INTERPLAY BETWEEN DEFAULT-MODE AND TASK-POSITIVE NETWORKS: FUNCTIONAL CHARACTERIZATION OF THE BRAIN'S LARGE-SCALE NEURAL SYSTEMS

by

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Dedication

In Memory of My Grandma

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List of Abbreviations

aMFC	Anterior Medial Frontal Cortex
ANOVA	Analysis of Variance
BA	Brodmann Area
BOLD	Blood Oxygen Level Dependant
CMS	Cortical Midline Structures
dACC	Dorsal Anterior Cingulate Cortex
DMN	Default-mode Network
DTI	Diffusion Tensor Imaging
fcMRI	Functional Connectivity Magnetic Resonance Imaging
FDR	False-Discovery Rate
FFA	Fusiform Face Area
fMRI	Functional Magnetic Resonance Imaging
HRF	Hemodynamic Response Function
IAPS	International Affective Picture System
ICA	Independent Component Analysis
IFG	Inferior Frontal Gyrus
IFG_Oper	Inferior Frontal Gyrus/Operculum
IPS	Inferior Parietal Sulcus
MFG	Middle Frontal Gyrus
mm	Millimeter

MINI	Mini International Neuropsychiatric Interview
MNI	Montreal Neurological Institute
msec	Millisecond
PCC	Posterior Cingulate Cortex
PPI	Psychophysiological Interaction
PreCG	Precentral Gyrus
Pre-SMA	Pre-supplementary Motor Area
R	Right
ROI	Region of Interest
RT	Reaction Time
SE	Standard Error (of Mean)
SePT	Socio-emotional Preference Task
SFG	Superior Frontal Gyrus
SPGR	Spoiled Gradient Echo Pulse Sequence
SPL	Superior Parietal Lobule
SPM	Statistical Parametric Mapping
SPSS	Statistical Package for the Social Sciences
STG	Superior Temporal Gyrus
TID	Task-induced Deactivation
TPJ	Temporal-parietal Junction
vMFC	Ventral Medial Frontal Cortex
Z	Z-score

Abstract

Recent work has demonstrated that the human brain is functionally organized into distinct large-scale networks, with particular attention focused on the default-mode network (DMN) and the anti-correlated “task-positive” networks. Despite the growing evidence that these neural systems are *intrinsically* connected at rest and during the performance of cognitive functions, little is known about network relationships during tasks that actively recruit DMN, such as social cognition. Characterizing how the functions and the interactions of the DMN may modulate brain activity in other large-scale neural systems may be a critical step in advancing our understanding of network dynamics. Using behavioral and functional magnetic resonance imaging (fMRI) experiments, this dissertation aims: 1) To characterize network dynamics when functions carried out by the DMN are required, and 2) to determine the modulatory effects of task demand on network dynamics in processing these functions. Four experiments were developed to address these aims. Using a task that probes a fundamental aspect of social cognition - appraising another individual, experiment 1 showed *parallel* recruitment of the DMN (medial prefrontal and posterior cingulate cortices) and the task-positive network (pre-SMA, dACC, bilateral fronto-parietal cortices). Connectivity analyses (psychophysiological interaction) further showed functional interaction within the DMN, and with the task-positive network, both vary as a function of social preference. In another set of experiments, a novel dual-task paradigm was developed that parametrically manipulated factors known to affect cortical activity in the default-mode and task-positive networks: social cognition and spatial working memory demand, respectively. Two behavioral experiments showed selective interference, manifested as a drop in working memory accuracy, between spatial working memory and the evaluative appraisal of self, suggesting functional overlap. Finally, a neuroimaging experiment adopted this dual-task paradigm to examine the interactions between DMN, social cognition and task demand. Significant social cognition-by-task demand interactions were present in multiple regions of the DMN (medial prefrontal regions) and the task-positive networks (primarily posterior parietal foci). Overall, these results suggest that network dynamics, at least between the two neural systems considered herein, are dependent on social cognition as well as task demand. Investigating the interaction between the default-mode and task-positive networks in healthy individuals may advance our understanding and treatment of mental disorders with impaired social and cognitive functioning.

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CHAPTER I

INTRODUCTION

It has been long assumed in modern neuroscience that the brain operates through distributed networks, with functions segregated over different anatomical systems, but only recently have descriptions of these networks emerged. There is now substantial evidence showing the existence of distinct large-scale networks, such as the default-mode network (DMN), the most consistent and well-studied. Investigators have also proposed other networks, such as the executive-control and salience networks, which are often found to co-activate to mediate a wide variety of cognitive functions. This dissertation will address some of the many questions about these networks and their interactions. For this chapter, the accumulating studies that characterize the functions and the interactions of these distributed cortical systems will be reviewed, and the aims and methods of the four experiments will be delineated.

An Emergent Brain System: The Default-Mode Network (DMN)

Over a decade ago, two meta-analyses with a total of approximately 200 subjects converged on a conclusion that there is a set of brain regions that are highly active at rest with eyes closed, as well as during visual fixation and passive viewing of simple visual stimuli (Mazoyer et al., 2001; Shulman et al., 1997); At the same time, Raichle and colleagues suggested that this set of regions constitute an organized network, the default-mode network (DMN), which supports a ‘baseline default mode of brain function’ (Raichle et al., 2001). Since then, the concept of the DMN has rapidly become a central theme of investigation in the field of neuroscience and as of late 2009, has appeared as a keyword in 306 articles.

Components and Physiological Properties of the Default-Mode Network

The key components of this large-scale network includes structures in the midline of the human cerebral cortex (cortical midline structures, CMS), including the anterior medial frontal cortex (aMFC), ventral medial frontal cortex (vMFC), and posterior cingulate cortex (PCC), as well as some regions within the inferior, posterior lateral cortices (BA 19/22/39/40). A signature property of this set of brain regions is the maintenance of high metabolism at rest and task-induced deactivation (TID) across a wide range of cognitive tasks, a remarkably consistent phenomenon that first led to the discovery of the DMN in the 1990’s (Mazoyer et al., 2001; Raichle et al., 2001; Shulman et al., 1997). This pattern of TID is stable across fMRI design (block and event-related) (Buckner et al., 2008), and the magnitude of TID is known to increase with task difficulty (McKiernan et al., 2003).

Besides the task-non-specific deactivations, the DMN is also characterized by intrinsic low frequency neuronal oscillations that synchronize across its distributed regions. Functional connectivity magnetic resonance imaging (fcMRI) has been used to detect brain regions whose spontaneous fluctuations in the fMRI blood oxygen level-dependent (BOLD) signal correlate across time in task-free or 'rest' settings. To date, both fcMRI approaches employed to understand the dynamics of the spontaneous activity, seed voxel functional connectivity (Fox et al., 2005; Fransson, 2005; Greicius et al., 2003) and independent component analysis (ICA) of the resting state (Damoiseaux et al., 2006; De Luca et al., 2006; Greicius and Menon, 2004), converge on the finding that the default-mode 'network' exists as an intrinsically connected resting state network (RSN). It is worth noting that for the seed voxel-based connectivity approach, regardless of seed selection (e.g. PCC, vMFC, inferior parietal cortex), the slow waxing and waning of activity (0.1 to 0.01 Hz) in the seed still correlates with the remaining components of the DMN.

Further cementing the concept of a network, Greicius and colleagues recently employed diffusion tensor imaging (DTI) and provided structural evidence that the spatial locations of the nodes within the DMN substantially mirror the underlying structural connectivity between brain regions (Greicius et al., 2008), further bolstering the validity of this organized network.

Functional Significance of the Default-Mode Network

Representing only 2% of the total body weight, the brain accounts for approximately 20% of the oxygen consumption of the body, and expends the majority of the energy maintaining high metabolism in the baseline ('resting state')

(Clark and Sokoloff, 1999). Up to 80% of this baseline consumption is devoted to the functional aspects of synaptic transmission (primarily glutamate cycling), implying significant functionality at rest (Sibson et al., 1997; Sibson et al., 1998). Of interest, the ratio of oxygen used by the brain to oxygen delivered by flowing blood, or the brain oxygen extraction fraction (OEF), is remarkably uniform across brain in the eyes closed, resting state. This uniformity of the OEF indicates equilibrium between local metabolic requirements necessary to sustain neuronal activity, and the level of blood level in the region. Hence, this equilibrium state has been proposed to define the baseline level of neuronal activity, such that the mean OEF of the brain represents the physiological basis of a default mode of brain function (Gusnard et al., 2001b; Raichle et al., 2001).

What are the exact functions served by the DMN? Although not fully characterized, it is thought that the DMN directly supports internal mentation in general. In the absence of a task that requires deliberative processing, the mind is occupied with the stimulus-independent thoughts (SIT), i.e. "mind wandering", a psychological baseline from which people depart when attention is required elsewhere and to which they return when tasks no longer require conscious supervision (Antrobus et al., 1970; Smallwood and Schooler, 2006). Multiple studies combining thought sampling and brain imaging have implicated the DMN in the internal production and awareness of SIT during rest and various cognitive tasks (Binder et al., 1999; Christoff et al., 2009; Mason et al., 2007; McKiernan et al., 2006; McKiernan et al., 2003), such that activity within the network positively correlates with the frequency of reported SIT. Other related functions of the

DMN also include monitoring one’s own internal affective state (Gusnard et al., 2001a), thoughts (D'Argembeau et al., 2005; Schneider et al., 2008), and simulating mental events required for processing autobiographic memory (Andreasen et al., 1995) or envisioning the future (Buckner et al., 2008; Buckner and Carroll, 2007). All of these functions require an internal focus of attention, hence the conclusion that the DMN supports inwardly-directed mentation,

Additionally, it is worth noting that recent advances in social neuroscience have also implicated DMN in various aspects of social cognition. Within the DMN, structures along the cortical midline (the medial prefrontal and posterior cingulate cortices) are the most clearly delineated nodes for processing social-cognitive information (e.g. Amodio and Frith, 2006; Northoff and Bermpohl, 2004; Uddin et al., 2007), such as emotion processing (Phan et al., 2002), person perception (e.g. Iacoboni et al., 2004; Mitchell et al., 2005c; Narumoto et al., 2001), attribution of mental states (e.g. Castelli et al., 2000; Frith and Frith, 1999; Mitchell et al., 2005a; Walter et al., 2004), and self-referential processing (e.g. Gusnard et al., 2001a; Johnson et al., 2005; Kelley et al., 2002; Northoff and Bermpohl, 2004), all of which are functions allowing individuals to interact and navigate the day-to-day social world (Frith and Frith, 2007). In addition, human brain lesion studies further highlighted the involvement of these cortical midline default nodes in social cognition: Patients with aMFC damage have difficulty with social reasoning (Adolphs, 1999; Apperly et al., 2004), in spite of otherwise intact intellectual ability. Following vMFC damage, adults with previously normal personalities develop abnormal social conduct, deficits in empathy, impaired emotional perspective-taking ability and difficulty assessing trustworthiness (Damasio et al., 1990; Hynes et al., 2006; Moretti et al., 2009). Although, as will be demonstrated in Chapter 2, social cognitive functions also rely upon non-DMN networks nodes.

Other Large-Scale Networks of the Brain

Besides the DMN, a number of other large-scale networks have been proposed, based on functional connectivity by both seed voxel analysis and ICA. Featuring typically activated brain regions, the neural systems identified include the motor network (Biswal et al., 1995), the sensory network (Damoiseaux et al., 2006; Hunter et al., 2006), the executive-control network and the salience network (Fox et al., 2006; Seeley et al., 2007). The nodes of these networks have strong structural connectivity with each other (e.g. Barbas, 2000; Bohland et al., 2009; Ongur and Price, 2000; Pandya and Yeterian, 1996; Vogt et al., 2006). Of these large-scale networks, functional interaction of the DMN with the later two neural systems will be the focus of this dissertation.

The executive-control network (comprised principally of the dorsolateral frontal and parietal neocortices) and the salience network (comprised of the dorsal anterior cingulate (dACC) and frontal operculum) were originally identified as a unitary neural system that is (still) commonly referred to as the ‘task-positive’ network in the literature. In response to cognitive task demand, component brain regions of the task-positive network increase activity, whereas DMN nodes decrease activity; Cabeza and colleagues, for instance, reviewed

275 functional brain imaging studies designed to study the neuroanatomy of cognitive functions, and found that co-activations in prefrontal, parietal, and anterior cingulate cortices are highly prominent during working memory, memory retrieval (episodic and semantic) and sustained attention (Cabeza and Nyberg, 2000). Moreover, the connectivity dynamics between this task-positive network and the default-mode network have been characterized by fcMRI as '*anti*-correlated' (Fox et al., 2005; Fransson, 2005). In other words, the phase of activity in these networks is 180 degrees out of phase with the low frequency activity in the DMN nodes, even during passive, resting states.

Emerging evidence in the past few years, however, has begun to support the notion that the task-positive network may be composed of two separate units. Studies employing cognitive subtraction paradigms have illuminated that the executive-control network is critical for working memory processes and adaptive goal-directed behaviors, such as monitoring, maintaining goal representations, organization, planning and subsequent performance adjustments (Curtis and D'Esposito, 2003; Ridderinkhof et al., 2004). On the other hand, the salience network responds to the degree of subjective salience (any threats to homeostasis, whether cognitive or emotional) (Craig, 2002; Critchley, 2005; Seeley et al., 2007), and has been implicated as the 'core' task-set system that converge across all or nearly all tasks (Dosenbach et al., 2006). Studies employing fcMRI methods (ICA and Granger causality analysis) have lent further support to this conclusion. Seeley *et al* showed that the executive-control and salience networks are two distinct networks that minimally correlated with one another, despite the fact that both *anti*-correlated with the DMN (Seeley et al., 2007). Sridharan *et al* recently demonstrated that the salience network (especially the frontal operculum) serves a critical, possibly causal, role in the switching between the default-mode and executive-control networks (Sridharan et al., 2008).

In sum, neuroimaging findings across various cognitive tasks and analytical methods have characterized two large-scale brain systems, the executive-control network and the salience network, that functionally interact with the default-mode network. Many questions remain about all of the networks identified, such as the role of low frequency fluctuations (carrying information? binding regions? epiphenomena?), the relative permanence/plasticity of the networks, the distribution of functions within a network (nodes appear to have different roles), the mechanism(s) by which the nodes link together and the manner in which they interact. It is this last question that will be one of the central aims of this dissertation.

Functional Links between the Default-Mode and the Task-Positive Networks

Taken together, findings from imaging studies using two different analytical approaches (fcMRI and cognitive subtraction paradigms) converged to suggest that the functional interactions between networks may be *competitive* in nature. Briefly, resting state fcMRI show inverse correlations between the default-mode and task-positive (executive-control and salience) network (Fox et al., 2005; Fransson, 2005). Second, during performance of cognitively demanding tasks, activity increases in the task-positive network are accompanied by decreases in the DMN. As task demands increase, activity in the task-positive network increases, whereas activity in the DMN decreases. Subjects also reported less mind-wandering during difficult task conditions than during easier conditions (McKiernan et al., 2006; McKiernan et al., 2003), and the trait tendency to mind wander is associated with less TID (Mason et al., 2007). These observations have been interpreted as reflecting the reallocation of (limited) neural resources between the large-scale networks serving different functions, such as having stimulus-independent thoughts (DMN) and performing cognitive functions (task-positive network).

Behavioral Manifestations of the Competitive Between-Network Interaction

Three studies thus far have linked the failure to deactivate the DMN to impaired cognitive functions, including greater interference in a verb generation task (Persson et al., 2007a), increased attention lapses (indexed by longer reaction time) in a attentional-control task (Weissman et al., 2006), and more response errors in a flanker task (Eichele et al., 2008). For example, Persson and colleagues showed a significant correlation between cognitive task-induced deactivation magnitude and task performance, such that in response to increasing cognitive demand, subjects who showed the largest deactivation had the least interference effect, as reflected by shorter reaction time (Persson et al., 2007*a*).

Therefore, existing evidence seems to hint at an important functional link between the default-mode and task-positive networks during the performance of cognitively demanding tasks. Unfortunately, none of the above studies have attempted to measure changes in functions associated with the DMN (e.g. mind-wandering, having self-referential thoughts etc.), therefore no concrete conclusions can be drawn about the nature of the *reduced deactivation* observed.

Mental Disorders Involving Dysfunctional Large-Scale Networks

Altered functional connectivity in resting state networks, particularly the DMN, have been documented in individuals with schizophrenia (Bluhm et al., 2007), depression (Greicius et al., 2007), autism (Kennedy and Courchesne, 2008) and ADHD (Castellanos et al., 2008), and abnormal (antagonistic) *between*-network dynamics have been suggested to underlie psychopathology (Broyd et al., 2009). These mental disorders are characterized by altered functions served by the large-scale networks, such as abnormal social cognition or impaired cognitive functioning or both. However, our current understanding of the mechanism through which the DMN and the task-positive network interact has been primarily informed by using (cold) cognition paradigms. This in itself highlights the significance of characterizing network dynamics while actively involving functions carried out by the DMN (such as social cognition) - a topic that has received relatively little attention in the field and remains to be explored.

Findings from healthy individuals may advance our understanding, and ultimately progress toward informed treatment of these debilitating mental disorders.

Purposes of this Dissertation

Despite the emerging interest and growing evidence that there are several widely distributed neural systems that are *intrinsically* connected at rest, and also during performance of cognitive functions, to date, relatively little work has been done to explore the network relationships using tasks that actively engage functions served by the DMN, such as social cognition. Characterizing how the functions and the interactions of the DMN may modulate brain activity in other large-scale neural systems may be a critical step in advancing our understanding of network dynamics. Ultimately, this investigation may benefit the treatment of psychiatric disorders marked by dysfunctional network relationships.

Using behavioral and functional magnetic resonance imaging (fMRI) experiments, this dissertations aims: 1) To characterize network dynamics when functions carried out by the default-mode network are required, and 2) to determine the modulatory effects of task demand on network dynamics in processing these functions. Four experiments were developed to address these aims and the findings from these studies are discussed in Chapters 2-4. In Chapter 2, a socio-emotional preference task, 'SePT', was used to probe a fundamental social cognitive function, in which subjects were asked to appraise their likes or dislikes toward social encounters. A psychophysiological interaction connectivity analysis was performed to address the functional interaction within the DMN and between nodes of the task positive networks. Chapter 3 describes the development of a novel dual-task paradigm that parametrically manipulated factors known to affect cortical activity in the default-mode and task-positive networks: social cognition and spatial working memory demand, respectively. Chapter 4 adopted this dual-task paradigm, validated in Chapter 3, to examine the network dynamics underlying the observed behavioral interference. Overall, these results suggest that network dynamics, at least between the two neural systems considered herein, is dependent on social cognitive functions as well as the task demand.

CHAPTER II

FUNCTIONAL NEURAL CIRCUITRY MEDIATING SOCIAL PREFERENCE

Introduction

Social cognition is the set of functions allowing individuals to interact and navigate the day-to-day social world (Frith and Frith, 2007). Recent advances in social neuroscience have implicated the DMN in social cognition – Within the DMN, structures in the midline of the human cerebral cortex (cortical midline structures, CMS, including aMFC, vMFC and PCC) are the most clearly delineated nodes for processing social cognitive information (e.g. Amodio and Frith, 2006; Northoff and Bermpohl, 2004, such as emotion processing {Phan, 2002; Uddin et al., 2007), person perception (e.g. Iacoboni et al., 2004; Mitchell et al., 2005c; Narumoto et al., 2001), attribution of mental states (e.g. Castelli et al., 2000; Frith and Frith, 1999; Mitchell et al., 2005a; Walter et al., 2004), and self-referential processing (e.g. Gusnard et al., 2001a; Johnson et al., 2005; Kelley et al., 2002; Northoff and Bermpohl, 2004).

One critical part of interpersonal behavior is social preference – namely, one’s likes and dislikes toward others. As eminently social animals, humans have evolved efficient processes for judging other individuals. Empirical evidence suggests that first impressions form quickly (<100 msec), and may be evolutionarily important for rapid identification and coping with social encounters (Hassin and Trope, 2000; Willis and Todorov, 2006). This ability to rapidly form opinions of other people, however, does not necessarily preclude the involvement of higher-level cognitive mechanisms in extracting meanings from the deliberately shared social world (Frith and Frith, 2007). Appraising whether one likes a person or not also entails the attribution of personal relevance to the person, by weighing what matters to the individual (de Greck et al., 2008; Enzi et al., 2009); furthermore, data suggest that the importance and meaning of the stimulus for the individual is associated with self-relatedness (See: Northoff et al., 2006 for a critical meta-analysis). Although the neural correlates for forming first impressions about others has been recently identified (Schiller et al., 2009), the neurobiological underpinnings for elaborating social preference have received little attention.

Among the previous work investigating the neural correlates of social cognitive functions, those with explicit cognitive components such as elaborating introspective appraisals or evaluative decisions of stimuli often co-activate higher cortical regions that mediate cognitive control processing. For instance, when using paradigms that require the reflective appraisal of one’s personal characteristics (e.g. Fossati et al., 2003, Kelley et al., 2002)(Moran et al., 2006), affective experiences (e.g. Gusnard et al., 2001a, Taylor et al., 2007), and the explicit evaluation of attitudes toward concepts or famous names (Cunningham et al., 2003, Cunningham et al., 2004), activity tends to increase in both medial and lateral frontoparietal cortices. The regions involved include aMFC, vMFC, and PCC, the core structures for social cognition, as well as the pre-supplementary motor area (pre-SMA), dorsal anterior cingulate (dACC), lateral frontal and lateral parietal cortices, a set of cortical structures commonly activated during the performance of cognitive tasks (termed the ‘task-positive’ network (Fox et al., 2005)). This latter set of regions has been associated with the continuous internal monitoring of actions and adjustment of goal-directed behaviors (Ridderinkhof et al., 2004), and is consistent with the notion that explicit appraisal of social cognitive information depends on controlled processing to guide contextually appropriate behavior. Nevertheless, co-activation does not necessarily reflect a functionally interacting network. Therefore, the network mechanism through which the core nodes for social cognition (aMFC, vMFC, PCC) integrate within themselves and with the structures that mediate controlled processing to enable goal-directed social-cognitive behaviors remains unclear.

With this framework in mind, we sought to investigate the neural correlates of, and the network properties underlying, social preference. In service of our first goal, we devised a 'socio-emotional preference task' (SePT), in which subjects viewed faces, with varying emotional expressions, and made appraisals of whether or not they liked the face (*Preference*). As a control condition, subjects also identified the gender of faces (*Gender*), which when contrasted with the social preference evaluations (*Preference*), permitted the isolation of the underlying process of evaluating subjective preference toward others while matching perception, decision-making and motoric responses. On the basis of the previous findings reviewed earlier, we first hypothesized that *Preference* (relative to *Gender*) would recruit more activity in cortical midline structures of interest: aMFC, vMFC and PCC. Additionally, increased activity in structures mediating cognitive control processes was also predicted.

A second contrast condition -- a passive baseline (a centered white fixation cross on a black screen) -- was also included in our paradigm to identify task-induced activity changes relative to a resting baseline. Recent neuroimaging research has identified a ‘default-mode network’ that includes these midline regions as well as the posterior lateral cortices (BA 19/22/39/40). A signature property of this network is that it maintains high metabolism during resting states and exhibits task-induced deactivation (TID) across a wide range of cognitive tasks (e.g. Gusnard et al., 2001b; Mazoyer et al., 2001; Shulman et al., 1997), accompanying increased activity in the task-positive network (Fox et al., 2005). The reciprocal, ‘see-saw’ activity between the two networks during cognitive task performance has been suggested to reflect reallocation of processing resources, such that TID reflects the suspension or interruption of processes that are carried out by the default-mode network when the mind is not engaged by external cognitive demands (McKiernan et al., 2006; McKiernan et al., 2003). If this is true, then one might expect that by engaging subjects in a social cognitive task (such as *Preference*) that demands activity from cortical midline structures, the default-mode network would be less susceptible to task-induced deactivation typically observed with cognitive/perceptual tasks (such as

Gender). Hence, we further predicted that the cortical midline activity (aMFC, vMFC and PCC) observed in the *Preference* > *Gender* contrast would reflect decreased deactivation in the *Preference* condition (relative to passive baseline).

The second goal of this study was to analyze medial-cortical network properties that underlie social preference. A few reviews and meta-analysis have laid out a theoretical framework relevant for understanding the neural mechanisms underlying social cognitive processing, inclusive of making appraisals where one's self is the explicit referent (Amodio and Frith, 2006; Northoff and Bermpohl, 2004; Northoff et al., 2006). *Within* the CMS, it has been suggested that each node is associated with a distinct process important for the explicit appraisal and coding of everyday stimuli. Specifically, vMFC is primarily involved in the initial rapid appraisal and representation of the value of an environmental stimulus; whereas aMFC is characterized as a functional division for reappraisal, evaluation and explicit reasoning of the incoming stimulus. With its strong connection with the hippocampus implicated in autobiographic memory, PCC has a central role in integrating the temporal context of the stimuli. Additionally, strong reciprocal anatomical connections (Ongur and Price, 2000) and resting state *intrinsic* connectivity measured by low frequency BOLD fluctuations (Fox et al., 2005; Greicius et al., 2003) have been established among the cortical midline structures (aMFC, vMFC, and PCC), both providing grounds for a functionally interacting medial-cortical network for social cognition. Regarding the interaction *between* the CMS and higher-cognitive structures, a dorsal system including aMFC, pre-SMA/ dACC, lateral frontal cortex, among others, is proposed to integrate cognitive processes important for regulating behaviors (Ochsner and Gross, 2005; Phillips et al., 2003). Furthermore, widespread anatomical connections among these cortical structures bolster the possibility for a network-based functional interaction.

We employed a psycho-physiological interaction analysis (PPI) to identify functional networks that subserve neural processes underlying the SePT, as opposed to functionally-isolated structures that simply co-activate (Friston et al., 1997). PPI provides a *within*-subject measure of functional interactions (‘coupling’) between brain regions in relation to the experimental design. Based on the assumption that structures involved in the same functional network ‘co-modulate’ activity while carrying out specific tasks, connectivity is inferred by significant changes in correlation, as a function of task manipulation, between the time courses of regional neuronal activity at the *within*-subject level. On the basis of the neuroimaging literature reviewed above, we hypothesized that the cortical midline structures (aMFC, vMFC and PCC) co-activated during the SePT represent nodes of an interacting functional network, which may serve as a probable mechanism to integrate the distinct component processes relevant for social cognitive processing. We also hypothesized network interaction between the CMS and the task-positive network, potentially serving as a mechanism to integrate cognitive processes to guide contextually appropriate social-cognitive behavior.

Methods

Subjects

Twenty-one healthy individuals between the age of 23 and 51 years (15 males, mean age = 40 +/- 9.6 years, mean education = 16 +/- 3 years) were recruited from community advertisements. Subjects had normal or corrected-to-normal vision, reported no significant abnormal neurological or psychiatric history, and were not taking medication. Subjects gave written, informed consent for study participation after explanation of the purpose and risks of the study, in accordance with procedures approved by the University of Michigan institutional review board (IRBMED). After completion of the study, subjects were debriefed and reimbursed for their participation and time.

Stimuli and task

The SePT consisted of three sets of human facial emotions: positive (happy), negative (primarily fearful) and neutral expressions, all selected from a published dataset (Gur et al., 2002). Each facial emotion set contains an average of 22 faces, and the same actors portrayed different expressions for each set. Each stimulus was repeated for up to 7 times, and a total of 288 face instances were used throughout the study. For the *Preference* task, subjects were instructed to judge whether they liked the face, based on their immediate experience, without concerns for being right or wrong. As an experimental control condition for general face-processing, decision-making and motor response-related activities, a gender identification task was used (*Gender*). Subjects saw each face for 3 sec, with a word above indicating task condition (either *Preference* ["Like?"] or *Gender* ["Gender?"]). Subjects made their response with a button press of the index or middle finger of the right hand (yes/no for *Preference*, male/female for *Gender*). In neither task were subjects required to make their decisions based on valence of the stimuli.

Stimulus control and response recording occurred with E-prime (Psychology Software Tools, Inc.). Subjects viewed the stimuli via reflection using angled mirrors and a back-projection system. Each task block was twelve-second long, with 4 different face instances of the same valence. There were 18 pseudo-randomized task blocks per run, and each block was separated by a centered fixation cross (the ‘passive baseline’) which was presented in a jittered manner (range = 4 - 8 sec, mean = 6 sec).

Data acquisition

Magnetic resonance imaging (MRI) scanning occurred on a General Electric (Waukesha, WI) 3T Signa scanner (LX [8.3] release). The scanning began with structural acquisition of a standard T1 image (T1-overlay) for anatomic alignment. Functional images were acquired with a T2*-weighted (GRE; repetition time, 2000 msec; echo time, 30 msec; flip angle, 90°; field of view, 22 cm; 40 slices; 3.0 mm slice thickness/0 mm skip, equivalent to 64 x 64 matrix size), reverse spiral acquisition sequence, a method sensitive to signal in ventral medial frontal regions (Yang et al., 2002). T2* images were prescribed identical to the T1-overlay. The fMRI scans were made while subjects performing tasks: 166 volumes (including 4 initial, discarded volumes to allow for equilibration of scanner signal) were acquired each run, for a total of 664 volumes. After acquisition of functional volumes, a high-resolution T1 image (T1-spgr) was obtained for anatomic normalization.

Data analysis

Data processing began with the following preprocessing steps: fMRI data were first reconstructed off-line using custom code written in C (Noll et al., 1991). Subsequently, slice-timing and motion correction were done using the "slicetimer" and the "mcflirt" routines of the FSL fMRI analysis package (http://www.fmrib.ox.ac.uk/fsl/slicetimer/index.html) (Jenkinson et al., 2002). Re-alignment parameters were inspected as a proxy for subject movement, in order to ensure that movement did not exceed either 3 mm, or 1° rotation within a run. The remainder of preprocessing and image analysis was performed using Statistical Parametric Mapping SPM2 package (Wellcome Institute of Cognitive Neurology, London, United Kindom). The high-resolution T1 image (T1-spgr) was normalized to the Montreal Neurological Institute (MNI) 152 brain-template, yielding anatomical parameters that were applied to the co-registered time-series of functional volumes. An isotropic 5mm full-width half-maximum Gaussian kernel was then used to smooth the functional volumes. In the primary model to analyze effects of tasks, the design matrix consisted of 4 runs; each had six regressors of interest (two tasks crossed with the three face valences), and the passive baseline was modeled implicitly. All regressors were convolved with a canonical hemodynamic response function (HRF). The statistical model was estimated including a high pass filter (128 sec) and AR (1) temporal autocorrelation. Subsequently, the parameter estimates were derived from the magnitude (height) of the HRF. The focus of the present report is on the difference between *Preference* and *Gender* tasks, thus regressors for the different face valences were collapsed within each task. Contrast images, testing for difference relative to the implicit baseline and for task differences, were smoothed with a 5 mm Gaussian kernel to stabilize variance properties, and entered into a second-level random effect analysis. The group significance of the task effect was thresholded at p= 0.05 (FDR-corrected for whole brain multiple comparisons), and minimal cluster size of 15 contiguous voxels (equivalent to 405-mm^3).

A psycho-physiological interaction analysis (PPI) allows one to test whether inter-regional correlation (‘functional coupling’) in neuronal activities (one from ‘Seed ROI’, one from ‘Coupled Region’) changes significantly as a function of task condition, while discounting mean activity due to task differences. Hence, this ‘functional connectivity’ analysis differs from the conventional activation mapping approaches (such as ‘cognitive subtraction’) in that PPI reveals differential interactions between brain regions on residual variances after removing task-related effects, and hence disambiguates inter-regional connectivity (‘truly covariant’) from differential task effects (Friston et al., 1997).

Focusing on the medial cortical areas, we first identified regions of interest (seed ROIs) from the main effect of task (*Preference* > *Gender*) at the second-level random effect analysis. Each seed ROI was a sphere of 9mm radius (corresponding to the approximate average smoothness of the image) centered at the local maximum. For each seed ROI, the time-series of the first eigenvariate (from the primary model) was extracted for each subject, then de-convolved with a canonical hemodynamic response function (Gitelman et al., 2003), and multiplied by a binary vector coding for the task ('psychological factor': 1 for the *Preference* condition, -1 for the *Gender* condition), yielding an element-by-element product. This product was then convolved with the canonical hemodynamic response function and entered as the psycho-physiological interaction term (PPI.ppi) in the PPI model, with a high pass filter (128 sec) as well as AR1 temporal autocorrelation. Subsequently, positive and negative contrast weights were placed on the 'PPI.ppi' regressor to test for positive and negative psycho-physiological interactions, respectively. As a result, a significant positive PPI for a voxel implies that the correlation between this voxel ('coupled region') and the seed ROI is greater during *Preference* than that during *Gender*, and vice versa. To test for significance at the group level, the contrast images generated were smoothed with a 5mm Gaussian kernel first, and then entered into a second-level random effect analysis. The same statistical threshold was used ($p<0.05$ FDR-corrected; minimal cluster size >15 voxels).

Since PPI interactions reflect the *change* of correlation slope between neuronal activities of two regions (a seed ROI and its coupled region) in two task conditions, we also repeated the analysis for *Preference* and *Gender* task separately, to determine the direction of the correlation (Etkin et al., 2006). Briefly, for each seed ROI at the fixed-effect level, the de-convolved time-series were multiplied by separate vectors for each task (‘psychological factor’: 1 for the *Preference* condition, 0 for the *Gender* condition; or, 0 for the *Preference* condition, 1 for the *Gender* condition), the products of which were then convolved with canonical hemodynamic response function to generate interaction terms for *Preference* and *Gender* task, respectively. Hence, the effects and interactions of the tasks were entered into the same model, but in separate columns. Contrast images for the interaction terms from each subject were similarly incorporated into a second-level random effect analysis, as previously described.

Results

Behavioral data

No significant effect of valence on gender identification accuracy was found [F (2,40) = 3.01, p=0.1]; In *Preference* task, the probability for a “Like” response varied as a function of valence: Subjects indicated that they liked positive faces more often than neutral faces, and neutral faces more often than negative ones [Ave. ± SE (%): 92.5 ± 2.4, 41.7 ± 5.8, 17.9 ± 4.5, respectively; F (2,40) = 99.38, p<0.001].

Mean reaction times for all our conditions of interest were calculated for each subject. There was a significant main effect of task, such that *Preference* took more time to perform than *Gender* [Ave. ± SE (msec): 1194.7 ± 35.6, 1106.2 ± 42.6, respectively; F (1,20) = 10.5, p=0.004].

Functional MRI data

<u>Group Analysis of task effects</u>

Relative to the resting baseline, both *Preference* and *Gender* tasks recruited: 1) Increased activity in a network typically seen for perceptual processing and task execution, including: occipital lobe (fusiform face areas, FFA, included), precentral gyrus, dACC, pre-SMA, bilateral PFC and superior parietal lobule (SPL); and 2) decreased activity in several structures along the cortical midline, including medial superior/middle frontal gyri, PCC, precuneus, retrosplenial cortex and the inferior temporal/parietal cortices (Table 2.1 and Figure 2.1).

Figure 2.1: Effect of Preference and Gender tasks (relative to baseline) on cortical activity

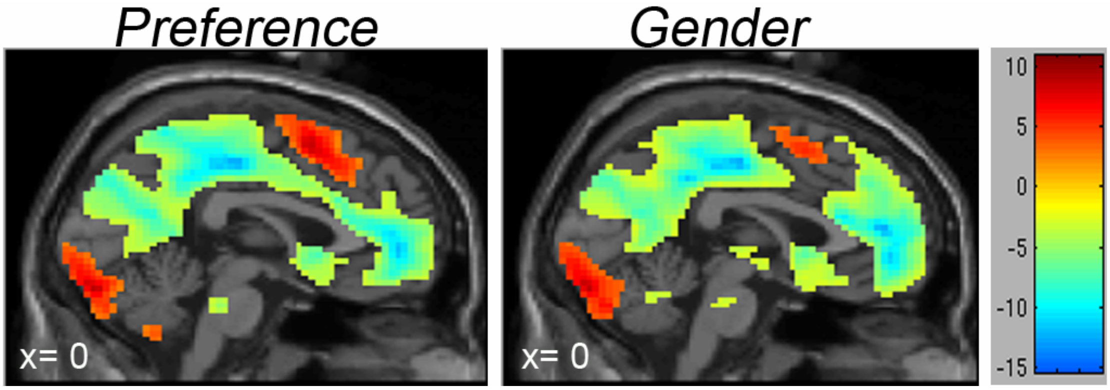


Table 2.1: Activation in response to Preference and Gender– Main effect of Task

	Preference			*Gender*		
Region	(x, y, z)[a]	Cluster[b]	Z-score[c]	(x, y, z)[a]	Cluster[b]	Z-score[c]
Increases relative to baseline						
Occipital lobe (BA 17/18/19/37)	51, -51, -24	3816[d]	6.27	-39, -90, -9	3806[d]	6.13
pre-SMA/ dACC (BA 6/8/32)	0, 12, 57	428	5.53	6, 21, 51	163	4.39
SFG/MFG/ IFG (BA 6/8/9/45/46/47)	48, 12, 30	908	5.42	48, 36, 33	378	4.72
	-45, 21, -3	114	4.36	39, 24, 3	81	3.83
SPL (BA 7/40)	33, -57, 48	246	4.66	33, -57, 48	289	5.06
	-36, -51, 45	156	3.85	-36, -48, 45	694	4.95
Precentral gyrus	-36, -3, 63	328	4.25	-45, 3, 33	99	4.21
Decreases relative to baseline						
PCC/ Precuneus/ Retrosplenial cortex (BA 7/31)	18, -54, 6	19714e	6.96	-18, -57, 3	18994e	7.03
Temporal gyri (BA 7/19/39/40/41/42)				60, -60, 21	282	4.46
				3, -21, 0	138	3.66

Abbreviations – SFG, superior frontal gyrus; MFG, middle frontal gyrus; IFG, inferior frontal gyrus; SPL, superior parietal lobe.

a Stereotactic coordinates from MNI152 reference, left/right, anterior/posterior and superior/inferior, respectively.

b Cluster size in voxels.

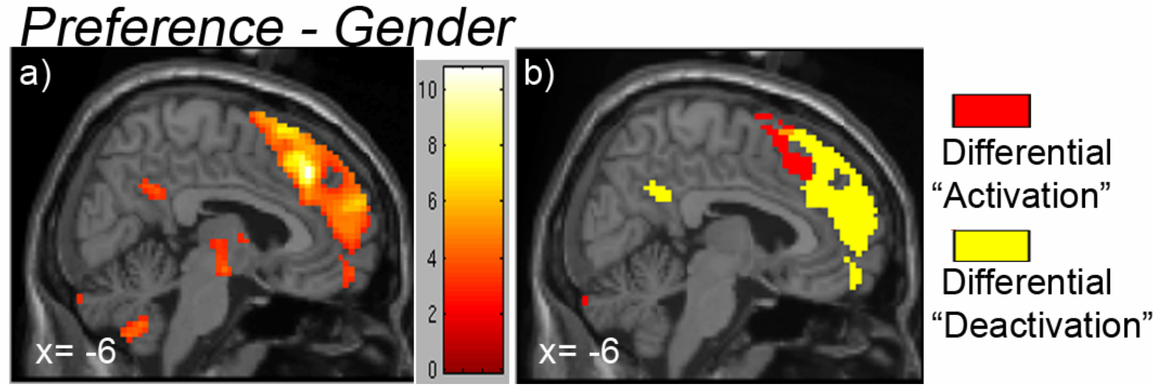
c All foci $p < 0.05$, FDR-corrected; Extend threshold: 15 contiguous voxels.

d Also extended into cerebellum.

e Also extended extensively into medial surface of SFG/ MFG, as well as temporal gyri.

Preference, when compared to *Gender*, recruited greater activity in several brain regions (Table 2.2), including the predicted foci on the medial cortical surface displayed in Figure 2.2a -- aMFC, vMFC and PCC, as well as the pre-SMA/ dACC. When examined relative to the passive baseline, this contrast (*Preference* > *Gender*) reflected two patterns of change, depending upon whether the region was deactivated relative to baseline (as seen in the default network activity) or active relative to baseline.

Figure 2.2: Differential cortical activity to Preference and Gender tasks



Two conjunction analyses ([*Preference* – *Gender*] ∩ [(Baseline-*Gender*)-(Baseline-*Preference*)]; and [*Preference* – *Gender*] ∩ [(*Preference* – Baseline)-(*Gender* – Baseline)]) revealed that the cortical midline foci could be separated into two major categories along the y-axis (anterior-posterior). The anterior component, including our medial cortical structures of interest (aMFC, vMFC and PCC), was deactivated for both the *Preference* and *Gender* tasks, but less for *Preference* (termed 'differential deactivation'; the yellow clusters in Figure 2.2b).

In contrast, the posterior component, including pre-SMA/ dACC as well as bilateral frontoparietal cortices (not seen from the medial view), reflected ‘differential activation’: Greater activity (relative to passive baseline) in *Preference* than *Gender* (the red cluster in Figure 2.2b).

Gender, when compared to *Preference*, recruited greater activity in precuneus and posterior lateral cortices (temporal-parietal junction, TPJ; and superior/middle temporal gyri, STG/MTG), and these differences reflected greater deactivation from resting baseline during *Preference* than *Gender* tasks.

Table 2.2: Activation in response to Preference relative to Gender

Region	(x, y, z)[a]	Cluster[b]	Z-score[c]
Preference > Gender			
pre-SMA/ dACC (BA 6/8/9/32)	-6, 33, 39	1690[d]	6.13
aMFC[e]	0, 54, 30	--[e]	4.97
vMFC	-3, 54, -18	34	3.37
PCC	-6, -51, 33	31	3.30
Lateral MFG/ IFG	-39, 21, -18	868	4.93
	48, 30, -12	536	4.79
	45, 21, 45	236	4.73
SPL/IPS	-54, -60, 30	112	4.84
	54, -57, 48	45	3.65
Cerebellum	-21, -84, -33	296	4.84
	36, -81, -33	231	3.93
	-6, -57, -42	88	3.66
Temporal pole	48, 6, -42	56	4.06
Caudate	-9, 9, 9	36	3.37
Gender > Preference			
Precuneus (BA 7/31)	3, -48, 63	8121[f]	5.45
STG/ MTG	60, -57, -6	43	4.30
	-54, -69, -3	97	4.10

Abbreviations – MFG, middle frontal gyrus; IFG, inferior frontal gyrus; SPL, superior parietal lobe; IPS, intraparietal sulcus; STG, superior temporal gyrus; MTG, middle temporal gyrus.

a Stereotactic coordinates from MNI152 reference, left/right, anterior/posterior and superior/inferior, respectively.

b Cluster size in voxels.

c All foci p<0.05, FDR-corrected; Extend threshold: 15 contiguous voxels.

d Also extended extensively into aMFC.

e Identified as a local maxima within the pre-SMA/ dACC cluster.

f Also extended into temporal-parietal junction.

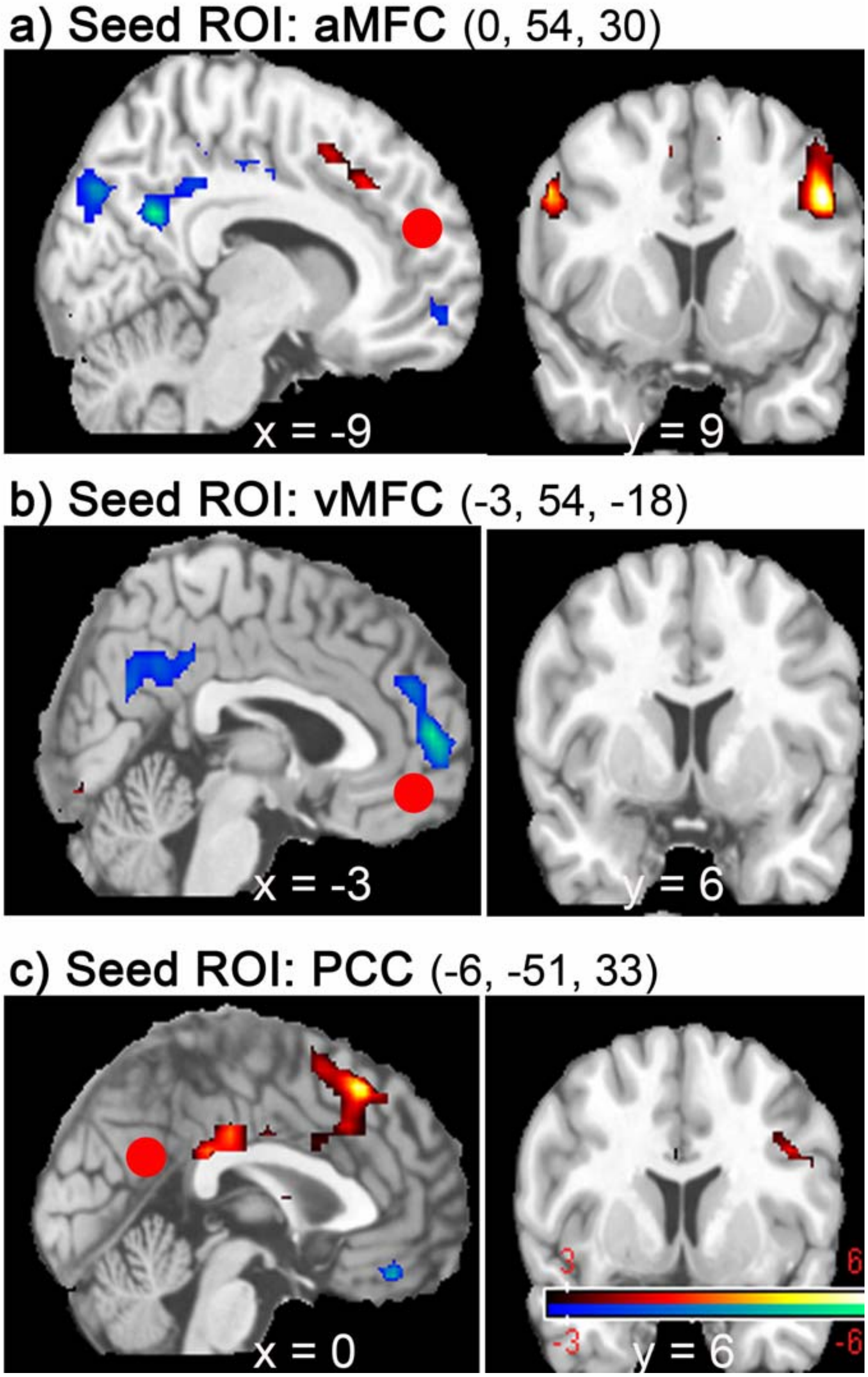
Functional connectivity analysis with PPI

For PPI analysis, we used the three cortical midline structures identified in the main subtraction analysis as seed ROIs to test for task-dependent ‘connectivity’: aMFC, peak activity (0, 54, 30); vMFC, peak activity (-3, 54, -18); PCC, peak activity (-6, -51, 33). As a function of social preference, each seed ROI identified overlapping, yet distinct, patterns of functional coupling with one another, as well as with the task-positive network.

Seed ROI – aMFC

When the seed ROI was placed at aMFC, PPI analysis showed that vMFC, PCC, pre-SMA/ dACC and bilateral frontoparietal cortices were among the very few regions that showed different functional coupling with aMFC between *Preference* and *Gender* task conditions (or, ‘task-dependent functional coupling’). More specifically, vMFC and PCC decreased correlation with aMFC as a function of social preference (*Preference* < *Gender*), whereas pre-SMA/dACC and bilateral frontoparietal cortices increased correlation (*Preference* > *Gender*; Table 2.3 and Figure 2.3a). When this interaction was examined further by testing for correlations between aMFC and the coupled regions for the two tasks separately, the analysis revealed that all these effects arose from differences in *positive* correlation (Figure 2.4). That is, for vMFC and PCC, the inter-regional correlation with aMFC was *less* positive during *Preference* than that during *Gender*; for pre-SMA/ dACC and bilateral frontoparietal cortices, the inter-regional correlation with aMFC was *more* positive during *Preference* than that during *Gender* (Figure 2.4b).

Figure 2.3: Cortical regions that showed task-dependent functional coupling with the seed ROI (marked with red circles): a) aMFC; b) vMFC; c) PCC



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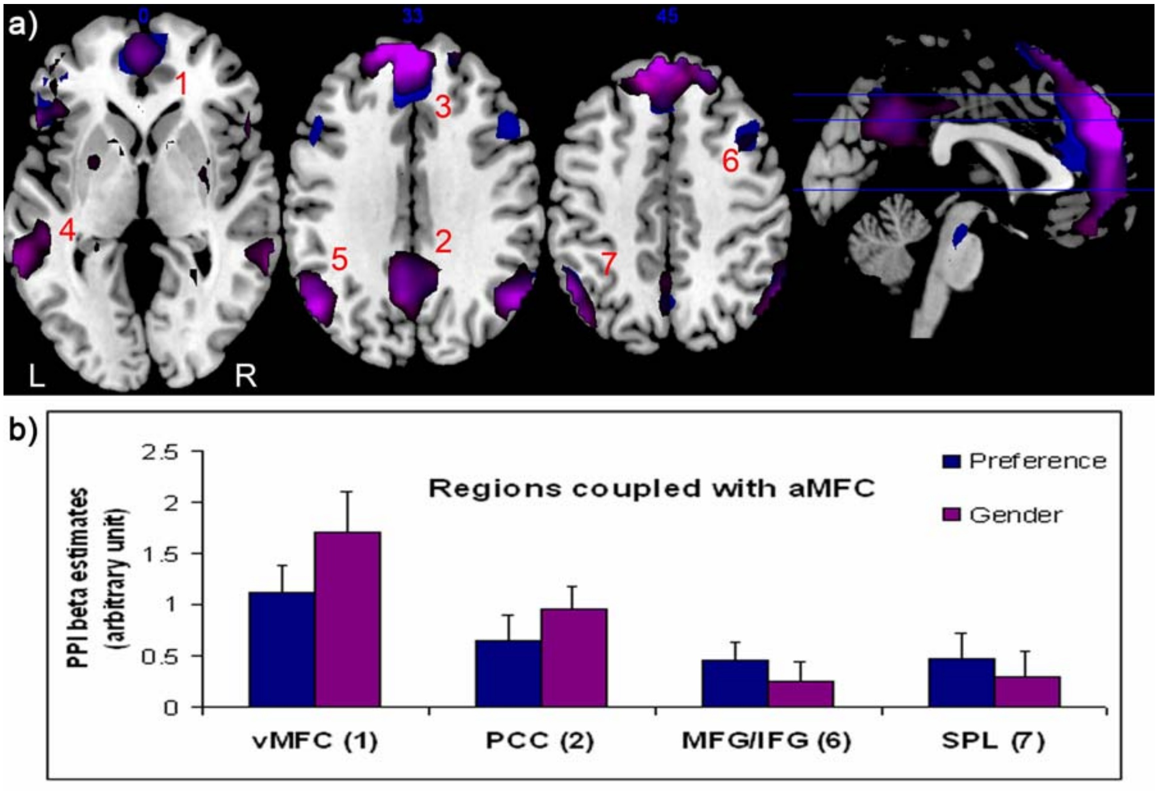


Figure 2.4 : Representative results of a PPI analysis modeling separate task conditions: Regions that showed inter-regional correlations with the seed ROI aMFC during Preference (blue-colored) and Gender (purple-colored) tasks, respectively, were overlaid onto the single subject brain template.

Seed ROI – vMFC

When the seed ROI was placed at vMFC, aMFC and PCC were the only regions that showed task-dependent functional coupling with vMFC. More specifically, both aMFC and PCC showed decreased correlation with vMFC as a function of social preference (Table 2.3 and Figure 2.3b); similarly, this occurred as a result of *less* positive inter-regional correlation during *Preference* than that during *Gender*.

Seed ROI – PCC

When the seed ROI was placed at PCC, PPI analysis revealed task-dependent functional coupling of the PCC with vMFC, with pre-SMA/ dACC, and with bilateral frontoparietal cortices, among few other regions. Specifically, vMFC showed decreased correlation with PCC as a function of social preference, whereas pre-SMA/ dACC and bilateral frontoparietal cortices showed increased correlation (Table 2.3 and Figure 2.3c); similarly, these were also found to be reflective of changes in *positive* correlation between the PCC and the coupled regions. That is, the inter-regional correlation between PCC and vMFC was *less* positive during *Preference* than that during *Gender*. For pre-SMA/ dACC and bilateral frontoparietal cortices, the inter-regional correlation with PCC was *more* positive during *Preference* than that during *Gender*.

In sum, the network interaction patterns revealed from PPI analyses showed that as a function of social preference (i.e. *Preference*, relative to *Gender*), there was a predominant pattern of *decreases* in *positive* coupling among all three cortical midline seed ROIs (aMFC, vMFC, PCC); on the other hand, only aMFC and PCC functionally interacted with the task-positive network mediating cognitive controlled processing, which was reflected as *increases* in *positive* coupling.

Table 2.3: PPI analyses -- Areas that showed task-dependent functional coupling with the medial cortical seed ROIs.

Abbreviations – STG, superior temporal gyrus; IPL, inferior parietal lobe; MFG, middle frontal gyrus; IFG, inferior frontal gyrus; SPL, superior parietal lobe; IPS, intraparietal sulcus
a Stereotactic coordinates from MNI152 reference, left/right, anterior/posterior and superior/inferior, respectively.
b Cluster size in voxels.
c All foci p<0.05, FDR-corrected; Extend threshold: 15 contiguous voxels.
d As a function of social preference (i.e. Preference, relative to Gender).

Seed ROI	Coupled Region	(x, y, z)[a]	Cluster[b]	Z-score[c]	Changes in Functional Coupling[d]
aMFC	**PCC**	-9, -57, 27	43	4.59	Decreased
	vMFC	0, 51, -6	55	3.85	Decreased
	STG	-60, -12, 0	72	4.11	Decreased
		-63, -33, 15	42	4.09	
	IPL	-45, -72, 33	46	3.87	Decreased
	Precuneus	45, 30, 27	25	3.67	Decreased
	MFG/ IFG	48, 9, 33	75	4.73	Increased
		-54, 12, 33	58	4.36	
		45, 30, 27	25	3.67	
	Pre-SMA/ dACC	6, 24, 48	29	4.23	Increased
	SPL/IPS	36, -57, 48	110	4.43	Increased
		-45, -48, 54	38	4.24	
	Fusiform	42, -60, -18	381	5.43	Increased
		-36, -69, -18	157	5.07	
vMFC	**aMFC**	-3, 57, 9	138	4.39	Decreased
	PCC	-6, -66, 27	124	3.96	Decreased
	Fusiform	-33, -69, -18	31	4.49	Increased
PCC	**vMFC**	0, 42, -21	38	3.96	Decreased
	IPL	-42, -48, 33	15	3.73	Decreased
	pre-SMA/ dACC	0, 27, 51	97	4.37	Increased
	SFG/MFG/ IFG	42, 6, 30	15	3.44	Increased
	SPL	45, -48, 42	93	3.88	Increased
	Fusiform	39, -63, -21	39	4.07	Increased
	Thalamus	12, -3, 15	28	4.00	Increased
		-15, -12,15	23	3.78	
	Mid Cingulate	-3, -33, 27	111	3.95	Increased

Discussion

As predicted, the SePT recruited cortical midline components of the default-mode network (aMFC, vMFC and PCC), reflecting reduced deactivation during *Preference* as compared to *Gender*. The SePT also activated brain areas involved in perceptual processing and task execution, reflecting increased activation during *Preference* relative to *Gender*. PPI connectivity analyses further provided evidence for network interactions of these three cortical midline structures that co-activated for the SePT. Specifically, our data showed that network interactions among the cortical midline structures, as well as that between the cortical midline structures and task-positive network vary as a function of engaging in social preference task. Together, the results provide important insights into how social preference is carried out by large-scale networks.

Social Functioning in the SePT and Default-Mode Network Activity

By employing an experimental design that allowed us to isolate the underlying process of evaluating subjective preference toward others (SePT), we first demonstrated the neural correlates of social preference and also tested the hypothesis that *Preference* modulates task-induced deactivations in the default-mode network. Our hypothesis was supported by direct comparison of the tasks, *Preference* and *Gender*, in combination with two conjunction analyses. As expected, several brain areas, including medial surface of SFG, vMFC, PCC and bilateral frontoparietal cortices, showed relatively greater activity in *Preference* than *Gender*. Moreover, the anterior portion of the frontal medial cluster (aMFC, along with vMFC) and PCC, resulted from *less deactivation* during *Preference* compared to *Gender*; the posterior portion of the same frontal medial cluster (pre-SMA, dACC), as well as bilateral frontoparietal cortices, arose from *more activation* during *Preference*.

The findings support and supplement the growing body of data for a CMS-based network invoked by social cognition. Current neuroimaging literature suggests that cortical midline structures support processes that integrate social information across time, allow representation and reflection of norms and intentionality, at a more abstract cognitive level (Uddin et al., 2007; Van Overwalle, 2008). Indeed, social preference requires an individual to attend to the social encounter beyond perceptual properties like gender. These preference evaluations may simply be based on emotion expression *per se*, or may involve more elaborative cognitive operations such as incorporating information from one's past experience, associations, or social stereotypes (e.g. squinty eyes tend to indicates untrustworthiness). Social preference lies in the eyes of the beholder – ultimately, it is up to the individual to sift through the available information, relate the information on a internal scale, and assess what is most personally relevant (de Greck et al., 2008; Enzi et al., 2009). Of note, a very recent study in impression formation also suggests that given the same person-descriptive information, the weights ascribed to each bit of information vary among individuals and can shape how first impressions are formed (Schiller et al., 2009). Further, Schiller and colleagues suggest PCC as part of a neural mechanism that codes for subjective valuation of social information. In line with the effect of expressing one's preferences for other individuals observed here in our study, a few other studies investigating the neural correlates of subjective preference for non-social objects (food or color) (Johnson et al., 2005; Paulus and Frank, 2003; Seger et al., 2004) have yielded similar results. Taken together, it is possible that the cortical midline signals in the present study may be attributed to the self-referential nature of the task (i.e. 'Do *I* like the person?), in addition to the processing of socio-emotional information inherently conveyed by the facial stimuli; however, the experimental design of the SePT did not permit the separation of these processes. Nonetheless, robust signals from the cortical midline suggest it is an effective task for probing this basic aspect of social cognition.

Our results with regard to the task-induced deactivations (TID) were consistent with the current understanding of the default network. Both attention-demanding *Preference* and *Gender* tasks decreased activity in default-mode network areas -- Medial PFC (aMFC & vMFC), PCC/ precuneus/ retrosplenial cortex, inferior parietal lobule (IPL) and lateral temporal gyri. Further, our hypothesis that attending to the *Preference* task 'counteracts' TIDs in the default-mode network was also supported, as *Preference* had less deactivation in aMFC, vMFC and PCC than *Gender*.

Since its conceptualization over a decade ago (Shulman et al., 1997), the nature of TIDs in the default-mode network still needs to be clarified, although many believe they occur as a consequence of limited processing resources. In order to meet cognitive demands, resources are reallocated from the default-mode network to the task-positive network: The more demanding the task, the stronger the deactivations (e.g. Buckner et al., 2008; Mason et al., 2007; McKiernan et al., 2006; McKiernan et al., 2003). An equally probable, but not mutually exclusive, mechanism for TID is the switch from attending to processes that engage the default-mode network to attending to goal-directed processes as required by the cognitive demands. For instance, emotion processing and self-referential tasks that require activity from the cortical midline structures have been shown to have less task-induced deactivations (e.g. Gusnard et al., 2001a; Johnson et al., 2005; Pallesen et al., 2008; Simpson et al., 2001).

Our findings that the *Preference* task recruited cortical midline components of the default-mode network (aMFC, vMFC, PCC), as well as the task-positive network (pre-SMA/ dACC, bilateral frontoparietal cortices) to process social preference showed that a reciprocal, ‘see-saw’, relationship between networks described as ‘anti-correlated’ does not appear to be a necessary condition for network functioning. Furthermore, the data corroborated more with the notion that attending to social cognitive functions (such as *Preference*) demanded activities from the cortical midline structures, thereby modulating TIDs in the default-mode network. It is worth noting that while it is possible that decreased deactivation observed during *Preference* reflected a less demanding task and not the social cognitive nature of the *Preference* task *per se*, this possibility is not likely for the following reasons: First, reaction time, a useful behavioral index for task difficulty and attentional demand, was greater in *Preference* than *Gender*. A more cognitive-demanding task usually increases the magnitude of deactivation (McKiernan et al., 2003). Second, at the neuronal level, *Preference* recruited more activity in pre-SMA/ dACC and bilateral frontoparietal corticies, areas associated with action selection and performance monitoring (Ridderinkhof et al., 2004) and usually increase with greater cognitive demands (McKiernan et al., 2003).

Within the medial frontal cluster evoked by the task contrast '*Preference* > *Gender'*, there was a clear dissociation with regard to activation and deactivation signals. In the anterior portion of the cluster (aMFC, vMFC and PCC), the signals arose from *less deactivation* during *Preference* than during *Gender*; this 'differential deactivation' was suggestive of a modulation of the TIDs in the default-mode network by social cognition. In contrast, signals in the posterior portion of the cluster (pre-SMA/ dACC, and bilateral frontoparietal cortices) represented more activation during *Preference*. Across diverse cognitive demands, this set of regions has been implicated in action selection and performance monitoring (Duncan and Owen, 2000; Ridderinkhof et al., 2004). Hence, this 'differential activation' is reflective of a greater cognitive demand posed by the explicit appraisal of social preference. Altogether, this co-activation may reflect a functional interaction through which contextually appropriate social preference decisions are facilitated.

For the reverse contrast (*Gender* > *Preference*), brain regions that showed greater signals, including precuneus, TPJ and STG, reflected more deactivation of these regions in *Preference* condition. While these regions are also components of the default-mode network and have been implicated in the processing of social information (e.g. Britton et al., 2006; Frith and Frith, 1999), the predominance of deactivations in these regions is potentially interesting. We suggest it is possible that subjects attended to the perceptual properties of faces to identify gender, and hence engaged more lateral frontotemporoparietal network (Lieberman, 2007; Van Overwalle, 2008).

Task-Dependent Functional Connectivity

We employed PPI analyses to investigate if the co-activated structures in the SePT functionally interacted, or 'co-modulated', with each other. As predicted, the three cortical midline ROIs identified overlapping, yet distinct, patterns of functional couplings as a function of social preference. In summary, of the three seed ROIs identified by the *Preference* > *Gender* contrast (aMFC, vMFC and PCC), all showed significant decreases in inter-correlations with one another as a function of social preference (i.e. *Preference*, relative to *Gender*). Moreover, such changes mainly reflected *less positive* coupling among the three regions when subjects performed the *Preference* task than *Gender*. For the task-positive network that also co-activated in the *Preference* > *Gender* contrast, on the other hand, significant increases in *positive* coupling during *Preference* occurred with aMFC and PCC.

Our current understanding of default-mode network connectivity is mainly based on seed voxel functional connectivity studies (Fox et al., 2005; Greicius et al., 2003) and independent component analysis of the resting state (Damoiseaux et al., 2006; Greicius and Menon, 2004). For example, Fox *et al.* analyzed band-pass filtered (0.009 < *f* <0.08 Hz) low frequency BOLD signal from subjects at rest, and found *positive* correlations within the default-mode network as well as *negative* correlations between the default-mode and task-positive networks (Fox et al., 2005). While *intrinsic* low frequency fluctuations in BOLD signals may inform us about brain organization in the absence of any task, they do not reveal connectivity dynamics of *evoked* BOLD responses during the performance of specific functions. Therefore, our PPI connectivity findings are complementary, and not necessarily in contradiction, to these resting state functional connectivity findings. Moreover, our data support and provide a network basis for social information processing.

Network interactions among co-activated cortical midline structures during social preference have implications for understanding the default-mode network. To date, only few studies have examined network properties of socio-emotional tasks (Das et al., 2005; Schmitz and Johnson, 2006). One particular intriguing observation from our data is how all three cortical midline default nodes (aMFC, vMFC & PCC) increase activity as a function of social preference, yet their residual variances showed decreased functional coupling. As each of the medial cortical default node has been associated with a distinct process in relation to social cognition (described above), it is tempting to speculate that this network interaction within the cortical midline default nodes may be a mechanism through which stimuli represented in vMFC are further modulated by an individual's cognitive evaluation (aMFC), as well as personal experience (PCC), in shaping social preference decisions (Uddin et al., 2007; Van Overwalle, 2008). However, a final interpretation of the PPI findings will require deeper investigation.

On the contrary, as the CMS and the task-positive network both increased activity in the *Preference* > *Gender* contrast, only aMFC and PCC showed increased functional couplings with the task-positive network as a function of social preference. These findings may be interpreted by two frameworks involving social cognitive functions laid out by Phillips (Phillips et al., 2003) and Northoff *et al* (Northoff et al., 2006). Reviewing findings from animal, human lesion and functional neuroimaging studies, Phillips and colleagues proposed two neural systems critical for emotion processing: A ventral system that includes vMFC and subserves the identification of the emotional significance of environmental stimuli and the production of affective states; and a dorsal system (including aMFC, pre-SMA/ dACC and bilateral PFC) important for the performance of executive functions to regulate the initial appraisal and guide contextually appropriate goal-directed behavior (Phillips et al., 2003). Northoff and colleagues, via cluster and factor analyses, further suggested that PCC is also essential for temporal integration of self-referential stimuli (Northoff et al., 2006). Taken together, our findings provide connectivity-based evidence to support both frameworks: aMFC-/PCC-coupling with pre-SMA/ dACC and bilateral PFC suggest on-line support from cognitive operations to carry out evaluative social decisions, e. g. ‘Do I like this person?’ (Koechlin and Hyafil, 2007; Schmitz and Johnson, 2006) We further suggest that during social information processing (especially those with explicit requirements for evaluation or judgment, such as social preference considered herein), PCC may also be a part of the dorsal system as the autobiographical context of an individual could be critical in guiding the appropriate goal-directed behavior (Buckner et al., 2008).

The vMFC did not exhibit functional coupling with the task-positive network, possibly reflecting the fact that the initial stimulus appraisal is rapid and requires little cognitive effort, in line with the role for the vMFC suggested by others (Phillips et al., 2003; Schmitz and Johnson, 2006).

Neuroanatomically, this ‘socio-emotional neural circuitry’ is feasible as both direct and indirect projections between aMFC, vMFC and PCC have been characterized in human and monkey (Morris et al., 2000; Ongur and Price, 2000; Vogt et al., 2006). In addition, collaborative activities from structures associated with action monitoring/control and relating action to consequence are made possible by the reciprocal anatomical projections that connect aMFC and PCC with pre-SMA, dACC and bilateral PFC (Ongur and Price, 2000; Petrides and Pandya, 1999; Vogt et al., 2006). In contrast, the sparse neuroanatomical connection between vMFC and these cognitive function regions is consistent with the lack of connectivity observed during the SePT (Pandya and Yeterian, 1996; Petrides and Pandya, 2006). Other interpretations are certainly possible, and conclusions about signals not observed may reflect Type 2 errors, but the findings reported here do appear to converge with other work.

Limitations

The psycho-physiological interaction data have to be interpreted within the right framework. Importantly, since PPI takes data from the entire time series and assumes time-invariance in inter-regional correlations, the ‘positive’ and ‘negative’ coupling derived from linear regression have mathematical interpretations that should not be interpreted as ‘activation’ or ‘inhibition’ between spatially distinct brain regions. Rather, they only refer to the relative difference between the correlation slopes of the seed ROI with the coupled region for each condition. Therefore, no inference about any causal inter-regional relationships should be made for PPI (Friston et al., 2003). In addition, systematic analyses in future studies that compare correlations at different frequency ranges may provide additional insights about the relationship of PPI to other connectivity measures, including resting state spontaneous BOLD fluctuations.

Another issue concerns that fact that we did not collect post-scan ratings of the emotion dimensions such as ratings for valence or intensity. Although the same facial stimuli were used in both task conditions to exclude any potential pictorial confounds, our blocked-design paradigm was not suitable to address the question of whether the social preference signals observed may be confounded by emotion dimensions. Future studies employing an event-related design with post-scan ratings of personal association as well as emotion dimensions are necessary to better distinguish the influence of personal relevance and emotion dimensions of valence and intensity on this socio-emotional neural circuitry.

CHAPTER III

BEHAVIORAL INTERFERENCE BETWEEN SOCIAL COGNITION AND EXECUTIVE FUNCTION

Introduction

Chapter 3 describes the development of a novel dual-task paradigm that parametrically manipulated factors known to affect cortical activity in the default-mode and task-positive networks: social cognition and spatial working memory demand, respectively. This dual-task paradigm was later adapted for a neuroimaging experiment in Chapter 4 (Study 4); ultimately, this paradigm aimed to provide a robust probe that allows for systematic characterization and better understanding of the interactions between large-scale networks.

In Chapter 2, we demonstrate that appraising whether one likes a person or not recruited activity from cortical midline components of the default-mode network (aMFC, vMFC and PCC) as well as the task-positive network (pre-SMA/ dACC, bilateral frontoparietal cortices). We also provide connectivity-based evidence and demonstrate positive coupling between the two functionally interacting networks, thereby facilitating contextually appropriate social–cognitive behavior. Our findings suggest that social cognitive functions, particularly those involving explicit appraisals or deliberative introspections of salient stimuli, put a demand on the cognitive resource which is capacity-limited in nature. As such, social cognitive functions may be compromised when cognitive load on executive control functions, such as working memory, is taxed (Chaiken and Trope, 1999; Kahneman, 2003).

Indeed, both social cognitive functions (those with explicit cognitive components) (Gusnard et al., 2001a; Moran et al., 2006) and executive control functions (Cabeza and Nyberg, 2000; Duncan and Owen, 2000) rely on the involvement of lateral frontal and parietal cortices. This anatomical overlap is suggestive of a plausible functional relationship, perhaps competitive in nature, between the two. In an effort to investigate the functional consequences, if any, to this overlap, as well as gain insight into the nature of the mechanism by which the two networks interact, we developed a dual-task paradigm. This novel paradigm independently manipulated, *within*-subject, executive control function (working memory load) via the difficulty of a delayed match-to-sample task, and social cognitive function in the form of evaluative appraisals of one's personal traits (See Figure 3.1 or Figure 3.4 for design). Two studies (study 2 & 3) included in this chapter examined the behavioral interference of these functions on outcome measures including appraisal latency and performance accuracy. Specifically, the current research asked the following two questions: First, do executive control functions (working memory), if taxed, disrupt social cognitive functions (evaluative appraisal of one's personal traits)? Second, does evaluative appraisal disrupt working memory performance?

A resource depletion framework was critical in motivating our approach. The notion that cognitive resource is capacity-limited has various implications in the field of social psychology and cognitive neuroscience. For instance, working memory, which maintains goal-relevant information, has severe capacity restraints (Cowan, 2001, 2005) and is often challenged by distracters that interfere with the attainment of goals; in particular, distracters that are emotional or personally relevant have been suggested to be especially potent in reallocating processing resource (Dolcos and McCarthy, 2006; Ellis and Ashbrook, 1988; Morey et al., 2009). Increased load on working memory that renders resources unavailable to actively maintain task priorities has greater interference by irrelevant low-priority distracters (Lavie, 2005; Lavie et al., 2004). Similarly, a large corpus of previous studies in social psychology suggests that the deliberative processing of self-relevant information also requires cognitive resource that is limited in nature (Baumeister et al., 1998; Baumeister and Vohs, 2003; Muraven et al., 1998). Various regulatory activities, such as regulation of cognition and thoughts, of emotion, of impulsive and appetitive behaviors, of self-presentation (Baumeister and Vohs, 2003; Vohs et al., 2005; Vohs and Heatherton, 2000) can temporarily deplete this limited resource, thereby reducing functions that are more effortful and controlled, such as reflecting upon one’s own characteristics (Lieberman, 2007; Todorov et al., 2006). For example, Vohs and colleagues asked participants first to engage in a form of self-regulation (e.g. emotion regulation during a comedic film versus no instruction to do so); later, participants who had to expend their resources to regulate emotion were found unable to present themselves optimally (e.g. describe themselves in a narcissistic, self-aggrandizing way) (Vohs et al., 2005)

We hypothesized a functional overlap between social cognitive and executive control functions, and predicted the following behavioral manifestations as a consequence of the overlap. First, as high working memory load is expected to engage more cognitive resource than the low load, thereby leaving less capacity for the processing of personality trait adjectives, we predicted that increases in working memory load would result in altered evaluative appraisal of one's personal characteristics. Second, we predicted that an individual's ability to maintain working memory would be impaired, to the degree that evaluative appraisals of self depends on the shared but limited cognitive resource.

Study 2

Methods

Subjects

Sixty healthy undergraduates between the age of 18 and 22 years were recruited from the University of Michigan community. The data of one subject from behavioral experiment 1 was excluded from analysis because of a failure in computer recording of his responses. Demographics are outlined in Table 3.1. All subjects were native English speakers and had normal or corrected-to-normal visual acuity. Written informed consent, approved by the University of Michigan Institutional Review Board (IRBMED), was obtained from all subjects prior to study participation. After completion of the study, subjects were given credits toward an undergraduate course (Introduction to Psychology).

Table 3.1: Participants Demographics – Study 2 & 3 (Behavioral)

	Study 2	Study 3
No. Participants (males)	59 (42 Males)	30 (21 Males)
Age (years)	19.10 ± 0.98	18.93 ± 0.94
Caucasian	46	24
African American	2	2
Hispanic	2	0
Asian	9	3
American Indian	0	1

Materials

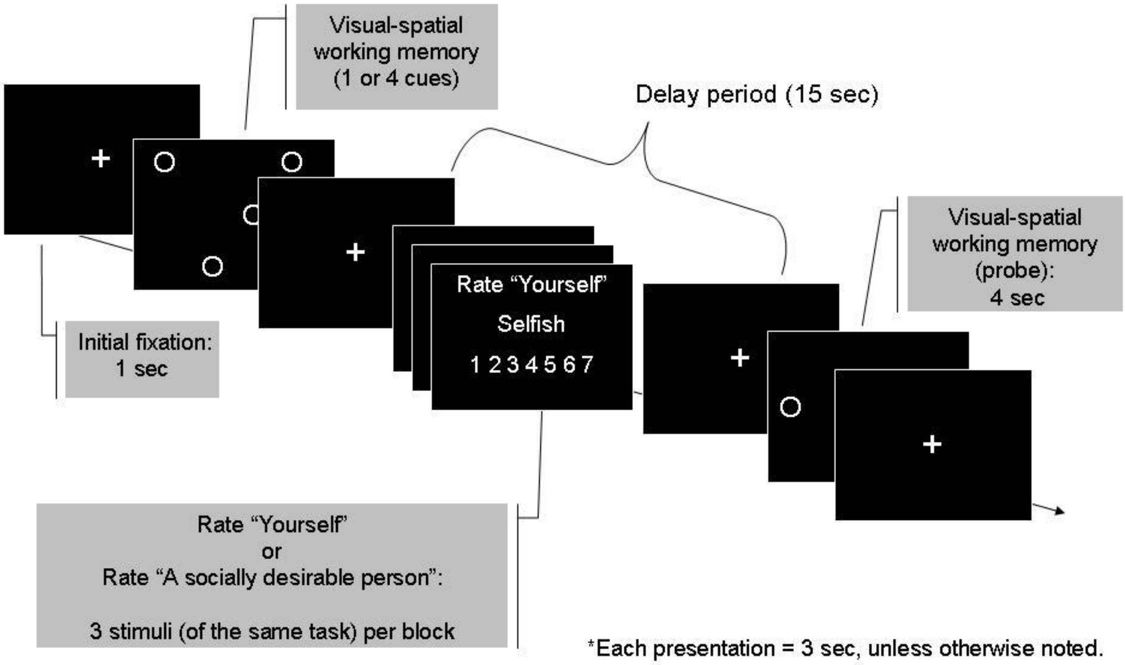
Four word lists, each containing 27 negative personality trait adjectives, were selected from a standardized trait-word set (Anderson, 1968) that has been used in many previous behavioral and neural studies of evaluative self-referential processing (Dunning et al., 1989; Fossati et al., 2003; Kelley et al., 2002). All negative words were selected from those with a mean likableness rating below 2.0 (scale 0-6: “least, to most, favorable or desirable”). The four word lists were matched for their overall average likableness rating, meaningfulness, familiarity, and verbal-/written-frequency; subsequently, the word lists were randomly assigned to each of the 4 dual-task trial types (2 working memory load cross with 2 appraisal targets).

For the working memory part of the dual-task, either one dot or four dots were presented (cue). The cue(s) appeared randomly at 1 of 5 possible distances on each 10 degree radius of a full circle, with no cues appearing on the cardinal axes, so namable locations (e.g. center, straight up, down, left, right) were avoided. Furthermore, the spatial locations in the memory set of each trial were pseudo-randomized so that no two dots were presented in the same quadrant in any single trial. This constraint was used to prevent random clustering of dots, which would make the task difficulty uneven. In half of the trials, the probe matched one of the locations in the memory set; in the other half, the non-matching probe was pseudo-randomly located in nearby target locations of the same quadrant.

Task Design and Procedure

Each trial began with an initial fixation of 1 sec, followed by a cue for 3 sec, a retention period (‘delay’) of 15 sec, and a probe screen for 4 sec (response). Subjects were instructed to make corresponding mouse-click (‘yes’ or ‘no’) to indicate whether the location of the probe matched any of the previously-encoded cue positions. During the 15 sec retention period that started and ended with 3-sec exposure of a fixation point, three trait adjectives were presented for evaluation for 3 sec each. The trait word was placed in the center of the screen, below task instructions indicating the target of trait-evaluation (‘Rate Yourself’, or ‘Rate a Socially Desirable Person’), and above a 7-point Likert scale (1: Not at all applies; 7: Applies a lot). The three trait-evaluation trials within the retention period had the same appraisal target. Subjects were instructed to make the evaluations “while keeping dots locations in mind” and “as quickly and as accurately as possible” by mouse-clicking the corresponding number. These events are shown in Figure 3.1.

Figure 3.1: Illustration of the Dual-task (Study 2)



Therefore, the novel dual-task structure involved a classical delayed match-to-sample working memory task temporally flanking a trait-evaluation task; The two independent variables were manipulated within subjects: working spatial memory load (either one cue location to memorize or four) and appraisal target (either how well each personality trait word applied to themselves ('self'), or to a socially-desirable person ('other')). Thus, there were four types of dual-task trials consisting of evaluating either 'self' or 'other' with concurrent spatial working memory that varied in load (i.e. low or high).

After explaining task instructions, subjects entered a practice session and were given approximately 12 practice trials (3 trials per dual-task trial type) to familiarize themselves with the task structure. For the formal experimental blocks, 36 trials were accommodated overall in the session (9 delayed match-to-sample working memory trials flanking 27 trait-evaluations per dual-task trial type); moreover, the four types of dual-task trials were pseudo-randomly presented so that no two trials of the same type were presented back-to-back.

Stimulus control and response recording occurred with E-prime (Psychology Software Tools, Inc.).

Analysis

To test on-task performance, the average trait endorsement (in ratings), working memory accuracy and the mean reaction times (time spent making trait endorsement response; time spent responding to the working memory probes) were examined. These dependent variables (ratings; accuracy; reaction times) were separately examined using 2 (load: low, high) X 2 (appraisal target: 'self', 'other') repeated-measures ANOVAs, and paired t-tests were used post hoc to assess significant differences among within-subject factors. In all behavioral analyses, an effect was considered significant if it reached a threshold of $p<0.05$. All behavioral data analyses were conducted using SPSS v15.0 (SPSS Inc., Chicago, IL).

Dependent variables presented in the following sections are all expressed as mean ± SE. Data from one subject was excluded for analysis due to technical error. Therefore, all reported data represented behavioral results from 59 subjects, unless otherwise noted.

Results and Discussion

Effect of Concurrent Working Memory Load on Trait-Evaluation

The two dependent variables from the trait-evaluation task, mean reaction time (time spent making trait endorsement responses) and average trait endorsement (in ratings) were calculated for each subject as trait-evaluation measures.

The repeated-measures ANOVAs showed that reaction times differed depending on working memory load (F(1,58)=12.18, p=0.001). Trait-evaluations under concurrent high working memory load (2190 ± 89 msec) were made significantly faster than those made under low working memory load (2328 ± 94 msec). No main effect of working memory load was found on trait endorsement (in ratings; p>0.35). This suggested that concurrent maintenance of 4 spatial locations in mind facilitated faster trait-evaluation responses (relative to when having to keep only 1 location in mind). As there was no change in ratings as a function of working memory load, one can infer that the evaluative appraisal was merely facilitated in speed, and not rendered more superficial (Figure 3.2).

There was a significant main effect of appraisal target on trait endorsement (in ratings; F(1,58)=72.9, p<0.001) such that subjects related (negative) adjectives more to themselves (2.49 ± 0.09) than to a socially-desirable ‘other’ (1.83 ± 0.06). The effect of appraisal target on reaction time was marginally significant (F(1,58)=3.9, p=0.052). The average time spent on making trait endorsement responses tended to be longer for ‘self’ (2304 ± 96 msec) than for ‘other’ (2214 ± 88 msec). However, no significant interaction between working memory load and appraisal target was found on either reaction time or ratings. Table 3.2 summarizes the trait-evaluation measures for the 4 dual-task trial types.

Figure 3.2: Effects on Trait-evaluation measures (Study 2)

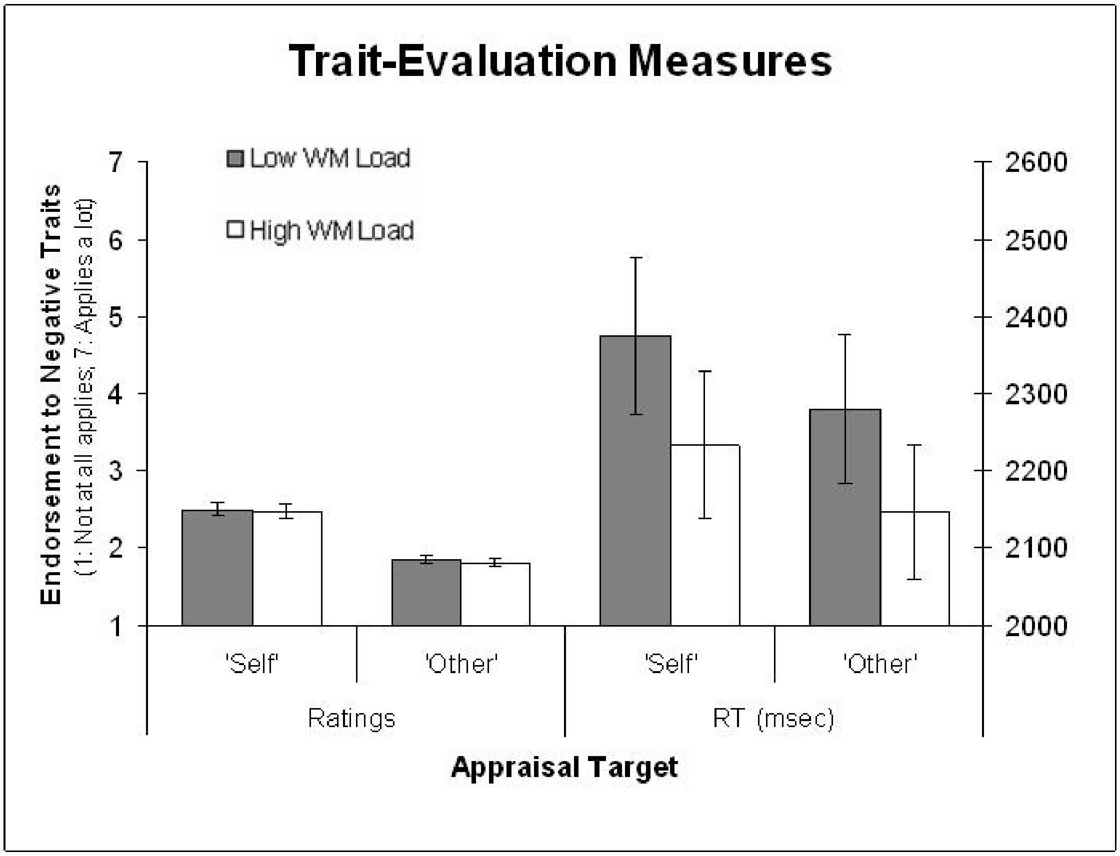


Table 3.2: Summary of Trait-Evaluation Measures (Study 2)

		Ratings (7-point scale)		Reaction Time (msec)[a]	
		Working Memory Load[b]		Working Memory Load[b]	
		1	4	1	4
Appraisal Target	'Self'	2.50±0.09	2.48±0.10	2375±103	2233±96
	'Other'	1.85±0.06	1.81±0.06	2280±96	2147±87

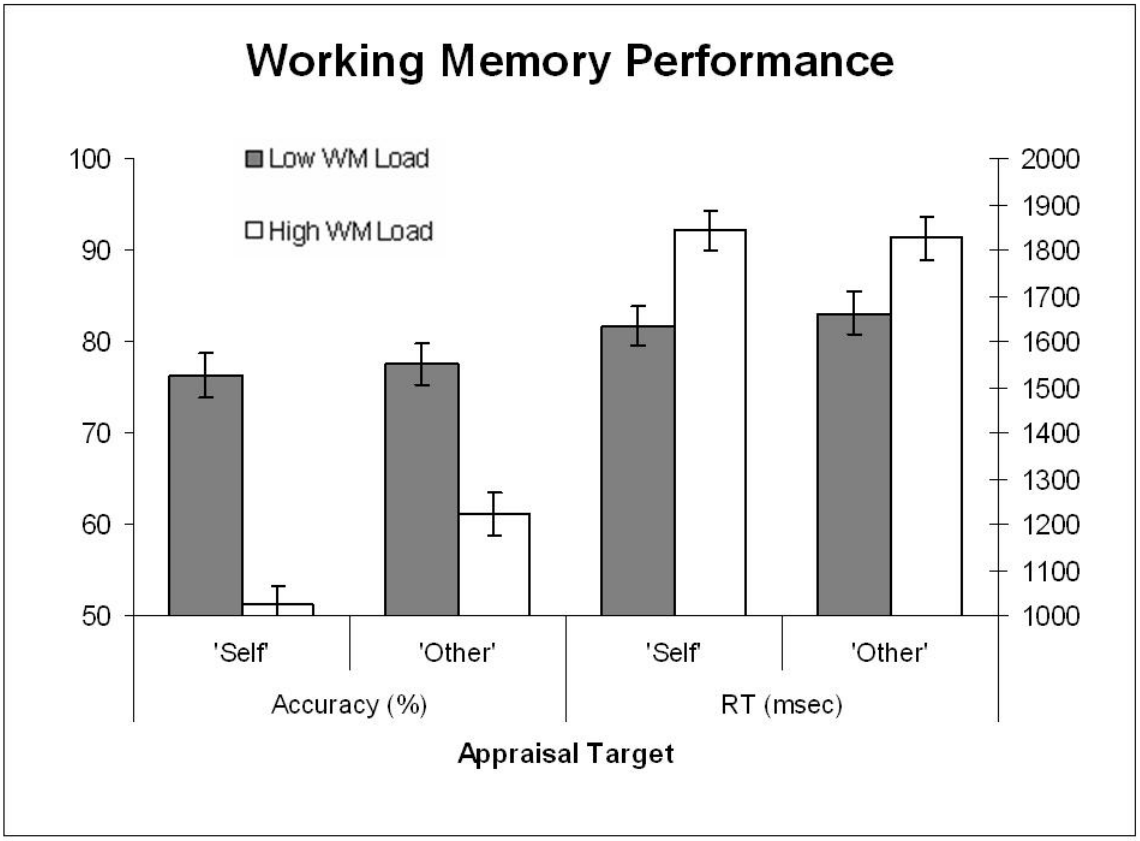
[a] *Average time spent on making trait endorsement responses*
[b] *The number of dot-location(s) to be held in working memory*

Effect of Trait-Evaluation on Delayed Match-to-Sample Working Memory Performance

The two dependent variables, accuracy and reaction time[a] during the working memory task ([a] to be distinguished from the reaction time measure in the previous section, which was the time spent on making endorsement responses), were calculated for each subject as indexes of working memory performance.

For working memory accuracy, the repeated-measure ANOVA showed a significant main effect of working memory load, F(1,58)=93.36, p<0.001, a main effect of appraisal target, F(1,58)=10.38, p=0.002, and a significant interaction between working memory load and appraisal target, F(1,58)=4.43, p=0.04 (Figure 3.3).

Figure 3.3: Effects on working memory performance (Study 2)



Follow-up paired t-tests revealed that the drop in working memory accuracy after evaluation ‘self’ (when compared to ‘other’) was only significant when the working memory load was high, $t(58)=-3.7$, $p<0.001$, but not when it was low, $p>0.63$. Furthermore, a one-sample t test compared this accuracy against 50%, $p>0.55$, suggesting that the working memory accuracy after evaluating ‘self’ under high memory load dropped to a level that was not significantly different from chance level.

A separate 2x2 ANOVA for the (working memory) reaction time dependent variable, on the other hand, revealed only a significant main effect of load

(F(1,58)=32.51, p<0.001), such that subjects spent more time responding to the probe when the memory load was high (1836 ± 43 msec) than when it was low (1648 ± 41 msec). Neither main effect of appraisal target (p>0.81) nor the interaction of load and appraisal target (p>0.41) was found. Table 3.3 summarizes the working memory performance for the 4 dual-task trial types.

Table 3.3: Summary of Working Memory Performance Data (Study 2)

		Accuracy (%)		Reaction Time (msec)[a]	
		Working Memory Load[b]		Working Memory Load[b]	
		1	4	1	4
Appraisal Target	'Self'	76.27±2.45	51.22±2.04	1634±44	1843±47
	'Other'	77.59±2.19	61.21±2.36	1663±46	1828±47

[a] Average time spent on making WM retrieval responses
[b] The number of dot-location(s) to be held in working memory

Because subjects spent marginally longer time evaluating themselves than the 'other' (p=0.052), this behavioral index for task difficulty and attentional demand suggests that it is possible that the selective interference observed between working memory and the evaluative appraisal of self (Figure 3.3; p=0.04) simply reflected a more demanding task ('self', relative to judging a nonspecific, socially-desirable 'other'), and not a functional overlap *per se.* We therefore employed two additional analyses to further address this issue and exclude this possibility. First, we selected a subgroup of subjects (n=35) whose overall mean reaction time to evaluate 'other' was significantly longer than to evaluate self (F(1,34)=7.24, p=0.011), and repeated the 2x2 ANOVA on working memory accuracy. Still, in this subgroup, the selective interference between working memory load and appraisal target persisted, F(1,34)=5.32, p=0.027, which was manifested as a significant decline in accuracy with concurrent self-referential processing (compared to 'other') during the retention of high memory load. Second, for the original group of subjects (N=59), we built a repeated-measures linear mixed model wherein reaction times to making trait endorsement responses for the 4 dual-task trial types were separately entered as covariates for working memory accuracy. This analysis showed not only that appraisal reaction time was a non-significant covariate of working memory accuracy (F=2.68, p=0.11), but also that the interaction between working memory load and appraisal target on accuracy remained significant (F=4.76, p=0.03).

One other issue concerns the robustness of the selective interference finding (p=0.04), which may potentially be limited by a 'floor effect' from a subgroup of subjects who performed working memory at chance level. Indeed, as working memory accuracy cannot go lower than 50%, it is possible that there is little room left to allow the difference between the appraisal targets ('self', or 'other') to manifest, especially during high load working memory conditions. To examine whether a floor effect is limiting the significance of the interaction finding, we performed the load by appraisal target repeated-measures ANOVA in a subgroup of 19 subjects whose accuracy level was over 55.56% (less than 4 errors per 9 trials) for all 4 conditions. The significant interaction between working memory load and appraisal target on accuracy persisted in this subgroup, F(1,18)=10.32, p=0.005, further confirms the robustness of the paradigm.

In sum, this first behavioral experiment (Study 2) provided preliminary evidence for selective interference between spatial working memory and the evaluative appraisal of self. This interference manifested itself as a significant decline in working memory accuracy in the presence of concurrent 'self' evaluation (relative to 'other') during the retention of high memory load. That is, we demonstrated that the 'cognitive cost' of the 'self' depends on the extent to which the shared limited resource is taxed, at least by memory load considered herein. We suggest that there is a functional overlap between the social cognitive and executive control functions, and that underlying mechanism may be competitive in nature.

Study 3

Study 3 served as a behavioral extension of Study 2 with several additional aims. The first aim was to further strengthen the argument that the overlapping underlying mechanism was between working memory per se and evaluative appraisal of self per se. Therefore, for the delayed match-to-sample part of the dual-task, we substituted the 'one dot' (low memory load condition) with 'two dots'; this was done to make the working memory load comparisons more compelling, as 1 item has a special status in working memory in that it resides within the focus of attention and is uniquely immediately accessible for cognitive operations (McElree, 2006; McElree and Dosher, 1989; McElree and McElree, 2001; Nee and Jonides, 2008). For the trait-evaluation part of the dual-task, we added a third value to the appraisal targets. This was done to experimentally address a possible alternative account for the results of study 2, in terms of a difference in cognitive demand between evaluating the ‘self’ and judging a nonspecific, socially-desirable ‘other’. We recognize the possibility that evaluating a ‘generally desirable person’ could be, for example, less engaging, less deliberatively processed, more stereotypical and abstract (i.e. not a specific person), thereby rendered working memory not as susceptible to interference.

As a result, in Study 3, the three experimental conditions of the trait-evaluation task were: ‘Self’ (“How much does the adjective describe yourself?”), ‘Other’ (“How much does the adjective describe your specific friend X?”) and ‘Semantics’ (“How socially desirable is the trait described by each adjective?”). It is worth noting that this ‘Semantics’ condition is analogous to the ‘(nonspecific) Other’ condition used in Study 2. The second aim was to extend the finding and examine whether the selective interference vary as a function of valence by including positive trait-adjectives. Finally, the third aim was to optimize the paradigm parameters to increase intra-subject sensitivity and get working memory accuracy off the chance level (i.e. 50%), as the floor effect may be limiting the difference between the appraisal targets to manifest, thereby limiting the interaction finding.

Methods

Subjects

Thirty healthy undergraduates (between the age of 18 and 22 years) who had not participated in Study 2 were recruited in compliance with the human subjects regulations of the University of Michigan Institutional Review Board (IRBMED), and completed the experiment to partially fulfill course credit (Introduction to Psychology); All subjects were debriefed upon study completion. All subjects were native English speakers, had normal or corrected-to-normal visual acuity, and demographics are outlined in Table 3.1.

Materials

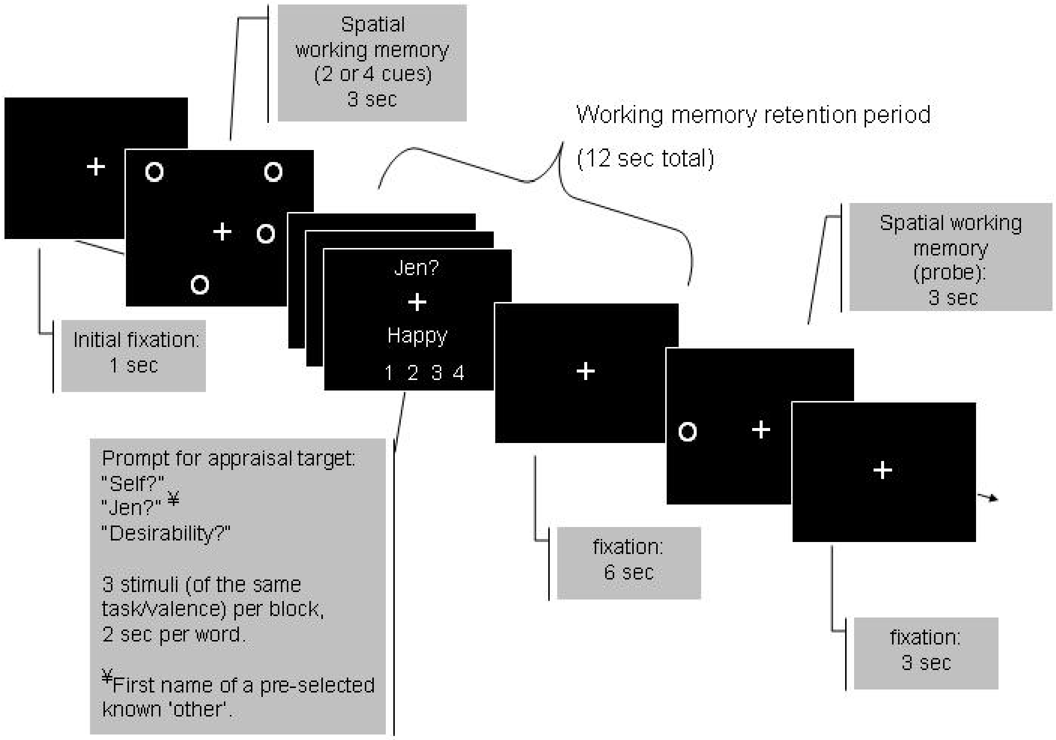
Twelve word lists (6 positive, 6 negative), each containing 30 personality trait adjectives, were constructed from the Anderson norms (Anderson, 1968). The positive and negative words were selected from the top 180 (mean likableness rating above 4.7) and bottom 180 (mean likableness rating below 1.3), respectively, of Anderson's sample (scale 0-6: "least, to most, favorable or desirable"). All 12 word lists were matched for their overall average meaningfulness, familiarity and verbal/written-frequency; the 6 positive and the 6 negative word lists were equated for their average likableness ratings within each valence. For each subject, a pair of positive and negative word list were randomly assigned to each of the 6 dual-task trial types (2 working memory load crossed with 3 appraisal targets); therefore, no verbal stimulus was used more than once, and each subject received a unique protocol. One separate word list selected from the middle 60 of Anderson's sample was set aside and used for instruction and practice trials.

Task Design and Procedure

The apparatus and software used were the same as those used for the previous behavioral experiment, Study 2.

The procedure was very similar to that of Study 2, with the exception of the following: First, for the delayed match-to-sample part of the dual-task, the memory load levels used were 2 and 4 dots (instead of 1 and 4); In addition, the location of the probe for mismatch trials (half of the total trials) was systematically controlled so that the foil could be either near (2.5°) or far (3°) from the target locations. For the mismatch trials, they were equally divided between near and far misses; retrieval period was shortened to 3 seconds (instead of 4), which was empirically shown to be more than sufficient in Study 2. Second, for the trait-evaluation part of the dual-task, a '(specific) other' condition was included as a person-specific experimental control for the 'self' condition. Upon entering the study, subjects were instructed to identify a neutral individual (e.g. from work or school; excluding best friend, significant other and family members) who they were personally familiar with, to be used as an evaluation target throughout the experimental session (e.g. "How much does the adjective describe Jen?"). We reasoned that this subject-specific 'other' subscription in our task design has advantage over the generic ‘other’ selection (e.g. celebrities or public figures, including President George W. Bush) in existing literature in that personal familiarity is controlled and affective association (response bias) is minimized. Paradigm parameters were also minimally revised in 3 ways: Two seconds per word (instead of 3) was allowed and the rating was revised to 4-point Likert scale (1: Not at all applies; 4: Applies a lot) to make responding more manageable within the time allowed. Lastly, the delayed match-to-sample retention period started with the trait-evaluation task (instead of a 3-sec fixation that preceded trait adjectives); this was done to optimize the effect of working memory load (on appraisal) (Jha and McCarthy, 2000). The revised event structures for Study 3 are summarized in Figure 3.4.

Figure 3.4: Revised trial structure of the Dual-task (Study 3)



Although Study 3 involve both positive and negative words, subjects were not required to directly rate the valence itself. Overall, 120 trials were accommodated in Study 3 (20 delayed match-to-sample working memory trials per dual-task trial type). Within each trial type, half (10) of the working memory trials temporally flanked positive trait adjectives, and the other half flanked the negatives.

Analysis

Same dependent variables as those in Study 2 were recorded by E-prime (Psychology Software Tools, Inc.). Briefly, on-task performance measures (average trait endorsement in ratings, working memory accuracy and reaction times for trait-evaluation and for working memory retrieval) were separately examined using 3-way ANOVA. The three within-subject factors were valence (positive, negative), working memory load (low, high) and appraisal target ('self', 'other', 'semantics'); post-hoc analyses were also performed to follow-up significant effects. An effect was considered significant if it reached a threshold of $p<0.05$.

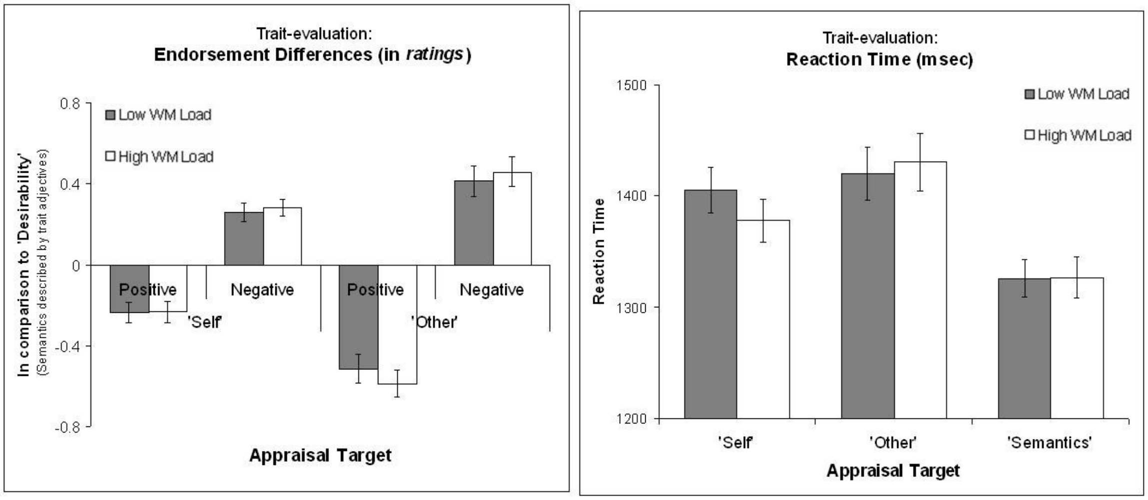
All statistical analyses were conducted using SPSS 15 (SPSS Inc., Chicago, IL), and dependent variables presented in the following sections are all expressed as mean ± SE.

Results and Discussion

Effect of Concurrent Working Memory Load on Trait-Evaluation

For trait endorsement (in ratings), the 3-way repeated-measure ANOVA showed a main effect of valence ($F(1,29)=336.4$, $p<0.001$), such that subjects on average endorsed more positive (3.13 ± 0.04) and less negative trait adjectives (1.59 ± 0.06), as well as a significant interaction between valence and appraisal target ($F(2,58)=28.6$, $p<0.001$). When this interaction was examined further by entering negatively and positively valenced words into 2 separate one-way ANOVAs, we observed a main effect of appraisal target on trait endorsement for negative ($F(2,58)=16.9$, $p<0.001$; replicating Study 2) as well as positive trait adjectives ($F(2,58)=28,8$, $p<0.001$). Pair-wise comparisons showed, when comparing themselves to the semantics described by each trait adjective (analogous to the ‘a general socially-desirable other’ condition used in Study 2), subjects characterized themselves to be not as desirable (i.e. more negative and less positive). In addition, when comparing themselves to personally-familiar peers, subjects endorsed less negative and more positive information as self-relevant (i.e. judged their own personality as more desirable than their peers’), all of which were in line with findings from social psychology (Chambers and Windschitl, 2004; Taylor and Brown, 1988) (Figure 3.5a). Neither the main effect of load ($p>0.56$) nor the interaction of load and appraisal target ($p>0.73$) was found on endorsement ratings.

Figure 3.5: Effects on Trait-evaluation measures (Study 3)



The other dependent variable for trait-evaluation, reaction time (time spent making trait endorsement responses), varied as a function of appraisal target as well (F(2,58)=19, p<0.001). Planned comparisons revealed that it took subjects significantly longer to evaluate themselves (1437 ± 21 msec) and their peer (1482 ± 30 msec), than to the semantics condition (1367 ± 19 msec); no significant difference between self- and other-evaluation was found. In contrast to Study 2, there was no main effect of working memory load on reaction time measure (F(1,29)<1, p=0.7) – Concurrent maintenance of high memory load (1426 ± 23 msec) did not facilitate nor interfere with trait-evaluation responses (relative to low memory load, 1431 ± 21 msec), which is likely due to the already short intervals allowed for trait-evaluation (2 seconds, versus 3 in Study 2). The interaction between memory load and appraisal target did not reach significance level, p>0.08 (Figure 3.5b) and pair-wise comparisons showed only trend significance in RT decrease when evaluating 'self' under high (versus low) memory load (p=0.078). For the purpose of simplifying the graphic display, we have collapsed across positively and negatively valenced words in Figure 3.5, as no significant effect of valence was found. Table 3.4 summarizes the trait-evaluation measures for all trial types.

Table 3.4: Summary of Trait-Evaluation Measures (Study 3)

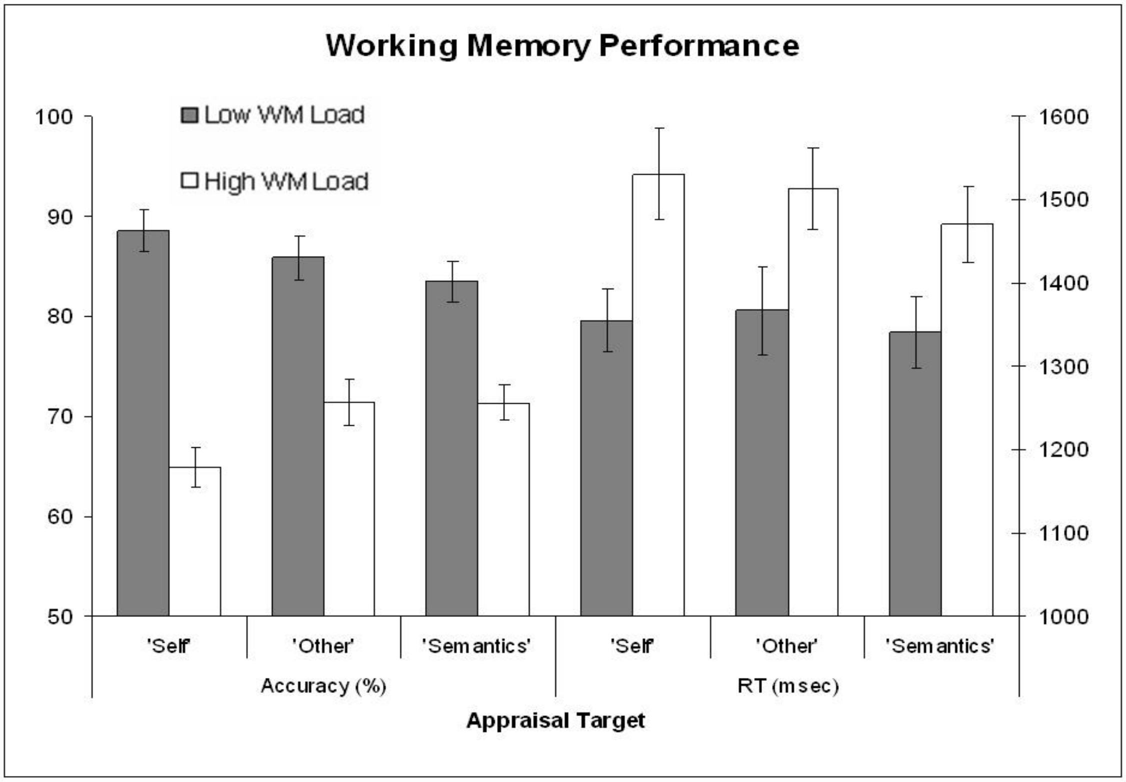
			Ratings (4-point scale) Working Memory Load[b]		Reaction Time (msec)[a] Working Memory Load[b]	
			2	4	2	4
Appraisal Target	'Self'					
		Positive	3.17±0.06	3.18±0.06	1428±25	1392±25
		Negative	1.64±0.06	1.58±0.07	1487±27	1440±32
	'Other'					
		Positive	2.85±0.07	2.84±0.07	1502±33	1472±30
		Negative	1.81±0.11	1.84±0.1	1446±35	1507±39
	'Semantics'					
		Positive	3.4±0.06	3.37±0.07	1354±24	1385±26
		Negative	1.34±0.06	1.31±0.05	1367±30	1361±28

[a] *Average time spent on making trait endorsement responses*
[b] *The number of dot-location(s) to be held in working memory*

Effect of Trait-Evaluation on Delayed Match-to-Sample Working Memory Performance

Findings here also replicated those from Study 2, despite the parameter changes (detailed in the Task Design and Procedure section), hence confirming the robustness and validity of this novel dual-task paradigm. As an intended manipulation check, there was a significant main effect of working memory load for both accuracy (F(1,29)=69.3, p<0.001) and reaction time (F(1,29)=29.5, p<0.001), such that subjects spent more time making memory retrieval responses (1504 ± 47 msec), albeit with less accuracy (69.22 ± 1.41 %), under high memory load than did low memory load (1354 ± 39 msec; 85.98 ± 1.68 %). No main effect or interaction was found to be significant for the within-subject factor 'valence'. As for the factor 'appraisal target', there was neither a main effect (on accuracy, p>0.42; on reaction time, p>0.18), nor any significant interaction with working memory load on reaction time (p>0.69). However, the interaction between memory load and appraisal target was, in line with Study 2, significant on working memory accuracy (F(2,58)=4.9, p=0.01; Figure 3.6).

Figure 3.6: Effects on working memory performance (Study 3)



When the interaction was examined further with 2 separate one-way ANOVAs, a main effect of appraisal target was found only when the memory load was high (F(2,58)=4.2, p=0.02), but not when it was low (p>0.095); pair-wise comparisons revealed that the effect of appraisal target (under high memory load) emerged as a result of working memory accuracy drop after self-evaluation.

Moreover, a one-sample t-test comparing against 50% showed that all 6 dual-task trial types were performed above chance level (all p<0.001), suggesting our manipulation to get accuracy off the floor was effective. Table 3.5 summarizes the working memory performance for the 6 dual-task trial types (valence types combined).

Table 3.5: Summary of Working Memory Performance Data[1] (Study 3)

		Accuracy (%)		Reaction Time (msec)[a]	
		Working Memory Load[b]		Working Memory Load[b]	
		2	4	2	4
Appraisal Target	'Self'	88.53±2.07	64.91±2	1355±38	1531±54
	'Other'	85.88±2.2	71.39±2.32	1367±53	1513±49
	'Semantics'	83.52±2.06	71.38±1.82	1341±43	1470±46

[1] Collapsed across valence, as neither main effect nor interaction with valence was significant
[a] Average time spent on making WM retrieval responses
[b] The number of dot-location(s) to be held in working memory

Last but not least, subjects reported during debriefing that they primarily adopted spatial strategies to perform the delayed match-to-sample task, which was further evidenced by a repeated-measures ANOVA crossing memory load (high, low) and distance of memory foil (near, far) – A significant main effect of foil distance was found (F(1,29)=5.7, p=0.024), such that there were more accurate trials to far (91.1 ± 1.4 %) than to near foils (84.2 ± 2.9 %) in a spatial-memory task, confirming the use of spatial strategies (Smith and Jonides, 1998).

Study 3 demonstrated again the selective interference, manifested as a decline in working memory accuracy, between spatial working memory and the evaluative appraisal of self. The critical observation was that, even with the inclusion of a (specific) 'other' condition that equated 'self' in cognitive demand (as indexed by trait-evaluation reaction time; both greater than evaluating 'semantics', $p<0.001$, but not significantly different from each other), the interference with high load of working memory was specifically limited to the 'self' condition. Therefore, with findings from the two behavioral studies included in this chapter, we suggest a functional overlap between executive control ('spatial working memory') and social cognitive functions ('evaluative appraisal of self'). Interestingly, the confirmed use of spatial strategy in the working memory task and the evaluative appraisal in the verbal domain further suggest that behavioral manifestation of this functional overlap may also be domain-general (i.e. selective interference not limited to only within the verbal or the spatial domain).

Two other effects also replicated Study 2. First, the effect of memory load on both working memory performance measures; reaction time to probes increased and accuracy decreased as a function of greater memory load suggesting that the findings did not result from speed-accuracy tradeoff. Second, the effect of appraisal target on trait-endorsement ratings showed that subjects judged their personality to be more desirable (i.e. claimed more positive and dismissed more negative traits) than their personally-familiar peers, but not as desirable as the “ideal” (i.e. the semantics described by the trait adjectives). These results are consistent with decades of findings from social psychology that people tend to be positively biased and self-serving when making self-evaluations (Chambers and Windschitl, 2004; Suls et al., 2002; Taylor and Brown, 1988). These two effects provided evidence for subjects’ engagement in our task. In addition, the modified parameters in Study 3 appeared to be effectively optimized and controlled to get the working memory accuracy off the ‘floor’ and boost the selective interference finding.

Lastly, the only significant effects of valence we found were on endorsement ratings -- a main effect (higher on positive, lower on negative trait adjectives), and an interaction with appraisal target. We did not find any other effects of valence, including the 3-way interaction (with memory load and appraisal target) on working memory accuracy. That is, the selective interference between spatial working memory and the evaluative appraisal of self may be generalized to stimuli of positive and negative valence. Alternatively, it is also possible that the failure to observe a valence effect here reflected a lack of statistical power or type 2 errors.

General Discussion

The main novel finding from the pair of behavioral studies included in this chapter is the selective interference, manifested as a decline in working memory accuracy, between spatial working memory and the evaluative appraisal of self; this evidence suggests a functional overlap between executive control and social cognitive functions. We also contribute to the literature by developing a novel dual-task paradigm that manipulates conditions flexibly on a trial-to-trial basis, in a *within*-subject design. By parametrically modulating factors known to affect cortical activity in the default-mode and task-positive networks, we suggest this probe is suitable for investigators to systematically characterize and better understand the functional interactions between large-scale networks.

Significance of the Dual-Task Paradigm

To the best of our knowledge, this is the first paradigm that allows one to interrogate the interplay between social cognition (e.g. evaluative appraisal of personality traits) and executive function (e.g. working memory), using a within-subject design that manipulates conditions on a trial-to-trial basis.

Previous studies adopting the resource depletion framework have traditionally used *between*-subject designs that arranged two resource-consuming tasks in a serial fashion. That is, participants are randomly assigned to be either ‘depleted’ or ‘non-depleted’ from a first task that demands cognitive resource (e.g. suppression of emotional expression while watching a funny movie clip); subsequently, participants’ ability to endure a second resource-demanding task (e.g. persistence on a unsolvable puzzle) are measured as a dependent variable (e.g. Baumeister and Vohs, 2003; Persson et al., 2007b; Vohs et al., 2005). In spite of having the capability to generate a more complete behavioral effect of resource depletion, this traditional design is not an optimal set-up for fMRI investigators studying network dynamics.

Using our novel dual-task paradigm, we were able to replicate the robust behavioral findings in 2 separate groups, suggesting that this is a promising probe to be used to understand the functional interactions between the default-mode and task-positive networks, at least in the context considered herein.

The Selective Interference and Implications

Our data consistently showed that the extent to which the evaluative appraisal of self interfere with working memory accuracy was crucially determined by the availability of working memory. This result is consistent with the notion that cognitive resource is capacity-limited and can be temporarily depleted. However, we failed to observe interference in the other direction, i.e. altered appraisal of self (in trait-evaluations), when working memory is taxed.

The notion that there is a ‘cognitive cost’ specifically and uniquely associated with the evaluative appraisal of self is novel and particularly interesting because of the potential relevance to the pathophysiology of major depression – a disorder characterized by excessive self-focus and impaired cognitive functions. Thus far, the functional relationship between cognitive load and social cognition has primarily been investigated in the context of emotion - a basic aspect of social cognitive function. Our everyday and clinical experience demonstrates a strong interaction between cognition and emotion (Drevets, 2001; Rauch et al., 2003). Previous behavioral and neuroimaging studies provide empirical evidence that emotional response to affective or personally-relevant stimuli reduces one’s ability to perform goal-directed tasks; furthermore, this cognitive interference is shown to be mediated by an functional interaction between the decreased activity in lateral frontoparietal cortices (task-positive network) and, the increased activity in amygdala and ventrolateral prefrontal cortex (Blair et al., 2007; Dolcos and McCarthy, 2006; Morey et al., 2009; Perlstein et al., 2002). These latter two regions belong to a ventral system critical for the initial rapid appraisal of, and automatic regulation of emotional responses to, the salient stimuli (Phillips et al., 2003). Unfortunately, analogous network dynamics has not yet been investigated for the interplay between cognitive load and higher-order social cognitive functions (e.g. the evaluative appraisal considered herein or that in Chapter 2) that also involve the dorsal system, which demands cognitive resource for evaluative appraisal (Phillips et al., 2003). Adapting this dual-task paradigm, we will examine in Chapter 4 the functional relationships between the default-mode and task-positive network that may mediates the selective interference observed here.

Lastly, we did not find any differential effect of working memory load on evaluative appraisal measures in either study. In contrast to expectations, the increased memory load did not lead to more positive (Baumeister and Vohs, 2003; Vohs et al., 2005) nor more negative (Fischer et al., 2007) self-descriptions. We argue that the lack of significance may be due to an insensitive measure (Likert-scale ratings, as opposed to visual-analogue scale), or a ‘trade-off’ between functions. More specifically, our high working memory load condition was expected to engage more cognitive resource, thereby leaving less for the processing of personality trait adjectives. Given that, we speculate the processing of trait adjectives in relation to self may be deemed significant for survival (the same way emotional stimuli are), and hence given priority in the competition for resource. As such, evaluative appraisal of self ‘hijacked’ resource from the working memory task and led to impaired memory accuracy. Despite the negative result, we did replicate the long-time finding that people tend to be positively biased when making self-evaluation, indicating that participants were engaged in the task. This result suggested that the lack of working memory load effect on evaluative appraisal of self was unlikely due to a failure in task engagement.

CHAPTER IV

FUNCTIONAL INTERACTION OF THE DEFAULT-MODE NETWORK, SOCIAL COGNITION AND EXECUTIVE FUNCTION

Introduction

A large corpus of past work on the default-mode network, the most consistent and readily extractable functional module of the brain, have primarily focused on exploring its interaction with other distributed neural networks at rest and in the context of a wide variety of attention-demanding cognitive tasks. In brief, during resting state the spontaneous fluctuations of hemodynamic activity within the DMN is in anti-phase with that of the task-positive network (e.g. Fox et al., 2005; Fransson, 2005) (Damoiseaux et al., 2006; De Luca et al., 2006). This ‘anti-correlated’ relationship between the networks extends into active task conditions when diverse (cold) cognitive operations are required (e.g. Mazoyer et al., 2001; Shulman et al., 1997); moreover, greater task demand leads to further decreased activity in the DMN and increase activity in the task-positive network (McKiernan et al., 2006; McKiernan et al., 2003). Taken together, investigators across various methodologies converge to suggest a competitive relationship between the default-mode and the task-positive networks, which has recently been demonstrated to have consequences for behavioral performance (Eichele et al., 2008; Persson et al., 2007a; Weissman et al., 2006).

Despite the emerging consensus of the DMN and its competitive relationship with other networks during relaxed resting and cognitive task performance, the network interactions during social cognitive challenges remains to be explored. Nevertheless, existing evidence has hinted at a *non*-competitive relationship between the DMN and the task-positive network, as activity in both networks increase while participants are instructed to engage various social cognitive functions, including but not limited to reflecting upon one's characteristics, affective states and opinions (e.g. Cunningham et al., 2003; Cunningham et al., 2004; Gusnard et al., 2001a; Kelley et al., 2002; Moran et al., 2006). Using a social-emotional preference task and connectivity analyses (psycho-physiological interaction) of fMRI data, we demonstrated in Chapter 2 (Study 1) a positive coupling between the default-mode (aMFC and PCC) and task-positive networks (pre-SMA/ dACC and bilateral frontoparietal cortices) that interact to facilitate contextually appropriate social-cognitive behavior. Altogether, current data seem to indicate that network interactions depend on whether there is on-line task demand (resting state vs. non-resting state), and whether the task implementation involves social cognitive functions (social cognition vs. cold cognition); it also clearly suggest that social cognitive functions rely on higher cognitive structures that mediate controlled processing, hence may be susceptible to modulation by factors known to tax cognitive resource, such as task demand. Although past work has made important progress characterizing the functions and the interactions of the DMN, no studies have systematically addressed the interaction between DMN, social cognition and task demand.

To address this question, we developed a novel dual-task paradigm that parametrically manipulated factors known to affect cortical activity in the default-mode and task-positive networks: social cognition and spatial working memory demand, respectively. In Chapter 3, we manipulated task demand by changing spatial working memory load in a delayed match-to-sample task, where social cognitive function was engaged at three different levels -- 'self', 'other' (a social control condition) and 'semantics (desirability; a non-referential, control condition)' -- through the evaluative appraisal of personality trait adjectives (e.g. "happy", "kind"). In particular, we demonstrate in Chapter 3 (Study 2 & 3) selective interference, manifested as a decline in working memory accuracy, between spatial working memory and the evaluative appraisal of 'self'; moreover, this selective interference was only evident under high task demand conditions.

In Study 4, we adapted the paradigm from Study 3 to the fMRI environment and sought to characterize functional mechanisms that may underlie this behavioral interference effect. Specifically, we aimed to determine whether having participants maintain a varying load of spatial working memory during a trait-evaluation task that requires explicit appraisal would modulate the ability of social cognition to engage activity in the DMN. In this study, we were primarily focused on the default-mode structures along the cortical midline (aMFC, vMFC, and PCC) because appraisal tasks requiring explicit evaluations about positive and negative trait adjectives consistently evoke robust activations in these CMS. Additionally, we also aimed to determine whether engaging participants in the evaluative appraisal form of social cognition while they maintain spatial information would influence their ability to engage and sustain activity from the task-positive network. For this network, we were mainly interested in the structures relevant for maintaining spatial working memory, including the right-sided fronto-parietal cortices. We hypothesized that task demand, as well as social cognitive functions, modulate the manner in which the DMN and task-positive networks interact. We also hypothesized that a functional overlap between the two interacting networks may be the neurobiological substrate underlying the deterioration in working memory accuracy when one is explicitly evaluating the self. As such, increased DMN activity and/or decreased task-positive network activity in the evaluative appraisal of self under high task demand conditions may lead to poorer behavioral performance.

Methods

Subjects

Eighteen healthy participants (age: 21.9 ± 0.7, 12 females) were recruited from advertisements placed at local universities and through word of mouth. All subjects were native-English speakers, right-handed, with normal or corrected-to-normal vision acuity and normal hearing. Exclusion criteria consisted of no history of heady injury, learning disability, psychiatric illness or substance abuse/dependence, as assessed by Mini-SCID (Sheehan et al., 1998). After explanation of the experimental protocol, all participants gave written informed consent, as approved by the University of Michigan Institutional Review Board.

After completion of the study, subjects were debriefed, and paid for their participation and time ($15 pro-rated per hour).

Materials

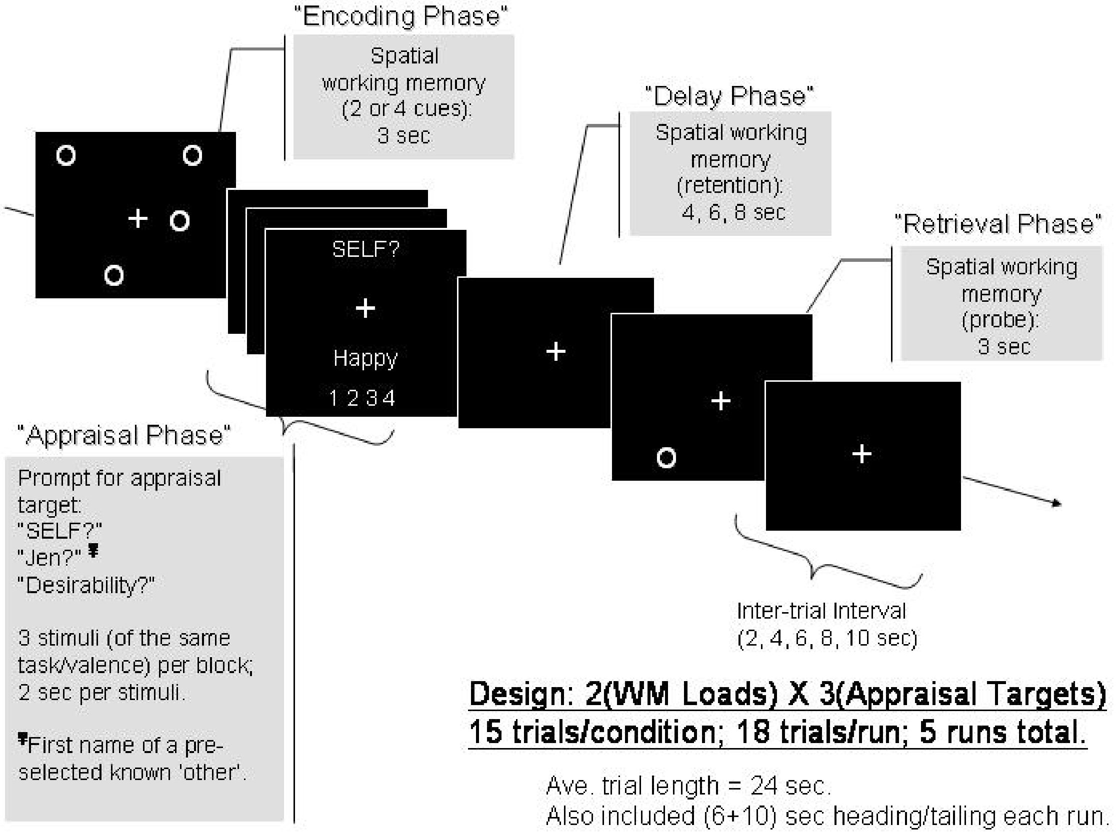
Verbal stimuli used were similar to those used for Study 3. Briefly, 12 wordlists (6 positive, 6 negative), each containing 24 personality trait adjectives, were constructed from the Anderson norms (Anderson, 1968). The positive and negative words were selected from the top 144 and bottom 144, respectively, of Anderson's norms. All 12 word lists were matched for their overall average meaningfulness, familiarity and verbal/written-frequency; the average 'likableness' ratings were also matched within the 6 positive and the 6 negative word lists. For each subject, a pair of positive and negative word list were randomly assigned to each of the 6 dual-task trial types (2 working memory load crossed with 3 appraisal targets); therefore, no verbal stimuli was used more than once, and each subject received a unique protocol. One separate word list selected from the middle 40 of Anderson's sample was set aside and used for instruction and practice trials.

Task Design and Procedure

Briefly, on each trial, subjects were presented with the spatial cues for 3 seconds (the 'Encoding Phase'), temporally followed by a block of three trait-adjectives (2 seconds/stimulus) as the trait-evaluation task (the 'Appraisal

Phase'), a delay period with a fixation cross centering the screen (4-8 seconds, mean = 6 seconds; the 'Delay Phase'), and finally a probe screen for 3 seconds (the 'Retrieval Phase'). A centrally-located fixation cross was presented on the screen in between trials, and this inter-trial intervals were jittered between 2-10 seconds (mean = 6 sec; the ITI). Therefore, the task design and parameters were identical to that of Study 3, with only 2 fMRI adaptations that both the 'Delay Phase' and ITI were jittered. Figure 4.1 illustrates the dual-task paradigm adapted for neuroimaging (Study 4).

Figure 4.1: Schematic for the Dual-task: fMRI version



Pre-scan Session

Participants were briefed about the study and asked to identify a specific neutral individual to be used as an evaluation target (‘other’) throughout their experiment session. Participants were instructed to select some acquaintance of theirs who they are personally familiar with to the degree of being able to evaluate their personality, but not too close and not eliciting strong feelings in them. In particular, participants were not allowed to select their best friend, significant other, or familiar members; instead, they were encouraged to identify some acquaintance from work or school.

Participants were given approximately 12 practice trials (2 trials per dual-task trial type) to familiarize themselves with the task structure. The practice session took place roughly half hour prior to the fMRI session.

fMRI Session

After completing a practice session outside of the scanner, participants were then escorted to the scanner room and placed comfortably within the scanner. Head movements during acquisition were minimized through instructions to participants and also through custom-fit foam pads that provided comfort and gentle immobilization. Ear plugs were provided to reduce scanner noise. While lying inside the scanner, stimuli were presented to participants via reflection using angled mirrors and a back-projection system. Stimuli were displayed using E-prime software (Psychology Software Tools, Inc.). In addition, E-prime recorded participants’ responses via right-handed button-glove.

There were 5 runs consisting of 18 dual-task trials each (which included 18 delayed match-to-sample working memory trials that temporally flanked 54 trait-adjectives), for a total of 90 dual-task trials throughout the fMRI session. The dual-task trials were pseudo-randomly presented so that no two trials of the same type were presented back-to-back. Each run included 3 trials of each of the 6 dual-task trial types. To allow for better baseline estimation, each run began and end with a fixation screen for 10 and 16 seconds, respectively. Overall, each run lasted 7minutes 28 seconds. There were 15 trials per dual-task trial types across the runs.

Behavioral Data Analysis

Behavioral responses were recorded by E-prime (Psychology Software Tool, Inc.) and all statistical analyses were conducted using SPSS 15 (SPSS Inc., Chicago, IL).

The same on-task performance measures as those in Study 3, including average trait endorsement in *ratings*, working memory accuracy and reaction times for trait-evaluation and for working memory retrieval, served as the behavioral dependent variables for this neuroimaging experiment (all expressed as mean ± SE in the following sections). All trials were included for calculating the means of the reaction times. These on-task performance measures were examined separately using 2 (valence: positive, negative) X 2 (working memory load: low, high) X 3 (appraisal target: ‘self’, ‘other’, ‘semantics’) repeated-measures ANOVA, and paired t-tests were used post hoc to follow up significant effects. In all behavioral analyses, an effect was considered significant if it reached a threshold of $p<0.05$.

In the sample that was scanned, we expected to replicate the same behavioral effects, including the selective interference, as those found in our previous work (study 2 & 3). Because such an effect would not be statistically reliable in a small sample, we assessed and reported the behavioral effects incorporating data from additional 30 participants tested in an almost identical design (Study 3), resulting in a total subject number of 48.

Functional MRI Data Acquisition and Processing

Scanning was performed on a General Electric (Waukesha, WI) 3T Signa scanner (Excite [2.0] release) using a standard radio frequency foil. The scanning began with structural acquisition of a standard T1 image (T1-overlay) for landmark identification to position subsequent scans. Subsequently, functional images were acquired. To minimize susceptibility artifact (Yang et al., 2002), whole-brain functional scans were acquired using T2*-weighted reverse spiral sequence with BOLD contrast (repetition time/TR of 2000 msec; echo time/TE of 30 msec; flip angle of 90°; field of view/FOV of 22 cm; 40 slices; 3.0 mm slice thickness/0 mm skip, equivalent to 64 x 64 matrix size). Each run began with 4 ‘disdaqs’ (subsequently discarded) to allow for T1 equilibration effects, then another 225 volumes were acquired while subjects performing tasks.

Therefore, a total of 1125 usable volumes were collected for each subject. After acquisition of functional volumes, a high-resolution T1 image (T1-spgr) was obtained for anatomic normalization.

Data processing began with the following preprocessing steps: fMRI data were first reconstructed off-line using custom code written in C (Noll et al., 1991). Subsequently, slice-timing and motion correction were done using the “slicetimer” and the “mcflirt” routines of the FSL fMRI analysis package (http://www.fmrib.ox.ac.uk/fsl/slicetimer/index.html) (Jenkinson et al., 2002). Re-alignment parameters were inspected as a proxy for subject movement, in order to ensure that movement did not exceed either 3 mm, or 1° rotation within a run. The remainder of preprocessing and image analysis was performed usiRyng Statistical Parametric Mapping SPM5 package (Wellcome Institute of Cognitive Neurology, London, United Kindom). The high-resolution T1 image (T1-spgr) was normalized to the Montreal Neurological Institute (MNI) 152 brain-template, yielding anatomical parameters that were applied to the co-registered time-series of functional volumes. An isotropic 5mm full-width half-maximum (FWHM) Gaussian kernel was then used to smooth the functional volumes. Each normalized image set was band pass filtered (high pass filter = 128 sec) to eliminate low frequency signals (Ashburner et al., 1997).

Functional MRI Data Analysis

Our method for analyzing within-trial patterns of activity has been described and validated elsewhere (Postle et al., 2000; Zarahn et al., 1997);

simulations using in-house Matlab scripts also have been performed to ensure that the regressors can be optimally estimated. In sum, we modeled each condition of each component task phase with a unique regressor (number of condition separately listed in parenthesis): ‘Encoding’ (2), ‘Appraisal’ (6), ‘Delay’ (6), ‘Retrieval’ (6), giving us a total of 20 regressors of interest per run; across the 5 runs, 100 regressors of interest were modeled and the passive baseline was modeled implicitly. The task phases were all modeled at the event onsets with durations specified as following: ‘Encoding’ - a mini-block spanning cue presentation (3 sec); ‘Appraisal’ – a 6-sec block spanning trait-evaluation task presentation; ‘Delay’ – a mini-block spanning the duration of fixation cross presentation (jittered among 4, 6, or 8 seconds); and ‘Retrieval’ – a 3-sec block during probe presentation. For each subject, each regressor epoch was convolved with a canonical hemodynamic response function (HRF). The general linear model also included regressors of no interest to model the effects of shifting signal levels across runs; the statistical model was estimated including a high pass filter (128 seconds) and AR (1) temporal autocorrelation. For each working memory load and appraisal target condition in each component task phase, statistical parametric maps were generated using *t* statistics to identify regions activated/deactivated according to the model.

For group analysis, a second-level random effect analysis was performed: Using one-sample t-tests on the contrast images obtained in each subject for each comparison of interest (including the difference relative to the implicit baseline), this analysis treated subjects as a random variable. This analysis estimates the error variance for each condition of interest across subjects, rather than across scans, and therefore provides a stronger generalization to the population from which data are acquired. The primary purpose of the random effect analysis served to identify brain regions that responded during the '*Encoding Phase*' of the dual-task – Because we were primarily interested in the cortical activity as a function of working memory load and appraisal target during the '*Appraisal phase*', defining functional regions-of-interest from a separate, preceding task phase should minimize ROI selection biases.

Unless otherwise specified, an intensity threshold of $p< 0.005$ (uncorrected; corresponding to a t-score > 2.9) and an extent threshold of 36 contiguous voxels were used for all random effect analyses. This thresholds combination corresponds to an equivalent of $p<0.05$ correcting for whole-brain multiple comparisons, as determined by Monte Carlo simulation (see AlphaSim in AFNI software). For completeness, we also reported activated regions that fell just below the cluster threshold (Table 4.3 and 4.4) and displayed figures with the threshold of $p<0.005$ uncorrected, $k>10$ voxels.

Region-of-Interest (ROI) Analysis

In addition to the whole-brain analysis, ROI analyses were also used in *a priori* regions to restrict the number of multiple comparisons and complement findings found in a voxel-wise manner. ROIs were defined on the basis of the whole-brain activation obtained during the *'Encoding phase'.* In brief, the DMN ROIs were functionally defined on the voxels that showed peak *deactivations* in a linear contrast comparison between the '*Encoding phase*' regressors (Low and High working memory load combined) and the implicit baseline (i.e. the inter-trial interval) in the current dataset, and that corresponded to cortical midline components of DMN in the literature (Raichle et al., 2001; Shulman et al., 1997)). They included the aMFC, vMFC and PCC. Similarly, the task-positive network ROIs were also functionally defined, from the '*Encoding Phase*', by regions that were sensitive to spatial working memory load (i.e. High versus Low working memory load), and that were implicated in the spatial working memory from previous work (e.g. for a representative meta-analysis, see: Cabeza and Nyberg, 2000). Regions included are pre-supplementary motor area/ dorsal anterior cingulate (pre-SMA/ dACC), middle frontal gyrus (MFG), inferior frontal gyrus/operculum (IFG_Oper), precentral gyrus (PreCG), superior parietal lobe (SPL) and inferior parietal sulcus (IPS). All the DMN ROIs passed the threshold for multiple comparisons of $p<0.05$, whereas the task-positive network ROIs survived $p=0.005$ (uncorrected) with at least 10 contiguous voxels. Peak coordinates are presented in Table 4.3 (DMN ROIs) and Table 4.4 (task-positive network ROIs). Each ROI was created by including activated voxels within a 10-mm sphere around the peak voxel showing the maximum effects in the contrasts of interest.

Overall, 3 ROIs from the DMN and 6 from the task-positive networks were used to further examine the magnitude of the '*Appraisal Phase'* activity as a function of working memory load and appraisal target. In service of characterizing the magnitude properties, parameter estimates (i.e. beta values) were derived, at the individual subject level, from the magnitude (height) of the HRF for the conditions of interest during '*Appraisal Phase*', and were subsequently extracted and averaged within each ROI. These beta values were later used as dependent variables for group analyses, and examined using 2 (working memory load: low, high) X 3 (appraisal target: 'self', 'other', 'semantics') repeated-measure ANOVAs. Paired t-tests were used to assess significant differences among within-subject factors.

Analyses performed on extracted fMRI data were also conducted in SPSS 15.0 (SPSS Inc., Chicago, IL) and an effect was considered significant if it reached a statistical threshold of $p<0.05$.

Results

Behavioral data

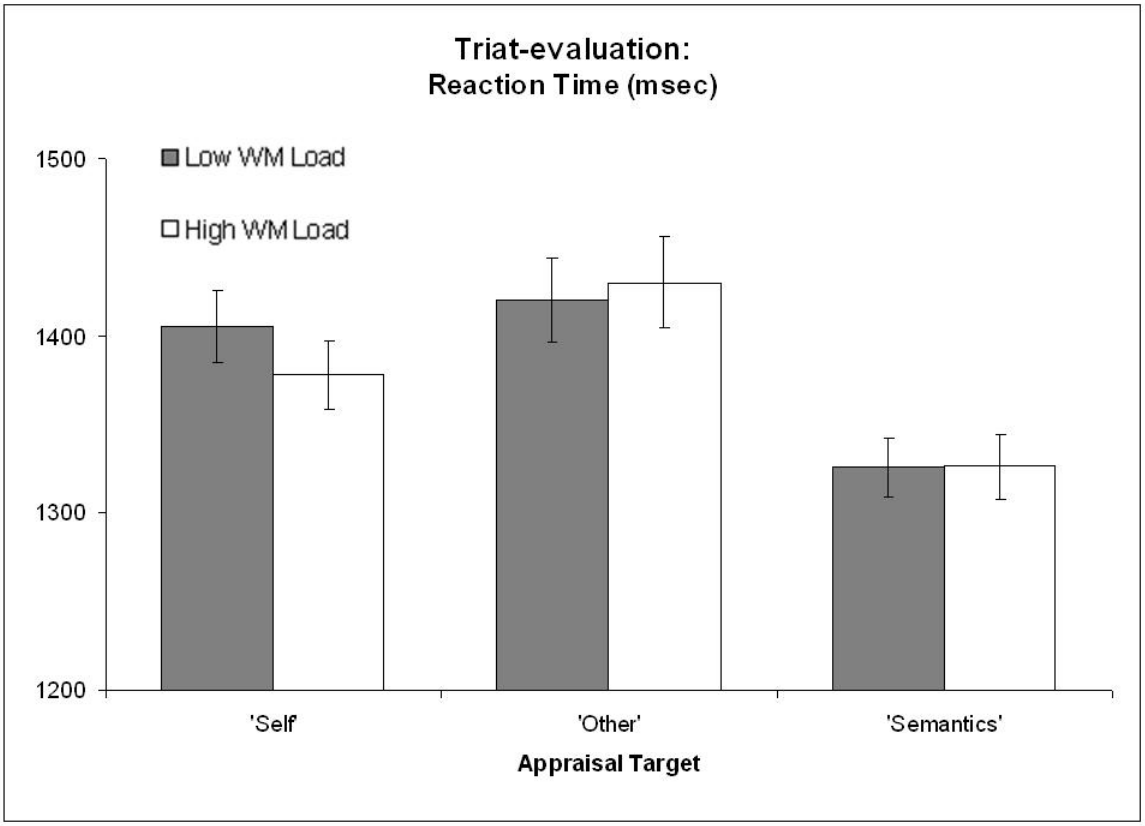
The Effect of Concurrent Working Memory Load on Trait-Evaluation

As in Study 3, the repeated-measures ANOVA showed that reaction times differed depending on appraisal target ($F(2,94)=28.2$, $p<0.001$). Paired t-tests revealed that subjects took more time to evaluate themselves (1392 ± 18 msec) and their peers (1425 ± 24 msec), than to evaluate the semantics condition (1326 ± 17 msec); no significant difference between the first 2 conditions was found (Figure 4.2).

For trait endorsement (in *ratings*), the repeated-measure ANOVA showed a significant main effect of valence (Ratings: positive= 3.1 ± 0.03, negative= 1.58

± 0.04; F(1,47)=550.9, p<0.001), as well as a interaction between valence and appraisal target (F(2,94)=50.7, p<0.001). In line with Study 3, planned comparisons showed that this interaction reflected a positivity-bias in self-evaluation: Subjects characterized themselves to be more desirable (i.e. claimed more positive and less negative traits) than their personally-familiar peers, albeit not as desirable as the semantics described by each trait adjective.

Figure 4.2: Effects on Trait-evaluation RT (N=48)



No other significant effect, including the interaction between memory load and appraisal, was found on either reaction time (p>0.12) or ratings (p>0.82). However, it was worth noting that pair-wise comparisons showed trend significance in RT decrease when evaluating ‘self’ under high (versus low) working memory load (t(47)=3.49,p=0.068). Table 4.1 summarizes the trait-evaluation measures for all trial types.

For completeness, here we also report behavioral effects on trait-evaluation measures within the fMRI sample alone (N=18). In brief, main effect of appraisal target on reaction time (F(2,34)=10.22, p<0.001); for endorsement ratings, there were a main effect of valence (F(1,17)=207.8, p<0.001), as well as a interaction between valence and appraisal target (F(2,34)=25.04, p<0.001). As with the large sample, no other significant effect was found.

Table 4.1: Summary of Trait-Evaluation Measures (N= 48)

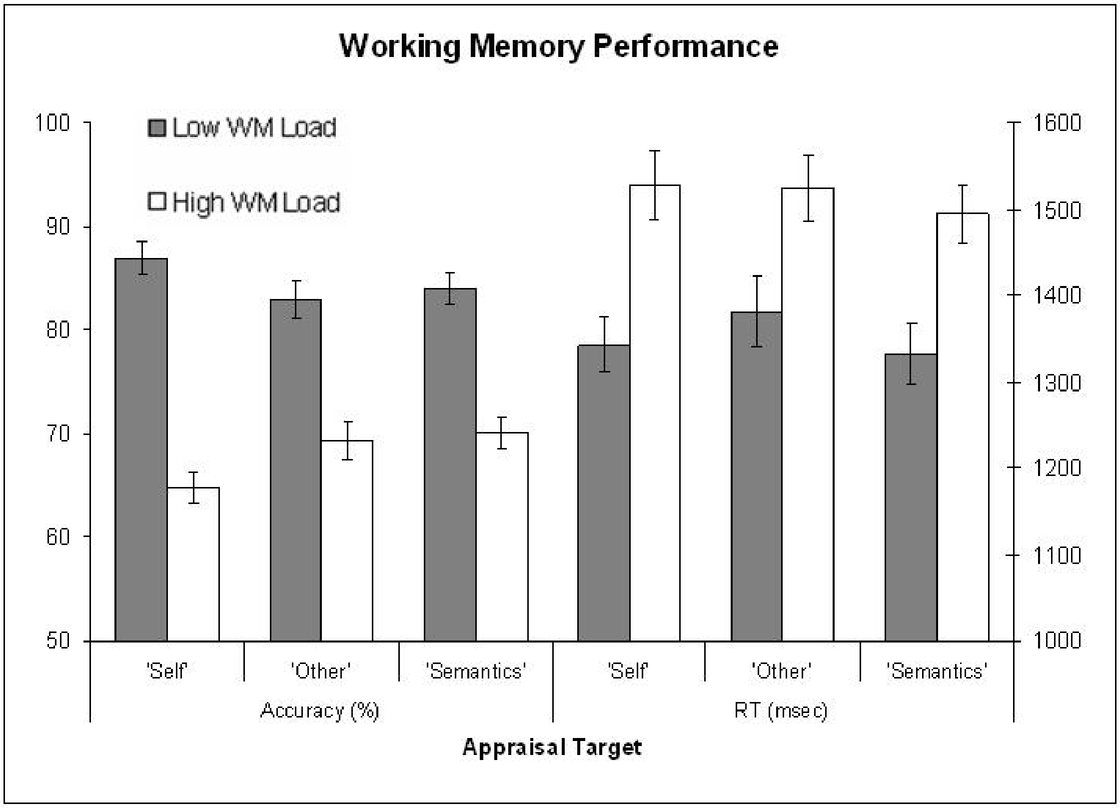
			Ratings (4-point scale)		Reaction Time (msec)[a]	
			Working Memory Load[b]		Working Memory Load[b]	
			2	4	2	4
Appraisal Target	‘Self’					
		Positive	3.11±0.04	3.13±0.05	1379±21	1366±20
		Negative	1.62±0.05	1.60±0.05	1432±23	1391±24
	‘Other’					
		Positive	2.84±0.06	2.78±0.06	1426±28	1414±24
		Negative	1.77±0.08	1.78±0.07	1415±25	1447±30
	‘Semantics’					
		Positive	3.35±0.05	3.37±0.05	1332±18	1332±22
		Negative	1.36±0.04	1.32±0.04	1320±23	1321±22

[a] *Average time spent on making trait endorsement responses*
[b] *The number of dot-location(s) to be held in working memory*

The Effect of Trait-Evaluation on Delayed Match-to-Sample Working Memory Performance

Performance accuracy decreased with increasing memory load ($F(1,47)=115.1$, $p<0.001$), whereas reaction time increased ($F(1,47)=61.16$, $p<0.001$). Additionally, in line with the findings in Chapter 2 (Study 2 & 3), the interaction between memory load and appraisal target was found to be significant for working memory accuracy ($F(2,94)=5.5$, $p=0.006$), but not reaction time ($F(2,94)<1$, $p>0.54$). When this significant interaction was examined further by two separate one-way ANOVAs, the effect of appraisal target was found to be significant under high memory load ($F(2,94)=3.9$, $p=0.024$), but only at trend level when under low memory load ($F(2,94)=2.8$, $p=0.068$); pair-wise comparisons revealed that concurrent self-evaluation impaired working memory accuracy when the load was high, but (marginally) facilitated accuracy when the load was low (Figure 4.3). No other significant effect was found on either working memory performance measures. Table 4.2 summarizes the working memory performance for all conditions. It is worth noting that working memory accuracy was above the chance level (50%) for all trial types, indicating that the subjects were engaged in the task.

Figure 4.3: Effects on working memory performance (N=48)



Lastly, a repeated-measures ANOVA crossing memory load and distance of memory foil (near, versus far) showed a main effect of foil distance that was significant for accuracy (F(1,47)=12.3, p<0.001) and a trend toward significant for reaction time (F(1,47)=3.7, p=0.061). Subjects performed better (i.e. higher accuracy, faster RT) when the memory foil was farther away from the target; this empirical data in combination with subjects' report during debriefing confirmed their use of spatial strategies.

Regarding the behavioral effects on measures of working memory performance within the fMRI sample alone, it is worth noting that while some significant effects persist, some no longer survive the significance threshold.

More specifically, robust main effect of memory load persists for both performance accuracy (F(1,17)=43.62, p<0.001) and reaction time (F(1,17)=34.48, p<0.001); participants also performed with higher accuracy when memory foil was farther away from the target (F(1,17)=7.12, p=0.016). Unfortunately, in this small sample, we were not able to detect significant interaction between memory load and appraisal target (memory accuracy (F(2,34)=1,44, p>0.25); reaction time (F(2,34)=1.75, p>0.19).

Table 4.2: Summary of Working Memory Performance Data[1] (N=48)

		Accuracy (%)		Reaction Time (msec)[a]	
		Working Memory Load[b]		Working Memory Load[b]	
		2	4	2	4
Appraisal Target	‘Self’	86.98±1.57	64.73±1.57	1343±32	1528±39
	‘Other’	82.91±1.84	69.24±1.79	1381±40	1524±38
	‘Semantics’’	84.01±1.47	70.17±1.52	1332±34	1494±34

[1] Collapsed across valence, as neither main effect nor interaction with valence was significant
[a] Average time spent on making WM retrieval responses
[b] The number of dot-location(s) to be held in working memory

Functional MRI data

The Effect of Delayed Match-to-Sample Task on Cortical Activity

As a quality check of the data, the first set of analyses compared our findings from the delayed match-to-sample task components (of the dual-task) with those from the previous literature.

By comparing activity during all trial-types (relative to fixation baseline), separately for each component phase – ‘Encoding’, ‘Delay’ and ‘Retrieval’, we first identified brain regions activated and deactivated by this spatial working memory paradigm. Most brain regions revealed by this comparison were involved in all three component phases of the working memory task (Table 4.3) – Consistent with previous studies investigating working memory using delayed match-to-sample paradigms, relative to fixation baseline, the task recruited: 1) Increased activity in a set of regions typically seen for spatial working memory and task execution, including the PFC, precentral gyrus, the parietal cortex, middle temporal gyrus, hippocampus, occipital lobe, cerebellum and subcortical areas (caudate and thalamus); and 2) decreased activity in several components of the DMN, including structures along the cortical midline (medial superior/middle frontal gyri, PCC, precuneus, retrosplenial cortex) and the inferior lateral temporal/parietal cortices. Based on this whole brain analysis, we functionally defined the three deactivated cortical midline structures (aMFC, vMFC, and PCC) and selected them as the DMN ROIs to be focused on in ROI analyses.

Table 4.3: Activation peaks -- Main effect of spatial working memory task, separating component phases

	Encoding Phase			Delay Phase			Retrieval Phase		
Region	(x, y, z)[1]	Cluster[2]	Z-score[3]	(x, y, z)[1]	Cluster[2]	Z-score[3]	(x, y, z)[1]	Cluster[2]	Z-score[3]
<u>Increases relative to baseline</u>									
PreCG	-54, 6, 33	9136[a]	6.29				-39, 6, 39	19	3.11
SFG/MFG/ IFG (BA 6/8/9/45/46/47)	36, 48, 33	43	4.48	27, 0, 60	900[b]	5.03	-33, 15, 6	11224[d]	5.85
				33, 54, -3	83	3.71	48, 18, 0	1776	5.56
(pre-)SMA/ dACC (BA 6/8/32)	0, 6, 27	14	2.92				3, 33, 39	494	5.25
SPL/IPS (BA 7/40)				-42, -42, 51	8555[c]	6.18			
Hippocampus/ ParaHippocampal gyrus	-27, -30, -6	20	3.74	-24, -24,-27	17	3.18			
	27, -27, -6	7	2.77						
MTG				-39, 3, -48	7	3.52	-54, -42,6	66	3.91
Occipital lobe (BA 17/18/19/37)	15, -69, 3	129	3.73						
cerebellum	-3, -63, -33	33	3.16	-3, -63, -30	8	2.88			
Thalamus	3, -15, 27	29	3.52	-6, -24, -3	145	4.12	-3, -21,27	30	3.41
caudate	-9, 3, 9	11	3.17						
	18, 18, 0	18	3.0						

	Encoding Phase			Delay Phase			Retrieval Phase		
Region	(x, y, z)1	Cluster2	Z-score3	(x, y, z)1	Cluster2	Z-score3	(x, y, z)1	Cluster2	Z-score3
Decreases relative to baseline									
vMFC/aMFC	**0, 42, -6**	866	4.72	-3, 42, -9	217	4.95	-6, 39,-15	625	5.73
	0, 63, 15 ǂ	-- ǂ	-- ǂ	3, 60, 30	407	4.64	-33, 39, -15	66	4.84
PCC/ Precuneus/ Retrosplenial cortex (BA 7/31)	12, -18, 45	698	4.7	12, -24, 48	258	4.75	-9, -45, 36	255	3.96
	6, -57, 33	104	4.2	-9, -57, 30	394	4.39	-15, -48, 60	203	3.95
Posterior lateral cortices, extending into insula (BA 7/19/22/39/40/41/42)	51, -66, 45	252	4.9	42, -12, 3	1014	5.15	63, -9, -21	403	4.82
	51, -9, 9	835	4.85	-42, -9, 0	765	4.56	-51, -69, 27	220	4.68
	-57, -3, 0	790	4.84	-51, -72, 27	190	4.44	-63, -12,-12	52	4.45
	39, 24, -24	127	4.02	57, -66, 27	36	3.73	-39, 18, -30	99	4.17
	57, -3, -33	44	3.4	24, -39, 66	96	3.71			
aMFG	-24, 33, 42	148	4.01				-30, 27, 51	218	4.27
	36, 24, 42	85	3.94						

Abbreviations – SFG, superior frontal gyrus; MFG, middle frontal gyrus; IFG, inferior frontal gyrus; SPL, superior parietal lobe; IPS, inferior parietal sulcus; MTG, middle temporal gyrus; aMFG, anterior middle frontal gyrus.

*The regions marked in **bold** were selected for ROI analyses (as DMN regions of interest).*

1 Stereotactic coordinates from MNI152 reference, left/right, anterior/posterior and superior/inferior, respectively.
2 Cluster size in voxels.
3 For completeness: All foci $p < 0.005$, uncorrected; Clusters with at least 36 voxels equates $p<0.05$ brainwise corrected significance. (AlphaSim)
a Also extended extensively into (pre-)SMA/dACC, bilateral SPL and IPL, and bilateral SFG/MFG/IFG.
b Also extended into (pre-)SMA/dACC.
c Also extended extensively into (pre-)SMA/dACC, bilateral SPL and IPL, left MFC/SFG, and occipital lobe.
d Also extended extensively into bilateral SPL and IPL, occipital lobe and cerebellum.
ǂ Identified as a local maxima within the vMFC/aMFC cluster.

We then examined how working memory load modulated activity in different cortical regions. Memory load increase was associated with greater activity in the ‘spatial working memory circuit’; the working memory load-sensitive regions included the PFC and the parietal cortex, and were primarily right-sided. The task-positive network ROIs used in subsequent ROI analyses were defined based on this voxel-wise comparison and listed in Table 4.4. Memory load increase was also associated with greater task-induced deactivations in various components of the DMN. Table 4.4 summarizes the effect of memory load upon cortical activity during the ‘Encoding’, ‘Delay’, and ‘Retrieval’ phases of the delayed match-to-sample task.

Table 4.4: Activation peaks -- Direct working memory load comparisons, separating component phases

	Encoding Phase			Delay Phase			Retrieval Phase		
Region	(x, y, z)[1]	Cluster[2]	Z-score[3]	(x, y, z)[1]	Cluster[2]	Z-score[3]	(x, y, z)[1]	Cluster[2]	Z-score[3]
<u>High WM Load > Low WM Load (‘Differential Activation’)</u>									
Occipital lobe (BA 17/18/19/37)	15, -102, 0	1830	5.38						
PreCG/MFG/ IFG_Oper (BA 6/8/9/45/46/47)	**54, 6, 36**	43	3.88	51, -18, 57	7	3.57	36, 27, 3	49	3.32
	-36, 30, 6	9	3.36	60, 9, 24	25	3.29	24, 15, 57	14	3.26
	45, 18, 6	19	3.34	27, 0, 63	5	2.89	-30, 27, 0	11	3.16
	27, -6, 51	12	2.85						
SPL/IPS (BA 7/40)	**27, -63, 45**	201	3.83	-18, -69, 57	19	3.31	42, -66, 36	22	3.37
	30,-48, 51╫	-- ╫	-- ╫						
	-24, -75, 42	20	3.41	36, -42, 60	58	3.3	-6, -48, 54	13	3.1
	39, -36, 42	6	3.07	18, -63, 57	31	3.13	6, -66, 45	13	2.88
(**pre-)SMA/ dACC** (BA 6/8/32)	**15, 9, 66**	14	3.35				-3, 24, 54	5	2.87
	0, 15, 51	14	3.21						
cerebellum				3, -66, -30	13	3.51			
MTG				51, -57, -9	11	3.2			

	Encoding Phase			Delay Phase			Retrieval Phase		
	(x, y, z)[1]	Cluster[2]	Z-score[3]	(x, y, z)[1]	Cluster[2]	Z-score[3]	(x, y, z)[1]	Cluster[2]	Z-score[3]
Low WM Load > High WM Load ('Differential Deactivation')									
vMFC/aMFC	3, 39, -3	5	3.56	6, 54, 42	38	3.23	-12, 51, -6	13	3.22
	-6, 60, 0	5	2.88	30, 66, 6	7	2.9	-15, 66, -12	8	3.14
PCC/ Precuneus/ Retrosplenial cortex (BA 7/31)	-15, -42, 45	76	3.69	3, -39, 48	161	4.07	-9, -54, 21	21	3.12
	9, -54, 27	76	3.35	-15, -63, 18	63	3.92	0, -45, 30	9	3.08
	12, -45, 57	7	3.26	9, -57, 39	18	3.38	-12, -51, 33	14	3.01
	12, -36, 39	7	3.02	12, -72, 39	27	3.13	-6, -54, 9	6	2.94
Posterior lateral cortices, extending into insula (BA 7/19/22/39/40/41/42)	-39, -78, 33	55	4.23	60, -51, 24	169	3.96	33, -54, -15	11	3.64
	57, -51, 48	78	4.21	-57, -60, 27	48	3.57	-39, -54,-21	10	3.51
	63, -60, 6	42	3.78				-48, -78, 30	54	3.5
	-48, -30, 24	12	3.53						
	-60, -57, 36	18	3.29						
aMFG	-30, 33, 48	8	3.45	-27, 42, 45	20	3.13	-27, 21, 48	11	3.08

Abbreviations – PreCG, precentral gyrus; MFG, middle frontal gyrus; IFG, inferior frontal gyrus; SPL, superior parietal lobe; IPS, inferior parietal sulcus; MTG, middle temporal gyrus; aMFG, anterior middle frontal gyrus.

*The regions marked in **bold** were selected for ROI analyses (as task-positive network regions of interest)..*

1 Stereotactic coordinates from MNI152 reference, left/right, anterior/posterior and superior/inferior, respectively.

2 Cluster size in voxels.

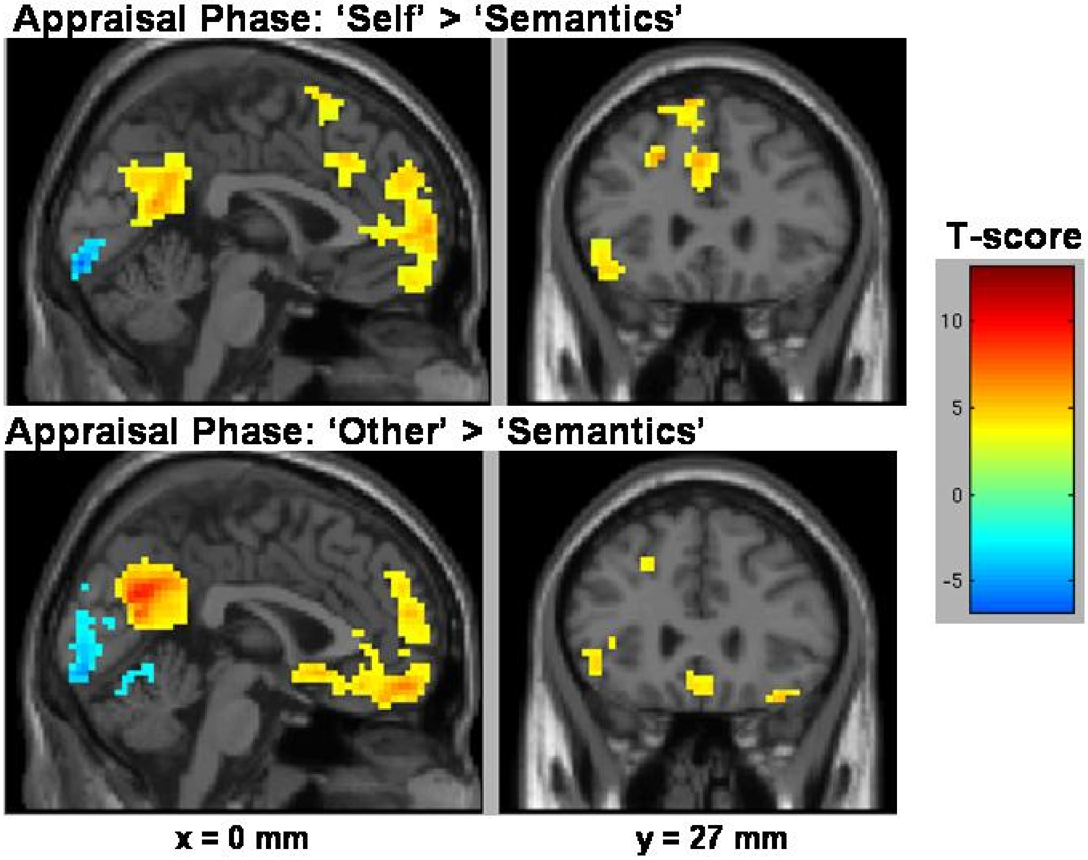
3 For completeness: All foci p < 0.005, uncorrected; Clusters with at least 36 voxels equates p<0.05 brainwise corrected significance. (AlphaSim)

╫ *Identified as a local maxima within the SPL/IPS cluster*

The Effect of Social Cognitive Functions on Cortical Activity during 'Appraisal phase'

We analyzed for brain regions associated with the evaluative appraisal of 'self' (contrast: 'self' – 'semantics') and 'other' (contrast: 'other' – 'semantics'), irrespective of working memory load. Consistent with others work and our own finding from Study 1, both contrasts revealed extensive activations in medial prefrontal (aMFC, vMFC) and posterior cingulate cortices, as well as bilateral PFC and pre-SMA/dACC (Figure 4.4), validating our experimental manipulation of the trait-evaluation task..

Figure 4.4: Common regions of activation in response to the evaluation of 'self' and 'other' during appraisal phase (irrespective of working memory load).



The Effect of Working Memory Load on Brain Responses to Trait-Evaluation

In service of our primary aim, we investigated the modulatory influences of task demand on both the default-mode and the task-positive network activity during social cognitive functions. To this end, we opted for ROI analyses that allowed for *a priori* hypothesis testing with greater sensitivity than whole-brain analyses. For each of the ROIs (functionally defined from the '*Encoding Phase*'), we characterize the magnitude of the cortical activity during the *'Appraisal Phase*' as a function of working memory load and appraisal target. A separate repeated-measure ANOVA crossing working memory load (low, high) and appraisal target ('self', 'other', 'semantics') was performed on the extracted beta values of each ROI.

Through investigating cortical activity in ROIs from both the default-mode and executive-control networks, we sought to determine factors that may modulate the functional relationship *within*- and *between*-networks. Here, the results for the two networks were presented separately.

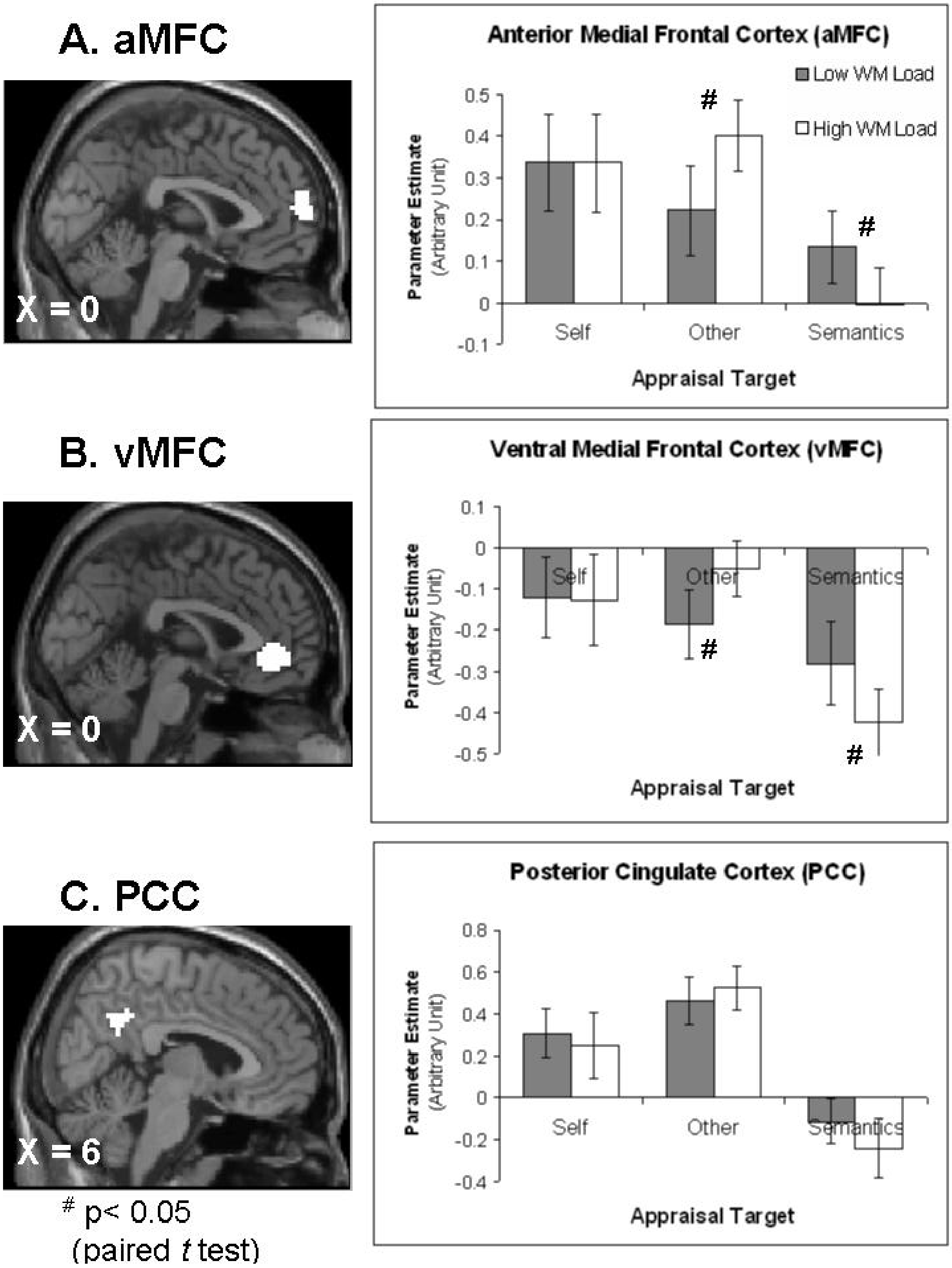
ROIs from the DMN

For aMFC, there was a main effect of appraisal target (F(2,34)=13.36, p<0.001), such that appraising stimuli for 'self' and 'other' relevance engaged more aMFC activity than did the 'semantics'. There was also a significant two way interaction between the working memory load and appraisal target (F(2,34)=4.8, p=0.014). Follow-up paired t-tests revealed that greater working memory load significantly reduced aMFC activity for evaluating the ‘semantics’ (t(17)=2.21, p=0.041), increased aMFC activity for evaluating the ‘other’ (t(17)=2.29, p=0.035); no significant effect of working memory load was found for the evaluative appraisal of ‘self’ (p>0.99) (Figure 4.5A).

A similar pattern was found for the other medial prefrontal ROI – vMFC. There was a main effect of appraisal target (F(2,34)=8.69, p<0.001) such that the magnitude of deactivation was greatest for ‘semantics’ than for ‘self’ or ‘other’; additionally, there was a significant target two way interaction between working memory load and appraisal (F(2,34)=4.76, p=0.015). Paired t-tests showed that high working memory load significantly modulated vMFC activity for ‘semantics’ (t(17)=2.35, p=0.03) and ‘other’ (t(17)=2.12, p=0.049), but not for ‘self’ (p>0.94) (Figure 4.5B).

As for PCC, only the main effect of appraisal target reached significance (F(2,34)=18.47, p<0.001), which reflected greater activity for ‘self’ and ‘other’ than ‘semantics’. Neither the effect of working memory load nor the interaction with appraisal target was significant (Fs <1) (Figure 4.5C).

Figure 4.5: ROI extractions from the a priori DMN nodes.



Left column displays the locations of the functionally defined nodes used for the ROI analyses. Right column displays the parameter estimates for each of the conditions relative to a fixation baseline. Error bars represent standard error of the mean.

ROIs from the Task-Positive Network

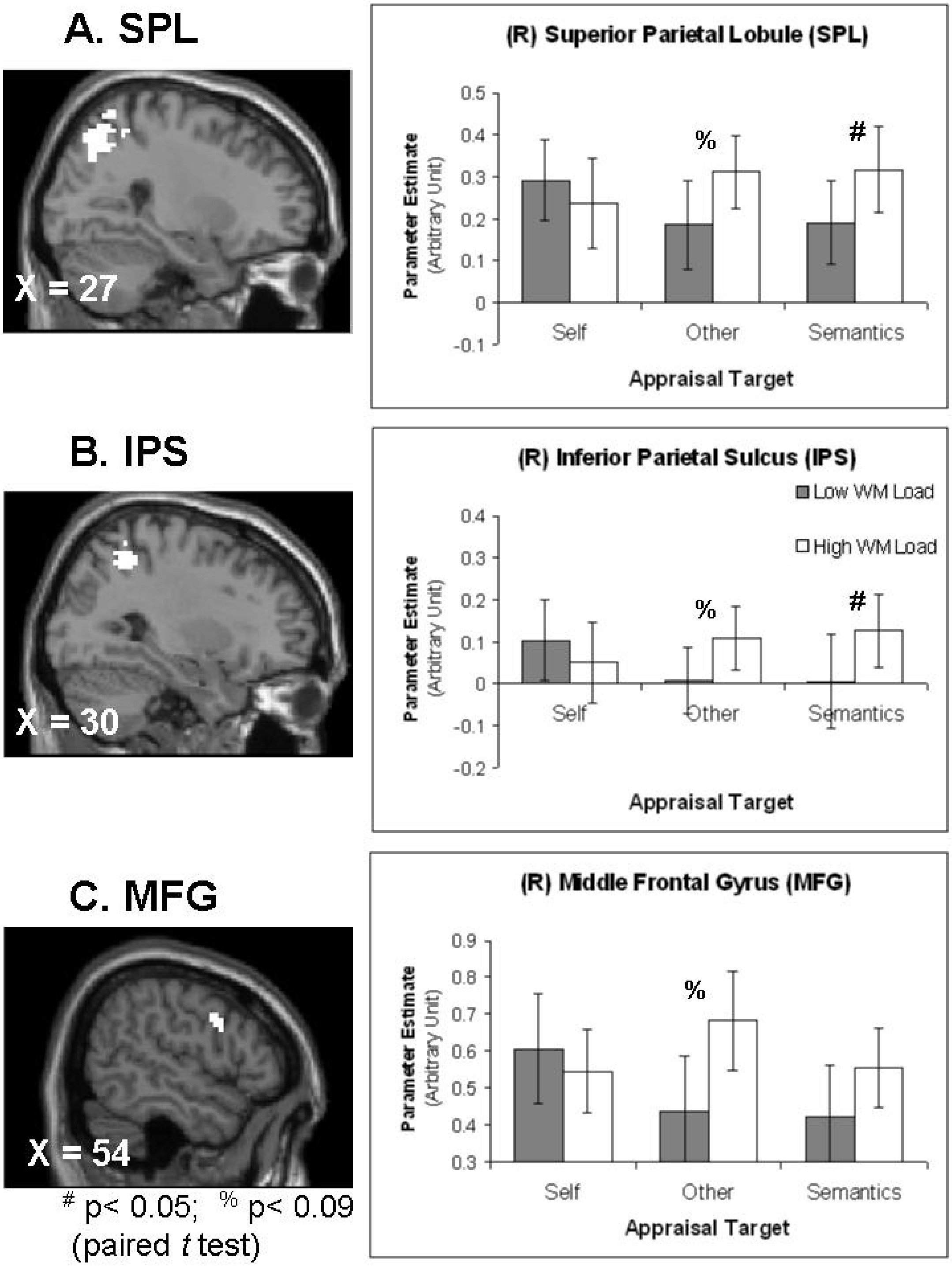
In the analysis of the task-positivel network, significant effects were found only in the right parietal cortical ROIs.

For the right SPL, there was a significant interaction between working memory load and appraisal target (F(2,34)=3.53, p=0.04) such that in response to high working memory load, activity in right SPL increased significantly for ‘semantics’ (t(17)=2.1, p=0.049), marginally for ‘other’ (t(17)=1.8, p=0.09) but not for ‘self’ (p>0.43) (Figure 4.6A).

Similarly, for the right IPS, a significant two way interaction was also found between working memory load and appraisal target (F(2,34)=3.69, p=0.035); Likewise, follow-up paired t-tests showed significant modulatory effect of working memory load for ‘semantics’ (t(17)=2.13, p=0.048); the effect of memory load for ‘other’ was only marginal (t(17)=1.84, p=0.08), and not significant for ‘self’ (p>0.36) (Figure 4.6B).

However, for lateral PFC ROIs, only right MFG showed a trend toward significant interaction between working memory load and appraisal target (F(2,34)=2.56, p=0.092); there was a marginal effect of memory load for ‘other’ (t(17)=1.89, p=0.076) (Figure 4.6C). No effect was found significant for other lateral PFC ROIs, including preCG, IFG/Operculum, pre-SMA/dACC (Fs <1).

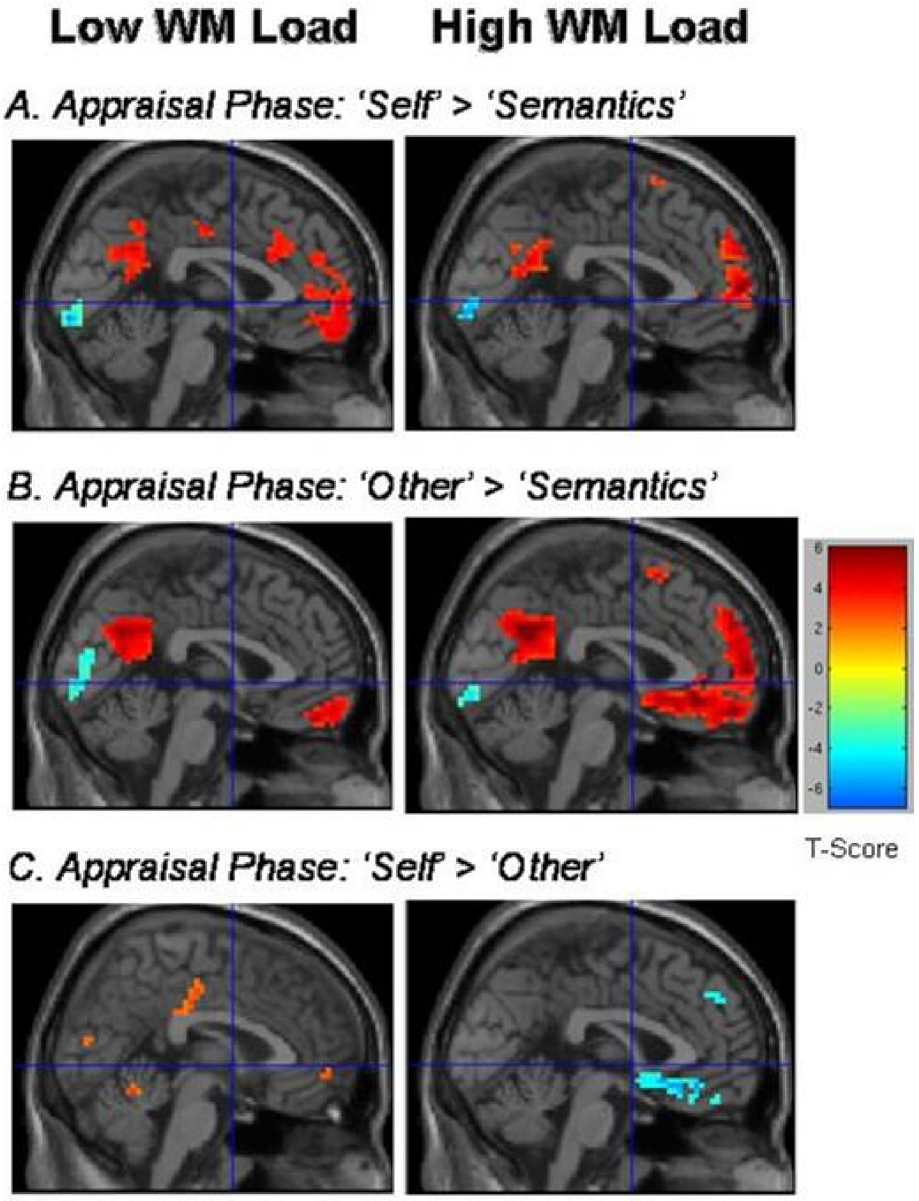
Figure 4.6: ROI extractions from the a priori task-positive network nodes.



Left column displays the locations of the functionally defined nodes used for the ROI analyses. Right column displays the parameter estimates for each of the conditions relative to a fixation baseline. Error bars represent standard error of the mean.

Lastly, we also displayed results from the whole-brain analyses that identified the effects of each working memory load on social cognition, at each voxel (Figure 4.7). The whole-brain analyses confirmed our findings from the ROI analyses. In brief, the evaluative appraisal of ‘self’ (relative to ‘semantics’) during the retention of low and high working memory load both engaged a similar network: aMFC, vMFC, PCC, pre-SMA/dACC and bilateral PFC; As for evaluative appraisal of ‘other’ (relative to ‘semantics’), only vMFC and PCC increased activity during the concurrent retention of low memory load, whereas extensive signals along the cortical midline (aMFC, vMFC, PCC, pre-SMA/dACC) and bilateral PFC were found while maintaining high memory load. When directly compare the effect of memory load on the evaluative appraisal of self versus a personally familiar other, we found increased activity in vMFC and PCC, among others, when memory load was low. Of interest, this vMFC [(12, 51, 0), Z=3.36] signal was in close proximity to an area commonly implicated in evaluating ‘self’ in the literature (e.g. Kelley et al., 2002 (10, 52, 2); Mitchell et al., 2005b (9, 57, 3)). On the contrary, when memory load was high, the evaluative appraisal of ‘other’ preferentially invoked signals extending along the dorsal-ventral axis of MFC. Here, we presented in Figure 4.7 the sagittal view from the cortical midline to emphasize the extensive modulatory effect of working memory load on DMN activity during social cognition.

Figure 4.7: Effect of working memory load on cortical activation during social cognition

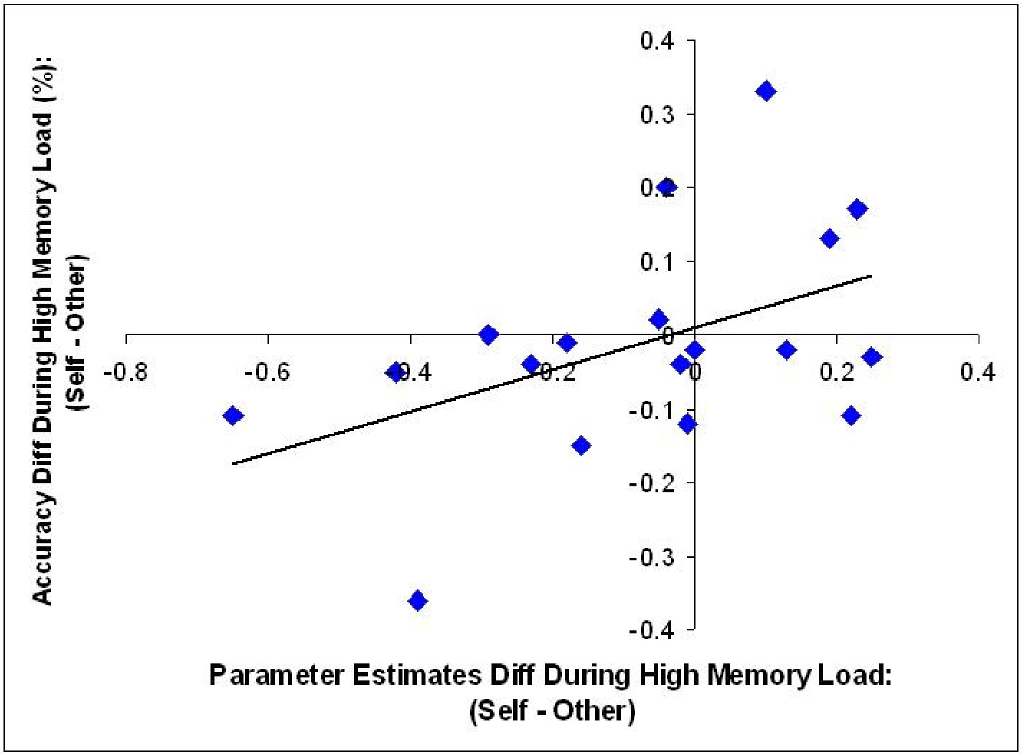


<u>*Correlation Analyses with Behavioral Performance*</u>

We sought to explore whether there is a functional link between cortical responses and behavioral performance, and determine if individual differences in deactivation of DMN and/or activation of task-positive network correspond to individual differences in behavior. Specifically, we were primarily interested in brain regions that may mediate the selective interference of self, manifested as a decline in working memory accuracy, observed during high memory load.

The right SPL ROI showed a significant correlation (r=0.48, p=0.045) between changes in cortical activation magnitude and changes in behavioral working memory accuracy between the appraisal of ‘self’ versus ‘other’ under high memory load. That is, those participants who activated the least in the right SPL during the evaluative appraisal of ‘self’ condition (relative to ‘other’) were those who showed strongest behavioral interference from the ‘self’ (Figure 4.8). However, no analogous correlation was found significant for the comparison between ‘self’ versus ‘desirability’ (p>0.87).

Figure 4.8: Correlation between the behavioral interference of ‘self’ (versus ‘other’) and cortical activity in the right SPL during ‘Appraisal’ (self vs. other)



Given that the reported correlation in the right SPL was only moderately robust and did not allow for strong statements, we suggest this correlation analysis between brain and behavior be interpreted with caution. However, considering that this *a priori* ROI has been implicated in spatial working memory, planning/executing actions (e.g. Cabeza and Nyberg, 2000) and in the allocation of visual spatial attention (Rushworth et al., 2001), this positive correlation makes intuitive sense that failure to sustain activity in the right SPL during the evaluative appraisal of 'self' is associated with poorer working memory accuracy.

However, contrary to the recent studies that showed an association between increased DMN activity (or, failure to deactivate DMN activity) during cognitive tasks and poorer behavioral performance (Persson et al., 2007a; Weissman et al., 2006), we failed to observe a similar phenomenon for all three of our DMN ROIs.

Discussion

The neuroimaging experiment described in this chapter (Study 4) set out to characterize the modulatory influences of task demand on the DMN activity in processing social cognitive functions, as well as its effect on the functional relationship between the default-mode and the task-positive networks. This current study has addressed the dynamics between the two large-scale networks in an innovative way: Importantly, in the present paradigm, we independently manipulated two factors known to affect cortical activity in the default-mode and task-positive networks, social cognition and task demand, respectively. The main novel finding emerges from this study is that the modulatory effects of task demand on network interactions depend on whether the task implementation involves social cognitive functions. More specifically, we have shown that, in line with others work, increase in task demand during cognitive tasks (such as normative semantic judgments of trait desirability) was associated with greater activation in the task-positive network and greater deactivation of the DMN. On the other hand, we also demonstrated that high load on working memory leads to increased activity in *both* the task-positive and default-mode networks during the evaluative appraisal of a personally familiar 'other', whereas no modulatory effect of task demand on cortical activity was found significant during the evaluative appraisal of 'self'.

Our results with regard to the effect of task demand on network interaction during cognitive tasks ('semantics') replicate previous work from other research investigators, and is consistent with the notion that a competitive, 'see-saw' relationship occurs as a consequence of (limited) neural resources being reallocated between networks (McKiernan et al., 2006; McKiernan et al., 2003). With regard to the social cognitive tasks, the resulting effects here is in line with our findings from Study 1 such that attending to social cognitive functions (for instance, thinking about likes or dislikes about another individual, or explicitly evaluation of personal characteristics in reference to one's self or another person) engage widespread cortical activity from the CMS. Moreover, here we provide new functional evidence suggesting that the default-mode and the task-positive networks operate in a 'coordinated, (non-competitive)' manner to facilitate social cognition regardless of task demand. We should, however, point out that no significant two way interaction between working memory load and appraisal target was found for the lateral PFC ROIs of the task-positive network (except for a marginal effect in right MFG, p=0.092), we suggest this lack of finding may reflect the fact that our delayed match-to-sample task involves primarily maintenance and minimum manipulation of information.

Several findings worth mentioning became apparent when we directly compare the modulatory effect of task demand on cortical activity during the two social cognitive tasks - evaluative appraisal of ‘self’ versus ‘other’. Under low task demand conditions, as expected and consistent with prior work, vMFC and PCC were preferentially engaged by the evaluative appraisal of self (e.g. Kelley et al., 2002; Moran et al., 2006). In contrast, the evaluative appraisal of a personally familiar ‘other’ (relative to ‘self’) evoked robust signals in aMFC and vMFC when task demand was high. The aMFC has been characterized as a functional division for reappraisal, cognitive evaluation and explicit reasoning of the incoming stimulus (e.g. Northoff et al., 2006; Ochsner and Gross, 2005; Phillips et al., 2003); the aMFC also has been implicated in mentalizing (Amodio and Frith, 2006; Mitchell et al., 2005a, b). Therefore, one likely explanation for this aMFC signal is that it may be a reflection of increased cognitive effort in understanding the minds of others under high task demand conditions. With regard to the vMFC signal (from the same contrast), the vMFC has been assigned a general role in assessing the salience of the incoming (emotional, or motivational) information (Amodio and Frith, 2006), regulating emotional responses accordingly (Phillips et al., 2003), possibly by resolving emotional conflict (Etkin et al., 2006); the vMFC also has been negatively associated with social judgment bias (for instance, the “above average” in self-evaluation), such that the more participants view themselves as more desirable than other people, the less they recruit the vMFC (Beer and Hughes, 2009). Therefore, it is tempting to speculate that the greater vMFC signal may be attributed to the more effort to regulate their emotional responses from thinking less of their peer when task demand is high. However, as there was no significant effect of memory load on the trait-evaluation measures behaviorally, a final interpretation of this vMFC signal requires further investigation.

Another significant finding emerged from the correlation analysis that examined the functional link between brain and behavior. We found a significant positive correlation between working memory-related changes in right SPL activity and changes in working memory accuracy (‘self’ versus ‘other’, under high task demand condition). Nonetheless, we did not find any significant relationship between changes in activity in the DMN (aMFC, vMFC and PCC) and changes in behavioral performance. Here, we speculate about a few possibilities for the failure to find a correlation. First, among the evidence that suggests a functional link between increased DMN activity and impaired cognitive task performance, often only the posterior node of the DMN (PCC) was implicated; therefore, the lack of two-way interaction in our PCC ROI in this study may contribute to the lack of variability for finding a robust correlation. Second, it has recently been proposed that behavioral variability is mediated by a competitive balance between the networks, rather than in the default-mode network *per se* (Kelly et al., 2008),

In sum, this study begins to elucidate the functional mechanism in which the default-mode and the task-positive network interact during social cognition. These findings may aid in our understanding of mental disorders characterized by altered functions served by these large-scale networks.

Limitations

Although the present results were generally positive, several experimental limitations need to be noted with regard to the dual-task paradigm. First, the experimental design may have suffered from lack of power. Fifteen trials per dual-task trial condition may not be sufficient to detect additional differences in brain regions that reflect behavior; for the same reason, the current design is not suitable to address any differential effect in evaluating positive versus negative personality trait adjectives. Future investigations with increasing power are clearly needed to determine if the significant social cognition-by-task demand interaction can be generalized to other types of social cognitive functions, as well as load manipulations in other domains of executive function (such as verbal working memory).

Secondly, our results might have suffered from recruiting unmatched sample groups – We had predominantly more male participants in both behavioral studies (Study 2 & 3), however, the majority of our participants for the fMRI experiment were females. Although there is currently no evidence for gender differences in the evaluative appraisal of personality trait, research has reported gender differences in brain responses to standardized emotional stimuli (IAPS pictures, faces) (e.g Fine et al., 2009; Wrase et al., 2003). This is considered a caveat of the study, and warrants further exploration.

CHAPTER V

CONCLUSION

Summary

Two intrinsically organized large-scale neural systems, the default-mode network and the task-positive network, have recently attracted increasing attention in the field of neuroscience. Advances in human brain mapping are approaching a consensus on the *competitive* functional relationships between the two networks at rest and during the performance of cognitive functions. This dissertation sought to investigate and address some of the many remaining questions about these networks and their interactions. This body of work focused on characterizing network dynamics during tasks that actively recruit DMN, such as social cognition. The first set of experiments, outlined in Chapter 2, were developed to examine brain activation and functional connectivity patterns in response to a fundamental aspect of social cognition – appraising one's likes and dislikes toward social encounters. Using a social preference task and connectivity analyses (psychophysiological interaction) of fMRI data, we addressed in Chapter 2 the interaction within the DMN and between nodes of the task-positive networks. We first demonstrated negative couplings among nodes of the DMN, potentially serving as an important mechanism for functional specialization of social cognition within the network. In addition, we demonstrated positive couplings between the default-mode and task-positive networks, indicating that social cognition (for instance, the expression of social preference) relies on higher cognitive functions that mediate controlled processing. This *complementary* functional relationship between the two networks delineated in Chapter 2 thus suggested that the brain regions involved in processing social cognition may be susceptible to the modulatory influences of task demand. We then explicitly investigated the effects of load manipulation and social cognition on the network interactions of the DMN in another set of experiments. Chapter 3 describes the development of a novel dual-task paradigm that systematically manipulated task demand by changing spatial working memory load in a delayed match-to-sample task, where social cognition (in the form of evaluative appraisal of personality traits) was engaged at three different levels. Two behavioral studies demonstrated selective interference, manifested as a decline in working memory accuracy, between spatial working memory and the evaluative appraisal of self, suggesting a plausible functional overlap. Finally, Chapter 4 adopted this dual-task paradigm to examine functional mechanisms underlying the observed behavioral interference, and to address the interaction between DMN, social cognition and task demand. As predicted, significant social cognition-by-task demand BOLD signal interactions were present in multiple regions of the default-mode and the task-positive networks. Taken together, these results suggest that network interactions of the DMN are dependent on factors including social cognition as well as task demand.

Overall, results from this body of work suggest that social cognition recruits widespread cortical activity in *both* the default-mode network and the task-positive networks; additionally, functional connectivity data suggests that nodes of the default-mode network and those of the task-positive networks functionally interact to facilitate social cognition. Lastly, we also provide novel evidence to suggest that the functional interactions, both within- and between-network, depend on whether there is on-line task demand (resting state vs. non-resting state), whether the task implementation involves social cognition (vs. non-social, cognitive tasks) and vary as a function of task demand. Results from this dissertation work extend our current understanding of network relationships obtained from task-free, or (cold) cognitively-demanding, settings, which have simply been described as ‘see-saw’, competitive or reciprocal.

The Functional Interactions of the DMN during Social Cognition

Several cortical midline components of the DMN, including the aMFC, vMFC and PCC, are responsive to our probes of social cognition. Indeed, we investigated two forms of social cognitive functions in this dissertation - one that is formed relatively quickly (Chapter 2; ‘social preference’) and another that takes more deliberative reflection (Chapter 4; ‘evaluative appraisal’); both engaged relatively greater activity in the CMS when compared to their control condition (See Figure 2.2 and Figure 4.4). Importantly, we demonstrated that these signals occurred as a result of decreased deactivation, reflecting the modulatory influences of social cognition on cognitive/perceptual task-induced deactivation (TID) in the DMN.

These findings support and supplement the growing body of data for a CMS-based network invoked by the processing of social cognitive information (e.g. Amodio and Frith, 2006; Northoff and Bermpohl, 2004, such as emotion processing (Phan, 2002; Uddin et al., 2007), person perception (e.g. Iacoboni et al., 2004; Mitchell et al., 2005c; Narumoto et al., 2001), attribution of mental states (e.g. Castelli et al., 2000; Frith and Frith, 1999; Mitchell et al., 2005a; Walter et al., 2004), and self-referential processing (e.g. Gusnard et al., 2001a; Johnson et al., 2005; Kelley et al., 2002; Northoff and Bermpohl, 2004). In particular, we add to the existing literature by examining the neural correlates of one basic, yet critical, part of interpersonal behavior – social preference. Judging likes or dislikes for other individuals requires one to look beyond perceptual properties like gender, sift through available social information, relate the information on an internal scale, and assess what is most relevant to the individual (de Greck et al., 2008; Enzi et al., 2009); as such, expressing social preference is mediated by aMFC, vMFC and PCC, the core structures for social cognition, as demonstrated in Chapter 2.

Outside of the DMN, we also demonstrated in both fMRI experiments greater activity in a set of higher cortical structures during social cognition. The task-positive regions involved include the pre-SMA, dACC, lateral frontal and lateral parietal cortices, all of which have been associated with the continuous internal monitoring of actions and adjustment of goal-directed behaviors (Ridderinkhof et al., 2004). Taken together, we showed *parallel* recruitment of the two networks, such that activity in both the default-mode and the task-positive networks increase during the explicit appraisal of social cognitive information. Greater activity in the task-positive network indicates that social cognition relies on controlled processing to guide contextually appropriate behavior, whereas the decreased deactivation in the DMN reflects the notion that explicitly attending to social cognitive functions demands activity from the CMS, thereby modulating the extent of TID observed across various cognitive tasks. Therefore, findings from both ‘activation tasks’ seem to converge on the notion that a reciprocal, ‘see-saw’, relationship between networks does *not* appear to be a necessary condition for network functioning, at least in the context of social cognitive tasks considered herein.

One novel and important contribution this dissertation work made to the field is the characterization of network interactions of DMN during social cognition. Through PPI analyses, we addressed the following question: What are the functional mechanisms by which nodes integrate the distinct functions relevant for the processing of social cognitive information? Put it simply, how do the parts contribute to the whole? We demonstrated in Chapter 2 (See Figure 2.3) functional interactions of DMN that fit nicely with the theoretical framework for social cognitive processing laid out by Northoff (Northoff and Bermpohl, 2004; Northoff et al., 2006) and Phillips *et al* (Phillips et al., 2003). First, within the DMN, we showed negative couplings among the nodes – As each of the medial cortical default nodes has been associated with a distinct function important in relation to social cognition (Northoff and Bermpohl, 2004; Northoff et al., 2006), our finding potentially reflects an underlying mechanism for functional specialization within the DMN. We interpret the reduced coupling between the nodes as differentiation of the specialized functions carried out in service of the preference task. With regard to the network interaction with the DMN, several nodes of the task-positive network were found to be positively coupled to the DMN. We suggest this provided connectivity-based evidence for a mechanism by which contextually appropriate social-cognitive behaviors are facilitated by higher cortical structures.

Modulatory Influences of Task Demand on Network Activity during Social Cognition

In order to further investigate the findings from Chapter 2, which indicate that networks involved in processing social cognition may be susceptible to load manipulation, Chapter 3 and 4 aimed to elucidate the behavioral and functional impacts of social cognition and task demand. In Chapter 3, we demonstrated that the social cognition is capable of interfering with the maintenance of spatial working memory. In particular, this effect was specific to the evaluative appraisal of personality traits where one’s self, but not ‘other’, was the explicit referent, when memory load was high. Importantly, it is worth noting that the reaction time, a useful behavioral index for task difficulty and attentional demand, was equated for evaluating traits related to ‘self’ versus ‘other’, indicating that attributing the observed selective interference to a difference in appraisal demand is not a likely explanation. Overall, behavioral evidence from Chapter 3 suggests that social cognition (in particular, evaluative appraisal of self) is a complex mental activity that functionally overlaps with the executive (working memory) system of the brain, a behavioral effect that may have reflected the connectivity relationship we found in Chapter 2 (Study 1). However, as the tasks in Study 1 differed from those in Study 2 and 3, the fourth study sought to localize this interaction effect in the brain.

In an fMRI experiment outlined in Chapter 4, we demonstrated that a significant social cognition-by-task demand interaction was present in the medial prefrontal cortices (aMFC, and vMFC), two of the three cortical midline default nodes hypothesized to mediate interaction effects. Much to our surprise, the significance of the two way interaction was mainly driven by the '*non*-self' conditions. More specifically, greater memory load significantly reduced CMS (aMFC, vMFC) activity when making semantic judgments (a non-referential, control condition), and increased CMS activity during the evaluation of the 'other'. Furthermore, there was no significant modulatory effect of task demand on CMS activity during the evaluative appraisal of self (See Figure 4.5). On the side of the task-positive network, two posterior parietal ROIs (right SPL, and right IPS) were sensitive to the interaction effects.

In sum, chapter 3 & 4 presents a novel set of behavioral and fMRI experiments that uniquely investigate network interactions of DMN through experimental manipulation. Importantly, this dissertation work has contributed to a dual-task approach that systematically characterized the mechanisms of social cognition and their interactions with executive functions. Although a significant social cognition-by-task demand interaction was present at both the behavioral and functional level, one intriguing observation arises when evaluating the results and inferences about the overall findings. That is, despite the significant behavioral interference of self, no neural correlates was found mediating this behavioral effect of the evaluative appraisal of self. How can one interpret the clear dissociation between behavior and BOLD signals detected? Several possibilities could explain these results. First and foremost, the behavioral interference of self manifested itself as a drop in working memory accuracy, which captured the overall effects (encompassing 4 task phases: *Encoding*; *Appraisal*; *Delay*; and *Retrieval*) of dual-task trials. Therefore, it may not necessarily be the case that there was a dissociation, as we only focused on the cortical activity during *Appraisal Phase*. Another possibility is simply that the networks are working in a more complicated, yet subtle, way than expected; for instance, it is possible that behaviorally the selective effect of self impairs the ‘relationship’ (e.g. connectivity strength), not the functional activity *per se*, of the task-positive frontoparietal cortices for working memory maintenance. As such, we were unable to detect any differences within the current limitations of our methodology. We suggest that future advances, e.g. a multivariate approach may detect some of the complex mental activity posited herein.

Significance and Future Directions

Taken together, findings from this series of studies converge to suggest that, in response to social cognition, widespread cortical activity are engaged from *both* the default-mode network and the task-positive networks: Contrary to the notion that task-induced deactivations in the DMN occurs as a consequence of reallocating (limited) neural resources to the task-positive networks to meet the external cognitive demand, functional evidence provided here suggest that this may not be the case for the processing of social cognitive information. In addition, through two different approaches - functional connectivity (Chapter 2) and experimental manipulation (Chapter 4), this body of work represents the first attempts, of which we are aware, to investigate the dynamics of the default-mode network activity during social cognition. From this work, it is possible to speculate about some of the specific functions carried out by the nodes studied here.

Default-Mode Network Regions & Functions during Social Cognition

The medial prefrontal cortex extending along the midline dorsal-ventral axis (aMFC & vMFC) and the posterior cingulate cortex (PCC) seem to play prominent roles in processing social-cognitive information, Taken together, activity in these cortical midline structures are preferentially evoked by tasks probing various functions of social cognition, such as emotion processing (Phan et al., 2002), person perception (e.g. Iacoboni et al., 2004), attribution of mental states (e.g. Mitchell et al., 2005a), and self-referential processing (e.g. Kelley et al., 2002). Taken separately, within these cortical midline structures, evidence is now starting to accumulate that suggest some form of functional specialization, such that each region is associated with a distinct process important for the social cognitive processing (Amodio and Frith, 2006; Northoff and Bermpohl, 2004; Northoff et al., 2006). Here we discuss these default-mode network regions separately; also incorporating our findings from these studies, we speculate their functions during social cognition.

Medial Prefrontal Cortex (aMFC & vMFC)

Both the aMFC and vMFC have been shown to be selectively engaged by appraisal of and decision about self-relevant stimuli, using paradigms requiring appraisals of one's personal characteristics (e.g. Kelley et al., 2002), affective experiences (e.g. Taylor et al., 2007), attitudes (e.g. Cunningham et al., 2003), and preferences (e.g. Johnson et al., 2005; Chen et al. *in press*); moreover, increase in self-relatedness or personal associations with stimuli has been shown parametrically modulate cortical activity in the medial prefrontal cortex (Northoff et al., 2009; Phan et al., 2004). Our data in Chapter 4 during low working memory load condition replicated this observation, such that evaluative appraisal of self engaged more medial prefrontal activity than that of 'other', whereas semantic judgment deactivated the activity the most. On the other hand, our data further suggest that high working memory load may interfere with the function of medial prefrontal cortex in processing self-relevant stimuli, or more specifically, in differentiating between self and another individual. This interpretation requires further investigation. For example, exploration is needed to determine whether the extent to which task demand may modulate the functional differentiation between self and a close/highly similar other.

With regard to the functional specialization within the medial prefrontal cortex, the vMFC has been primarily assigned a general role in assessing the salience of the incoming (emotional, or motivational) information (Amodio and Frith, 2006), whereas the aMFC has been described as a functional division supporting cognitive evaluation and reappraisal, including reasoning about the incoming stimulus (e.g. Northoff et al., 2006; Ochsner and Gross, 2005; Phillips et al., 2003). Altogether, on the basis of over 200 fMRI studies, the medial prefrontal cortex has been characterized as a module that allows representation and reflection of traits and norms at a more abstract cognitive level (Van Overwalle, 2008). Given the consistency of medial prefrontal activation for self across both low and high task demand conditions, it appears that the processing of traits in relation to self is immune to load manipulation, an effect we speculate as reflecting the obvious evolutionary significance and priority granted to self. On the other hand, increased medial prefrontal activity for 'other' during high task demand condition may reflect greater cognitive effort involved in abstractly processing the mind of another person.

Put more generally, data from this dissertation work added to the existing literature that task demand, as well as age (Gutchess et al., 2007), cultural context (Chiao et al., 2009a, b), and the degree of similarity/familiarity between the self and the other person (Mitchell et al., 2005b) are important factors that influence the processing of social cognitive information in the human prefrontal cortex. Future studies investigating the network interactions of DMN in the context of social cognition would benefit from systematically take into account of these factors of experimental conditions and individual differences.

Posterior Cingulate Cortex (PCC)

With its strong connection with the hippocampus implicated in autobiographic memory, the PCC has a central role in integrating the temporal context of the stimuli. The particular involvement of PCC in social cognition has been primarily linked to emotional processing, which has been suggested to occur as a consequence of this region's role in episodic memory (Maddock, 1999). Moreover, a very recent study in impression formation suggests PCC as part of a neural mechanism that codes for subjective valuation of social information and integrates personal experience across time (Schiller et al., 2009).

The comparison between our fMRI findings from Chapter 2 and Chapter 4 may appear contradictory at first glance. That is, Chapter 2 showed that PCC increased functional coupling with the task-positive networks in the context of social cognition (social preference), suggesting collaborative effort from higher cortical structures mediating cognitive controlled processing to facilitate social cognition. On the other hand, Chapter 4 showed that activity of PCC during social cognition (evaluative appraisal of self and other) is not modulated when cognitive load on executive functions (spatial working memory) is taxed. We speculate that that the findings from Chapter 4 may reflect the notion that first impressions are formed fast (< 100 ms) (Hassin and Trope, 2000; Willis and

Todorov, 2006), thereby less susceptible to task demand modulation. Although tempting, this interpretation clearly requires further investigation.

Concluding Summary for Future Directions

Overall, these studies are the first attempts to investigate the dynamics of the default-mode network activity during social cognition. We suggest that future studies on network interactions should take advantage of several more sophisticated tools, recently advanced in human brain mapping. First, future studies may benefit from the used of effective connectivity techniques that takes a step beyond simply calculating correlations and allows one to estimate the directions of influences between variables. As such, inferences about causal inter-regional relationships can be made through methods such as dynamic causal modeling (Friston et al., 2003), or structural equation modeling (Gonzalez-Lima and McIntosh, 1994). The capability to make causal inferences will be especially instrumental to further advance our understanding of network dynamics, for instance, with regard to the functional specialization within the DMN. One may then be able to make a more definite statement about whether social information initially represented in vMFC is subsequently modulated by the aMFC and/or the PCC. Second, our understanding of network interactions may advance exponentially with the use of concurrently rTMS and fMRI. For instance, one may consider utilizing this non-invasive brain stimulation tool to target specific brain areas in one network while engaging brain activity in another network through functional paradigm. We suggest that this state-of-the-art tool may potentially allow more effective and clean manipulations of the network activity than our dual-task paradigm can afford. Lastly, as psychiatric disorders are being understood as aberrant interaction between the DMN and the task-positive networks (Broyd et al., 2009), the insights gleaned from work laid out here may shed light on these debilitating mental disorders.

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