking of the future, or imagining unusual kinds of events occupies [...]*”. The total possible score on the daydreaming scale is 60; higher scores indicate greater daydreaming frequency. A daydreaming percentage score was used for each subject (e.g., 50% for an IPI score = 30/60).

3.4 Results

3.4.1 SART Results

3.4.1.1 Total SART Errors

Total number of errors was used as an objective measure of mind wandering on the SART. There was a significant effect of Group for total errors on the SART task ($H(3) = 6.57, p < 0.05$) (Figure 10). In a *post hoc* analysis, Mann-Whitney U tests were used to investigate this group difference. Bonferroni correction was applied for all *post hoc* analyses with a significance level of $p = 0.025$. Contrary to the main prediction, the MPFC and IPL groups made more errors on the SART (MPFC: $M = 12.5, SD = 17.1$; IPL: $M = 13.2, SD = 17.9$) than the BDC group ($M = 1.25, SD = 1.9$). Moreover, the greatest number of errors on the SART were committed by one patient from the MPFC group (43 errors) and IPL group (46 errors) respectively. Despite the high number of errors for the MPFC group, the difference between these two groups was not significant ($U = 4.5, r = -0.37, p > 0.05$). By contrast, the IPL group did perform significantly worse (committed more errors) than the BDC group ($U = 2.5, r = -0.64, p = 0.019$).

3.4.1.2 Thought Probes

Thought probes were used to categorize error performance on the SART based on self-reports (subjective measures) of mind wandering (“off-task” or “on-task” trials). All

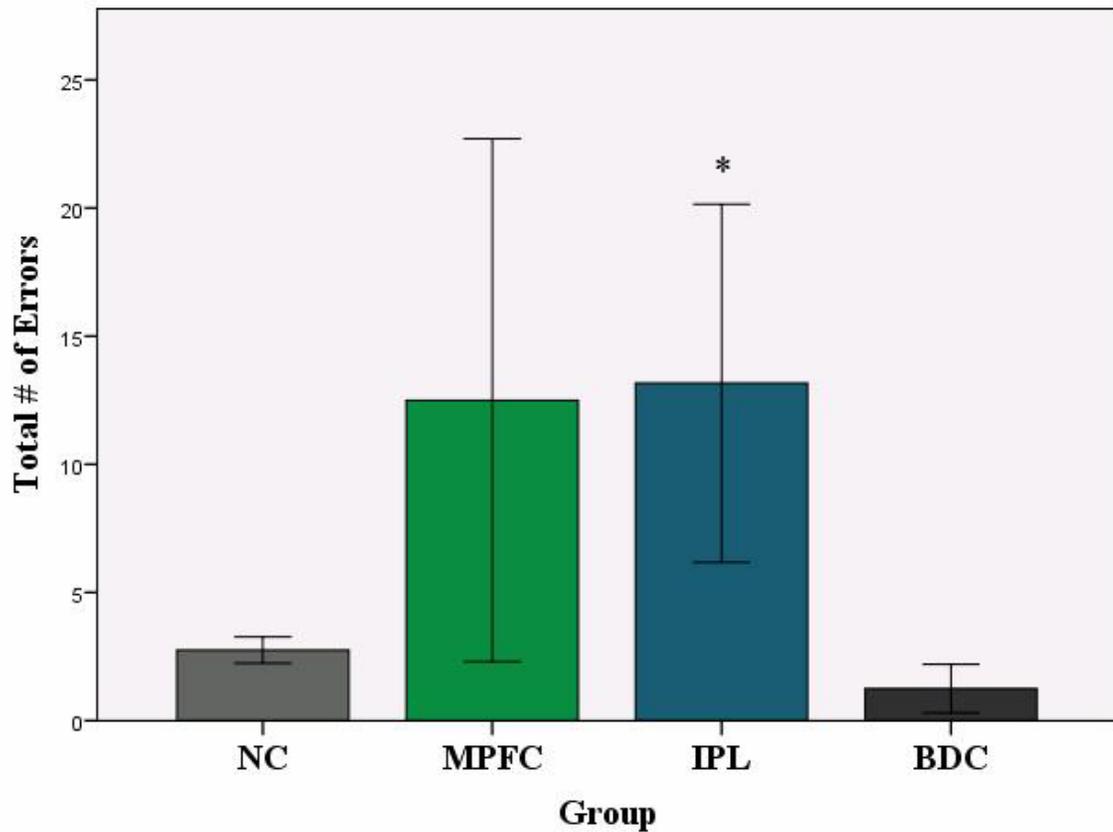
participants reported being “on-task” more often than “off-task” (See Figure 11). While the IPL group did appear to report the highest percentage of “off-task” trials ($M = 30.2\%$, $SD = 38.9\%$), there were no significant group differences in the self-reported proportion “off-task” trials ($H(3) = 5.50$, $p > 0.05$).

Next, I investigated whether there were group differences in error performance for intervals where subjects reported being “off-task”. There was a significant effect of Group for total number of errors made during “off-task” trials ($H(3) = 12.8$, $p < 0.01$). This effect was due to the IPL group, as this was the *only* group to make any off-task errors (IPL: $M = 2.2$, $SD = 2.9$).

3.4.2 IPI Mind Wandering Results

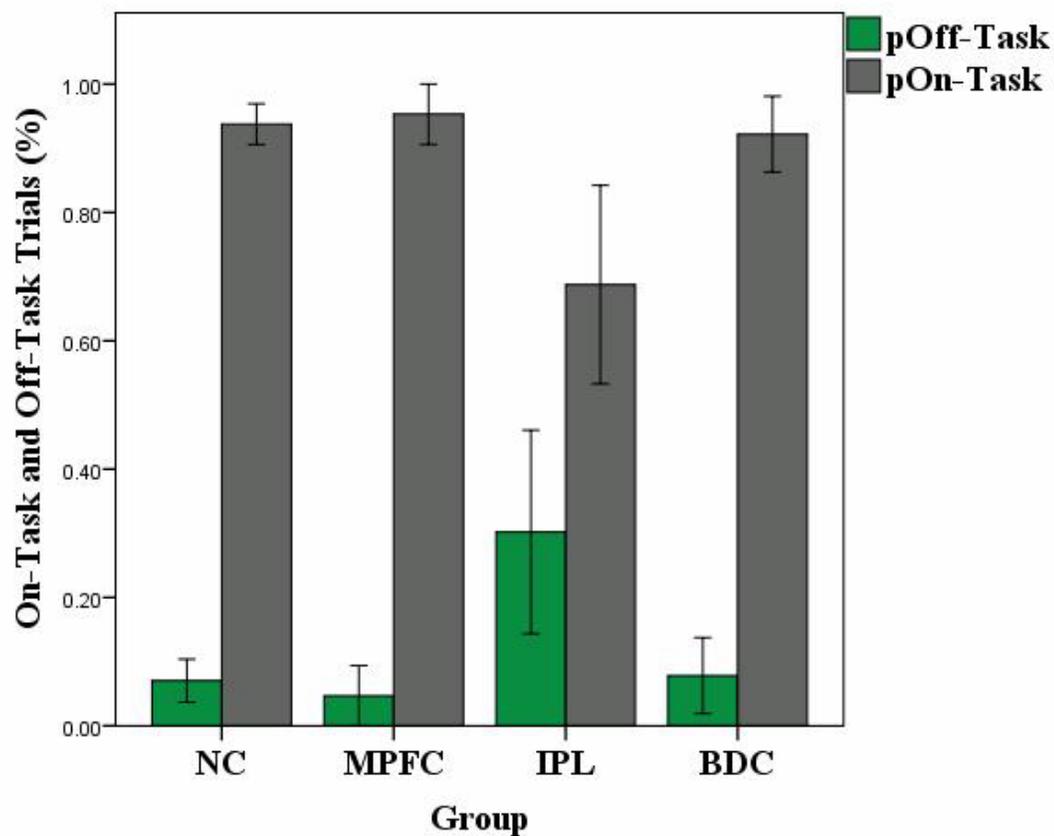
To further test the hypothesis that the DMN is critical for mind wandering, I analyzed self-reported mind wandering frequency as an “offline” subjective measure of mind wandering. Importantly, this IPI measure was shown to correlate with DMN activity during a well-practiced task (Mason et al., 2007). In support of the hypothesis that the DMN is critical for mind wandering, there was a significant effect of Group for mind wandering frequency ($H(3) = 5.77$, $p < 0.05$), and MPFC and IPL groups reported mind wandering significantly less than the NC group (MPFC v NC: $U = 14$, $r = -0.37$, $p < 0.05$; IPL v NC: $U = 31$, $r = -0.35$, $p < 0.05$), with a trend toward less mind wandering than the BDC group (MPFC v BDC: $U = 3$; IPL v BDC: $U = 5$; each $p = 0.07$) (See Figure 12).

Figure 10. Mean number of errors on the SART task.



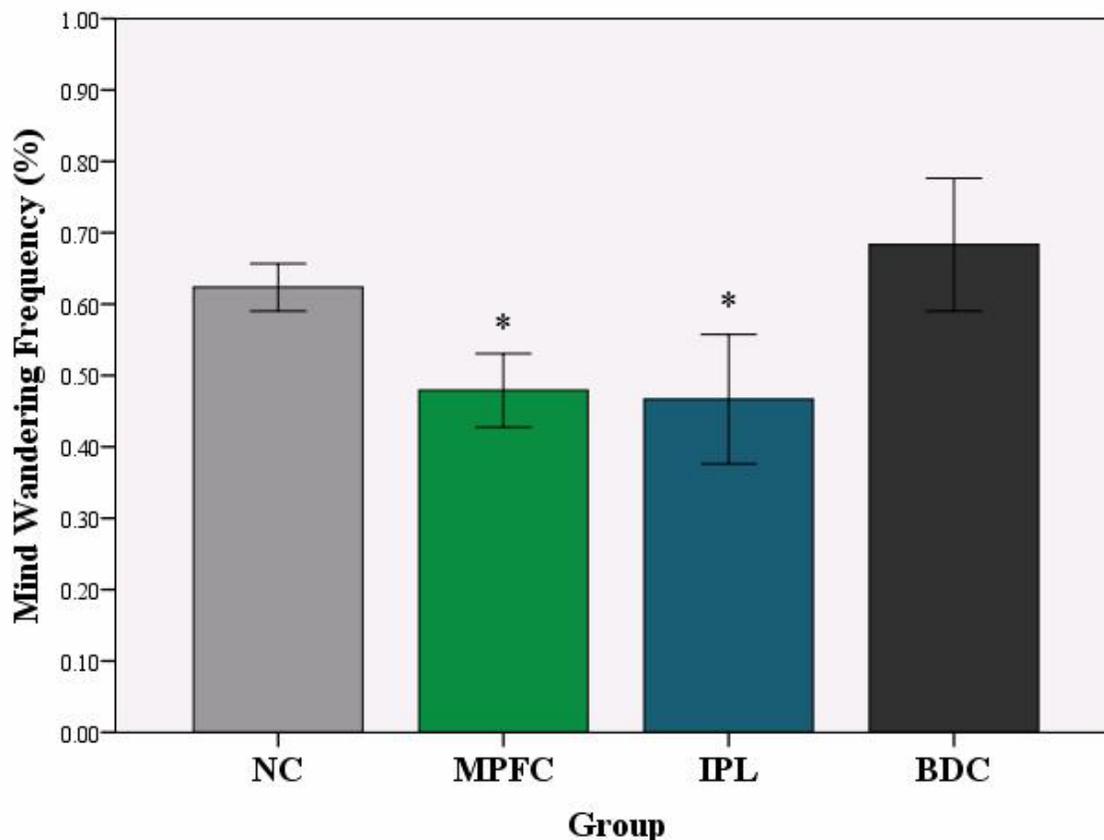
Note: Group means are reported for the total number of errors committed on the SART task. The IPL group made significantly more errors than BDC group. * $P < 0.05$, Kruskal-Wallis; $P < 0.05$ (IPL v BDC), pairwise comparison, 1-tailed. Error bars correspond to 1 standard error of the mean.

Figure 11. Mean proportion of on-task and off-task trials.



Note: Means are reported for self-rated “on-task” and “off-task” trials from the SART. A self-reported “off-task” rating served as a subjective measure of mind wandering on the SART. Error bars correspond to 1 standard error of the mean.

Figure 12. Mean mind wandering frequency (%) based on the Imaginal Processes Inventory (IPI).



Note: Group means are reported for mind wandering frequency on the IPI. * $P < 0.05$, Kruskal-Wallis; $P < 0.05$ (MPFC v BDC, IPL v BDC), pairwise comparisons, 1-tailed. Error bars correspond to 1 standard error of the mean.

3.5 Discussion

In the present study, I examined whether the DMN hubs were *critical* for mind wandering. Mind wandering frequency was assessed in two ways, using complementary “online” (SART task) and “offline” (IPI daydreaming frequency scale) measures. The results from this study provide evidence for intriguing dissociations between the effects of DMN damage on *objective* versus *subjective* measures of mind wandering.

In contrast to the main prediction, damage to the DMN hubs was associated with greater mind wandering during the SART. Specifically, the IPL group made significantly

more total errors on the SART than the BDC group. Based on this objective measure of mind wandering, these results suggest that patients with IPL damage experienced more mind wandering during the task. Despite a similar increase in SART errors for the MPFC group, this effect was not significant. For the MPFC group, it is possible that individual variability in performance could have contributed to these nonsignificant effects. For example, one patient in the MPFC group committed the second highest number of errors across all groups; whereas other patients in the MPFC group did not have the same pattern of performance (Figure 10). In addition, the sample size of the MPFC group was relatively small ($N = 4$). Future studies are warranted, with larger sample sizes, to explore the reliability of this effect.

Together, the results from the SART task did not provide support for the main hypothesis that the DMN hubs are critical for mind wandering. Instead, they suggest that DMN hub lesions, in particular to the IPL, were associated with *increases* in mind wandering. These findings could provide partial support for an alternative hypothesis, that the DMN is critical for “stimulus oriented thoughts” (Gilbert et al., 2007). According to this competing hypothesis, lesions to the DMN hubs should be associated with *decreased* attention to external stimuli. In the context of this study, the greater number of errors on the SART could be consistent with this prediction. It will be important in future work to design experiments to explicitly test these competing hypotheses using a variety of complementary methods. For example, by implementing paradigms which orthogonally manipulate external attention and mind wandering (e.g., Andrews-Hanna et al., 2010), and by applying complementary thought sampling approaches (e.g., Christoff et al., 2009).

Besides the experience sampling approach (e.g., SART), a retrospective self-report measure of mind wandering (IPI daydreaming scale) was also used in this study to examine frequency of spontaneous thoughts. In contrast to SART task performance, and in support of the main prediction, patients with MPFC and IPL damage reported significantly *less* frequent mind wandering than the BDC group. These findings are consistent with numerous functional neuroimaging studies that have implicated the DMN in mind wandering (Andrews-Hanna et al., 2010; Christoff et al., 2009; Mason et al., 2007), some using the exact same scale (e.g., Mason et al., 2007).

However, these results should be interpreted with caution as there are at least two alternative explanations which highlight potential limitations in this measurement approach. First, the IPI scale relied on retrospective self-report. Therefore, it is possible that autobiographical memory impairments in the MPFC and IPL groups prevented them from recalling specific situations (episodic events) when they had mind wandered. The results from Experiment 1a of this dissertation provide some support for this claim, as lesions to these regions (MPFC, IPL) were associated impairments in autobiographical memory retrieval. Second, deficits in self-monitoring could have contributed to inaccurate reporting of mind wandering in this study. Neuropsychological evidence suggests that MPFC and IPL damage can be associated with inaccurate knowledge of one's own behavioral and psychological impairments (i.e., in anosognosia) (e.g., Damasio, 1994; Heilman et al., 2003; Orfei et al., 2006; Stuss & Benson, 1986). In summary, while these results were in support of the main prediction, it seems that based on the noted limitations, "online" experience sampling approaches (e.g., SART) might be more useful and valid (at least in neurological populations).

Taken together, the results provide evidence for dissociable effects of DMN damage on mind wandering, with both *increases* and *decreases* found. However, due to limitations in the accuracy of self-report and the memory required for the retrospective assessment of mind wandering, the self-reported decreases might be unreliable. Given the findings from the SART task, it seems that mind wandering was still present in both IPL and MPFC patient groups. However, it remains unclear whether these patients were indeed engaging in self-reflection on past, present, and future events. An interesting direction for future research will be to explore the effect of DMN lesions on qualitative aspects of mind wandering and self-referential processing (i.e., the content of thoughts), as well as the awareness of such thoughts (e.g., meta-awareness). For example, there could be differences between spontaneous thoughts that are conscious (i.e., self-reflecting and thinking about one's past) and those that are unconscious (i.e., zoning out). Moreover, it is possible that the neural mechanisms underlying these different types of spontaneous thought could be independent.

3.6 Chapter Conclusions

In conclusion, DMN hub lesions were associated with both *increased* objective measures of mind wandering and *decreased* subjective self-reports of mind wandering. These findings raise some fascinating questions about the neural mechanisms of mind wandering, and the potentially segregated and integrated functions of the MPFC and IPL as components in the DMN. Future work could explore the neural mechanisms of mind wandering further by combining functional neuroimaging studies with lesion approaches to investigate the impact of functional connectivity within spared regions of the DMN

(and other resting state networks) in patients with lesions to single hubs (e.g., MPFC, IPL).

CHAPTER 4

CONCLUSION

Theoretical frameworks and neuroscientific perspectives of *self* have begun to converge on candidate neural systems responsible for engendering self processes across modalities and domains. Two separate lines of functional neuroimaging research have provided evidence for an overlap between the DMN and brain regions implicated in self-processing. With this background, the experiments presented in this dissertation addressed the intriguing hypothesis that the DMN constitutes a network *critical* for self-processing.

4.1 Self-Representation and the DMN

In the first three experiments, damage to DMN hubs was associated with deficits in the retrieval, encoding, and accuracy of self-knowledge. In the autobiographical memory (AM) experiment, patients with damage to the MPFC and IPL hubs of the DMN were impaired in their ability to retrieve AMs from their past. However, the AM impairments were not restricted to the DMN hubs as medial and lateral temporal structures (parts of an extended DMN) were also implicated. These results are compatible theoretical and phenomenological conceptions of AM. In other words, personal memories are complex, multimodal, and multisensory, and as such may depend on the integration of a network of brain regions in the retrieval process. The findings also suggest that, while not otherwise engaged in a cognitive task, DMN activity may indeed facilitate the spontaneous recollection of past AMs (e.g., Andreasen et al., 1995; Buckner et al., 2008), both episodic and semantic.

In the second experiment, MPFC and IPL groups showed a diminished SRE, but for different reasons. Whereas damage to the MPFC abolished the SRE with a *self* specific recognition impairment, damage to the IPL was associated with a lower SRE with an *other* specific recognition improvement. Interestingly, these results suggest that the MPFC and IPL may contribute to distinct aspects of self-referential processing. Specifically, it is possible that the MPFC contributes to the valuation of stimuli as self-relevant (e.g., Schmitz & Johnson, 2007), whereas the IPL may be more important for shifting attention between self and other perspectives or stimuli (e.g., Vogeley et al., 2001; Decety & Somerville, 2003). In the personality trait accuracy experiment, DMN hub lesions were associated with less accurate self-knowledge of one's personality traits. However, the specificity of the effects remains unclear as there were no group differences in trait accuracy ratings. In addition, the BDC group also had lower accuracy in personality ratings. Interestingly, the results from the AM experiment could help explain the findings for the BDC group. Specifically, patients with lesions to the ventral temporal and occipital regions, the same regions damaged in the BDC group, showed impairments in semantic AM retrieval. Thus, it is possible that patients in the BDC group had some disruption in the retrieval of semantic AM which affected their ability to accurately report their personality traits. However, the results from this trait accuracy experiment should be interpreted with caution due to low subject numbers and variability within patient groups.

Taken together, all three experiments provided partial support for the claim that the DMN is critical for the representation and retrieval of self-knowledge. In the next chapter, I addressed the role of the DMN in spontaneous self-referential thoughts or mind wandering.

4.2 Spontaneous Self-Referential Processing and the DMN

In Chapter 3, damage to the DMN hubs was associated with both *increases* in objective mind wandering (MW) and *decreases* in subjective self-reports of MW frequency. Intriguingly, the discrepant results could help inform competing hypotheses about the role of the DMN in spontaneous thought. Specifically, the results from objective measures of MW on the SART provide support for the hypothesis that the DMN is critical for attention to external stimuli (Gilbert et al., 2007). Whereas the subjective measures of MW based on the self-report questionnaire are consistent with the hypothesis that the DMN is critical for MW. While each of these hypotheses can account for one aspect of the findings, neither can fully explain the results (from objective and subjective measures). An alternative hypothesis could be that the DMN is not critical for MW, but instead contributes to the maintenance of conscious awareness (including of mind wandering) (see Mason et al., 2007 for discussion; Schooler, 2002). In the context of the present experiment, deficits in meta-awareness could help explain both the *increased* MW on the SART and *decreased* self-report of MW on the questionnaire. The meta-awareness hypothesis would also be in line with neuropsychological studies which have implicated MPFC and IPL regions in the awareness of impairments or behavioral changes (i.e., anosognosia) after brain injury (e.g., Damasio, 1994; Heilman et al., 2003; Orfei et al., 2006; Stuss & Benson, 1986). Of note, there were also limitations to the MW experiments as subject numbers were low ($N = 4$ or 5) for the patient groups. Thus, it will be imperative to measure MW with larger patient samples to examine the reliability of this effect. Moreover, in order to inform research on the precise role of the DMN in

spontaneous cognition it will be important in future studies to merge functional imaging and lesion work. Specifically, functional neuroimaging data could be collected in lesion patients (with damage to single hubs of the DMN) to evaluate neural activity and connectivity within spared regions of the network during MW episodes.

4.3 Implications for Integrated and Network Perspectives of Self

Together, the results from the experiments in this dissertation provided some support for a critical role of the DMN in self-referential processing. The studies in this dissertation focused primarily on the tasks requiring self-knowledge and autobiographical memory, self-processes which have been the focus of many theoretical accounts of the DMN (e.g., Andreasen et al., 1995; Andrews-Hanna, 2011; Buckner et al., 2008; Raichle et al., 2001). In comparison to different theoretical and neuroscientific perspectives of self, literature on the DMN has focused on specific types of self-processes and particular brain regions. Thus, while the results from this dissertation suggest that the MPFC and IPL hubs of the DMN may be critical for the integration, retrieval, and maintenance of autobiographical memory (semantic and episodic), it remains unknown whether the DMN is necessary for other self-processing domains (e.g., interoception). In addition, research on the DMN has focused on the cortical midline hubs of the DMN, with less discussion of the potential contribution of subcortical regions to self-referential processing and resting state brain activity (see Andrews-Hanna, 2001 for an exception). Taken together, it will be important in future research to explore the role of the DMN in different types of self-processing, and to examine whether subcortical regions contribute to self-processes and resting state activity in the DMN. This line of research would

complement recent theoretical and neuroscientific frameworks for self which propose that cortical-subcortical networks are critical for instantiating self-processing across domains (e.g., Damasio, 2010; Northoff & Panksepp, 2008; Schmitz & Johnson, 2007).

While the DMN has received considerable attention over the past decade, one could question whether theories regarding the role of the DMN in self-processing can fully account for the complexities of the self, above and beyond what is already explained in the network perspectives of self-processing described above (Damasio, 2010; Northoff & Panksepp, 2008; Schmitz & Johnson, 2007). Given the primary focus on the functional role DMN in self processes such as autobiographical memory, self-reflection, and self-knowledge, it remains unclear whether the DMN would also contribute to other types of self processes including bodily and sensory representations of an individual. Thus, investigations of the functional significance of the DMN could benefit from a more detailed characterization of the integrated and segregated functions individual hubs of the DMN. Moreover, it would be interesting to explore the time course of processing within the DMN in more detail with the use of EEG methodologies. Lastly, further research is warranted to examine the degree to which structural connectivity between hubs of the DMN contributes to the functional connectivity within the network. For example, it would be interesting in future research to examine the degree to which lesions to specific hubs of the DMN affect structural and functional white matter integrity within spared regions of the DMN and other resting state networks (e.g., attentional networks).

4.4 Resiliency, Redundancy, and the Neural Correlates of Self

More broadly, what conclusions can be drawn regarding the neural substrates of self? The results from this dissertation and observations of patients that participated in these studies suggest that the self-processing is robust and resilient to brain injury. While there were experimentally measurable (though perhaps arguably subtle) impairments in autobiographical memory, self-knowledge, and meta-awareness, there were no significant alterations in the basic sense of self. Despite damage to cortical regions purported to be critical for self-processing, all patients were conscious, self-aware, pleasant, and alert individuals. Further evidence for the resiliency of the self comes from a case of a patient studied from the lesion registry at Iowa. As a result of herpes simplex encephalitis, the patient had nearly complete destruction of the insular cortices bilaterally, the MPFC, anterior cingulate cortices (ACC), and the parietal cortices in the right hemisphere. Amazingly, despite a profound anterograde and some retrograde memory impairment, the patient demonstrated relatively preserved self-processing across a variety of self-processing tasks from basic mirror self-recognition to more complex self-reflective processes. Together, this apparent resiliency of the self in the face of brain injury suggests that it would be incredibly difficult to completely abolish all aspects of self-processing. As proposed by Damasio (1999) and others (e.g., Laureys et al., 2007), it may be the case that a loss of consciousness is required to lose the sense of self, such as in disorders of consciousness or coma following damage to brainstem and/or thalamocortical regions (e.g., Plum and Posner, 1983; Laureys et al., 2004).

From an evolutionary perspective, the apparently and arguably more complex sense of self present in humans (e.g., including autobiographical memories) could have evolved over time from more basic preconscious or prereflective types of self-processing

(i.e., somatotopic representations of the body). For example, the integration of sensory (e.g., visual, proprioceptive) and motor information within the organism is thought to contribute to the ability to perform basic self-other distinctions; to distinguish oneself from other objects and stimuli in the environment. In support of this perspective, Panksepp and Northoff (2009) suggest that there is a transpecies core self that is common across at least other mammalian species. Moreover, these and other network theories for self (e.g., Damasio, 2010; Northoff and Panksepp, 2008) propose that basic or core self processes (e.g., primordial feelings or bodily sensory representations) are instantiated in subcortical regions which are conserved across species. Based on this evolutionary perspective for self-processing, it is also possible that there is considerable redundancy built into the neural substrate. Neuroanatomical studies in animals and humans provide evidence of homologous or redundant processing in the brain (see Rossini, 2000 for a review) including for motor and somatosensory processes. Taken together, it seems plausible that substantial redundancy would exist in the brain for a process as integral to animal and human survival as the sense of self.

APPENDIX

COMPLETE LIST OF PERSONALITY TRAITS

1	deceptive	21	punctual
2	kind	22	neurotic
3	compulsive	23	annoying
4	refined	24	superstitious
5	meditative	25	disobedient
6	vivacious	26	undecided
7	quick	27	excited
8	wasteful	28	understanding
9	timid	29	orderly
10	thrifty	30	impulsive
11	uncompromising	31	moralistic
12	unhealthy	32	bright
13	trusting	33	open-minded
14	frivolous	34	suave
15	original	35	unproductive
16	talkative	36	disagreeable
17	disturbed	37	self-confident
18	sloppy	38	resentful
19	smug	39	nonchalant
20	envious	40	cordial

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