Title

Executive Control of Declarative Memory: Insights from neuroimaging, brain stimulation, and behavior

Author

Westphal, Andrew James

Publication Date

2017

UNIVERSITY OF CALIFORNIA

Los Angeles

Executive Control of Declarative Memory:
Insights from neuroimaging, brain stimulation, and behavior

A dissertation submitted in partial satisfaction of the
requirements for the degree Doctor of Philosophy
in Psychology

by

Andrew James Westphal

2017

ABSTRACT OF THE DISSERTATION

Executive Control of Declarative Memory:
Insights from neuroimaging, brain stimulation, and behavior

by

Andrew James Westphal

Doctor of Philosophy in Psychology
University of California, Los Angeles, 2017
Professor Jesse A. Rissman, Chair

The executive control of declarative memory is the goal-directed and volitional manipulation of representations from episodic and semantic memory systems and is thought to critically depend on the interactions between prefrontal cortex neural systems and the default mode network (Mitchell & Johnson, 2009; Spreng, Stevens, Chamberlain, Gilmore, & Schacter, 2010; Vincent, Kahn, Snyder, Raichle, & Buckner, 2008). The prefrontal cortex system itself is thought to be organized hierarchically along a rostrocaudal axis where increasingly anterior prefrontal cortex regions enact and represent more abstract executive control while more posterior frontal cortex regions exert progressively more concrete executive control interactions with motor systems

(Badre & D’Esposito, 2009; Koechlin & Hyafil, 2007). The first chapter of this dissertation provides the background on the fronto-parietal control network and default mode network neural systems that govern the executive control of declarative memory (Andrews-Hanna, 2012; Fox et al., 2005; Power et al., 2011; Vincent et al., 2008). The second chapter discusses research focused upon further understanding how rostrolateral prefrontal cortex, the most anterior prefrontal region, interacts with neural systems involved in declarative memory, to enable episodic retrieval and analogical reasoning. The first section of Chapter 2 discusses an fMRI study that was performed to disentangle the role of rostrolateral prefrontal cortex in episodic memory retrieval and analogical reasoning and presents data showing that this brain region is domain-general in nature and functionally couples with domain-specific neural systems for goal-directed cognition (Westphal, Reggente, Ito, & Rissman, 2016). The second section of Chapter 2 presents data from a transcranial direct current stimulation study that causally influenced the stimulation levels of rostrolateral prefrontal cortex during the memory and reasoning tasks and presents evidence that the stimulation of the fronto-parietal control and default mode networks simultaneously improves episodic memory retrieval. The third chapter discusses research focused on further understanding the fronto-parietal control and default mode network neural systems. The first section of Chapter 3 discusses an fMRI study that assessed whole-brain functional connectivity during reasoning and memory tasks and shows that performance in episodic memory retrieval benefits from more whole-brain connectivity, in contrast to reasoning (Westphal, Wang, & Rissman, 2017). The second section of Chapter 3 presents data from a behavioral study that was inspired from work showing that major depressive disorder is associated with aberrant connectivity between the fronto-parietal and default mode networks (Hamilton, Chen, & Gotlib, 2013; Marchetti, Koster, Sonuga-Barke, & De Raedt, 2012), where the retrieval of negatively-valenced autobiographical memories interferes with an ensuing visual working memory task. The fourth chapter summarizes the main findings from each research study and provides some concluding thoughts on what this body of work has revealed about the neurocognitive control processes that support declarative memory.

The dissertation of Andrew James Westphal is approved.

Barbara Knowlton

Martin Monti

Marco Iacoboni

Jesse A. Rissman, Committee Chair

University of California, Los Angeles

2017

DEDICATION

I dedicate this work to those who are seekers of truth and aspire for their work to reduce suffering in this world.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ACKNOWLEDGMENTS

This research was supported by UCLA startup funds provided to Dr. Jesse A. Rissman, Neuroimaging Training Program Fellowship NIH Grant 5T90DA022768-07, Neuroimaging Training Program Fellowship NIH Grant 5R90DA023422-10, and National Research Service Award NIH Grant 1F31MH110114-01.

I would like to thank Dr. Jesse A. Rissman, my dissertation chair, who I have worked with very closely over my graduate school career and who has really taught me a lot about cognitive science, quantitative analysis, and academia. I also want to thank Drs. Cameron Carter, Jong Yoon, and Allison Harvey who helped me develop as a young scientist prior to graduate school. Furthermore, I want to acknowledge my dissertation committee: Drs. Barbara Knowlton, Martin Monti, and Marco Iacoboni who provided valuable feedback and assistance at each stage of my dissertation, as well as Dr. Keith Holyoak. I want to thank my grandfather, Dr. Andrew L. Comrey, and my aunt, Corinne Byers, for always believing in me and pushing me to pursue my passions. I greatly appreciate the efforts of all of my family members, who have always sacrificed their time to help me when it was needed and helped motivate me throughout the marathon that is graduate school. I want to thank Tiffany Chow, who I shared this journey with and who was always kindhearted. I want to thank my labmates for their friendship and insights on my projects. Last, but not least, I would like to acknowledge the talented and dedicated undergraduate research assistants in the Rissman Memory Lab who have contributed their time and energy to help me complete my studies.

VITA

EDUCATION

2008 – Bachelor of Arts, Psychology
University of California, Berkeley
Berkeley, California

2012 – Master of Arts, Psychology – Cognitive Neuroscience
University of California, Los Angeles
Los Angeles, California

2015 – Candidate of Philosophy, Psychology – Cognitive Neuroscience
University of California, Los Angeles
Los Angeles, California

PUBLICATIONS

Mayda, A.B.V., **Westphal, A.J.**, Carter, C.S., & DeCarli, C. (2011). Late life cognitive control deficits are accentuated by white matter disease burden. *Brain*, *134,* 1673-1683.

Lesh, T.A., **Westphal, A.J.**, Niendam, T.A., Yoon, J.H., Minzenberg, M.J., Ragland, J.D., Solomon, M., & Carter, C.S. (2013). Proactive and reactive cognitive control and dorsolateral prefrontal cortex dysfunction in first episode schizophrenia. *NeuroImage: Clinical, 2,* 590-599.

Niendam, T.A., Lesh, T.A., Yoon, J.H., **Westphal, A.J.**, Hutchison, N.S., Ragland, J.D., Solomon, M., Minzenberg, M.J., & Carter, C.S. (2013). Impaired context processing as a potential marker of psychosis risk state. *Psychiatry Research: Neuroimaging, 221,* 13-20.

Yoon, J.H., **Westphal, A.J.**, Minzenberg, M.J., Niendam, T., Ragland, J.D., Lesh, T., Solomon, M., & Carter, C.S. (2014). Task-evoked substantia nigra hyperactivity associated with prefrontal hypofunction, prefrontonigral disconnectivity and nigrostriatal connectivity predicting psychosis severity in medication naïve first episode schizophrenia. *Schizophrenia Research, 159,* 521-526.

Westphal, A.J., Reggente, N., Ito, K. & Rissman, J. (2016). Unraveling the contributions of rostral prefrontal cortex to analogical reasoning and episodic memory retrieval. *Human Brain Mapping, 37,* 896-912.

Westphal, A.J., Wang, S. & Rissman, J. (2017). Episodic memory retrieval benefits from a less modular brain network organization. *Journal of Neuroscience, 37,* 3523-3531.

SELECTED PRESENTATIONS

Westphal, A.J., Reggente, N., Nawabi, Y., Fortuna, H.W. & Rissman, J. (2013). Shared and distinct contributions of rostral prefrontal cortex to analogical reasoning and episodic memory retrieval:Insights from fMRI functional connectivity and multivariate pattern analyses. Poster presented at the Cognitive Neuroscience Society Annual Meeting, San Francisco, CA.

Westphal, A.J., Reggente, N., Ito, K., Fortuna, H.W. & Rissman, J. (2013). Decoding cognitive task-sets from rostral prefrontal cortex functional connectivity patterns. Poster presented at the Organization for Human Brain Mapping Annual Meeting, Seattle, WA.

Westphal, A.J., Reggente, N., Ito, K., Fortuna, H.W., Nawabi, Y., Owens, E.R. & Rissman, J. (2013). Medial temporal lobe and its contributions to analogical reasoning and episodic memory retrieval: Common and dissociable activations at the local and network-level. Poster presented at the Society for Neuroscience Annual Meeting, San Diego, CA.

Westphal, A.J., Reggente, N., Ito, K., Fortuna, H.W., Nawabi, Y., Owens, E.R. & Rissman, J. (2013). Characterizing common and dissociable involvement of medial temporal lobe regions during episodic source memory retrieval and analogical reasoning. Poster presented at the Brain Research Institute Annual Neuroscience Series, Los Angeles, CA.

Westphal, A.J., Monti, M.M., Reggente, N., Yazdanshenas, O., & Rissman, J. (2014). Episodic memory retrieval benefits from a less modular brain network organization. Talk presented at the Society for Neuroscience Annual Meeting, Washington, D.C.

Westphal, A.J., Ngoy, C.D., Chow, T.E., Storozuk, L.A., Liao, V., Peters, M.A.K., Wu, A., Shams, L., & Rissman, J. (2016). Transcranial direct current stimulation to left rostrolateral prefrontal cortex results in divergent effects on memory and reasoning. Poster presented at the International Conference on Memory, Budapest, Hungary.

AWARDS

2004, 2005, & 2008 - *3x UC Berkeley Honor Roll*

2008 - *UC Berkeley Psychology Major Honors Thesis*

2008 - *UC Berkeley Distinction in General Scholarship (Cum Laude)*

2011 - *UCLA Distinguished University Fellowship*

2012 - *National Science Foundation GRFP Honorable Mention*

2012 - *Neuroimaging Training Program Fellowship, NIH Grant 5T90DA022768-07*

2012 - *UCLA Graduate Summer Research Mentorship Award*

2014 - *UCLA Graduate Summer Research Mentorship Award*

2014 – *UCLA Brain Research Institute Society for Neuroscience Travel Award*

2015 - *Neuroimaging Training Program Fellowship, NIH Grant 5R90DA023422-10*

2016 – *National Research Service Award NIH Grant 1F31MH110114-01*

CHAPTER 1

Background

The human brain is never truly at rest. When it is not occupied with a goal-directed cognitive task, the brain tends to automatically shift towards an introspective state where one's attention is withdrawn from the external environment and is instead focused on its internally-generated thoughts. This internally-oriented state involves the engagement of a distributed ensemble of brain regions collectively known as the default mode network (DMN), which show diminished fMRI activity during most externally-oriented cognitive tasks and elevated activity during undirected resting mentation (Raichle et al., 2001). While often associated with mind-wandering, the DMN supports a host of critically important functions, including the retrieval of semantic knowledge and episodic memories, prospection into future scenarios, and reflection on activated emotions (Andrews-Hanna, 2012). The DMN typically exhibits an antagonistic relationship with a separate "task-positive" neural system, whereby increased expression of one network is accompanied by reductions in activity of the other (Fox et al., 2005). The task-positive system was originally implicated in externally-oriented cognitive processes, such as visuospatial attention and working memory, but further studies demonstrated that this task-positive system in fact consists of at least two sub-networks – the dorsal attention network (DAN) and the fronto-parietal control network (FPCN) – that tend to work together in many task contexts (Vincent et al., 2008). Critically, the FPCN has been demonstrated to enact goal-oriented cognitive control processes through interaction with either the DMN or the DAN, depending on whether the task predominantly emphasizes attention to internal or external attributes (Fornito, Harrison, Zalesky, & Simons, 2012; Spreng et al., 2010).

In addition to the evidence that the FPCN can work in concert with the DMN to process and manipulate internally-generated representations, a series of studies have demonstrated that rostral lateral prefrontal cortex (RLPFC) regions within the FPCN enact executive control processes to facilitate memory encoding, search, and post-retrieval monitoring of mnemonic contents (Mitchell & Johnson, 2009). These RLPFC regions have been hypothesized to be at the apex of a putative rostro-caudal prefrontal executive control hierarchy (Badre & D'Esposito, 2009; Christoff & Gabrieli, 2000; Koechlin & Hyafil, 2007) and have been implicated in abstract executive control processes in relational reasoning (Bunge, Wendelken, Badre, & Wagner, 2005; Cho et al., 2010; Green, Fugelsang, Kraemer, Shamosh, & Dunbar, 2006; Green, Kraemer, Fugelsang, Gray, & Dunbar, 2010; Krawczyk, Michelle McClelland, & Donovan, 2011; Watson & Chatterjee, 2012; Wendelken, Nakhabenko, Donohue, Carter, & Bunge, 2008) and episodic memory retrieval (Lepage, Ghaffar, Nyberg, & Tulving, 2000; Ranganath, Johnson, & D'Esposito, 2000; Simons, Gilbert, Owen, Fletcher, & Burgess, 2005; Simons, Henson, Gilbert, & Fletcher, 2008). Importantly, the RLPFC is has also been implicated in the control of attentional switching between externally-oriented and internally-oriented attentional states (Burgess, Dumontheil, & Gilbert, 2007; Gilbert, Frith, & Burgess, 2005), suggesting that RLPFC may be the critical FPCN structure that regulates the flexibly coupling that is characteristic of this dynamic cognitive control network (Cole et al., 2013).

These findings demonstrate the essential relationship between the FPCN, putatively mediated by RLPFC regions, and DMN systems where executive control processes are needed to regulate the balance between attending to events in one's external environment and attending to one's internal states, including the reliving of past memories and the associated emotions that they evoke in addition to manipulating declarative knowledge due to changing task conditions. The following studies aim to clarify the neural mechanisms that support these distinct forms of cognition and that mediate the ability to flexibly shift between them.

CHAPTER 2

Rostral Prefrontal Cortex

SECTION 2.1.

Shared and distinct contributions of rostrolateral prefrontal cortex to analogical reasoning and episodic memory retrieval[1]

Abstract

Rostrolateral prefrontal cortex (RLPFC) is widely appreciated to support higher cognitive functions, including analogical reasoning and episodic memory retrieval. However, these tasks have typically been studied in isolation, and thus it is unclear whether they involve common or distinct RLPFC mechanisms. Here, we introduce a novel functional magnetic resonance imaging (fMRI) task paradigm to compare brain activity during reasoning and memory tasks while holding bottom-up perceptual stimulation and response demands constant. Univariate analyses on fMRI data from twenty participants identified a large swath of left lateral prefrontal cortex, including RLPFC, that showed common engagement on reasoning trials with correct valid analogies and memory trials with correctly retrieved source details. Despite broadly overlapping recruitment, multi-voxel activity patterns within left RLPFC reliably differentiated these two trial types, highlighting the presence of at least partially distinct information processing modes. Functional connectivity analyses demonstrated that while left RLPFC showed consistent

---

[1] This section was previously published as: Westphal, A.J., Reggente, N., Ito, K., and Rissman, J. (2016) Shared and distinct contributions of rostrolateral prefrontal cortex to analogical reasoning and episodic memory retrieval. *Human Brain Mapping*, 37(3), 896-912.

coupling with the fronto-parietal control network across tasks, its coupling with other cortical areas varied in a task-dependent manner. During the memory task, this region strengthened its connectivity with the default mode and memory retrieval networks, whereas during the reasoning task it coupled more strongly with a nearby left prefrontal region (BA 45) associated with semantic processing, as well as with a superior parietal region associated with visuospatial processing. Taken together, these data suggest a domain-general role for left RLPFC in monitoring and/or integrating task-relevant knowledge representations and showcase how its function cannot solely be attributed to episodic memory or analogical reasoning computations.

Introduction

Rostrolateral prefrontal cortex (RLPFC) is thought to support the highest level and most abstract forms of cognitive control and decision-making, given its position at the apex of a putative rostro-caudal prefrontal hierarchy (Badre & D'Esposito, 2009; Koechlin & Hyafil, 2007; Ramnani & Owen, 2004). This anterior-most segment of the frontal lobe, also referred to as frontopolar cortex, is generally considered to encompass lateral sections of Brodmann's Area (BA) 10, although its definition is often broadened to include immediately neighboring aspects of BAs 9, 46, 47 (e.g., Christoff & Gabrieli, 2000; Wendelken, Chung, & Bunge, 2012). Functional magnetic resonance imaging (fMRI) studies have reported RLPFC activations across a range of tasks requiring various high-level cognitive processes, including relational integration in analogical reasoning (Bunge et al., 2005; Cho et al., 2010; Green et al., 2006; Green et al., 2010; Krawczyk et al., 2011; Watson & Chatterjee, 2012; Wendelken, Nakhabenko, et al., 2008), initiating episodic memory search and evaluating retrieved contextual details (Lepage et al., 2000; Ranganath et al., 2000; Reynolds, McDermott, & Braver, 2006; Simons et al., 2005; Simons et al., 2008), task-set implementation and cognitive branching (Badre & D'Esposito, 2007; Charron & Koechlin, 2010; Koechlin, Basso, Pietrini, Panzer, & Grafman, 1999; Koechlin & Hyafil, 2007; Sakai & Passingham, 2002, 2006), storing situationally contingent intentions in the service of prospective memory (Beck, Ruge, Walser, & Goschke, 2014; Burgess, Gonen-Yaacovi, & Volle, 2011; Gilbert, 2011; Momennejad & Haynes, 2012), making counterfactual inferences that facilitate hypothesis-testing (Donoso, Collins, & Koechlin, 2014), and regulating the shifting between externally-oriented and internally-oriented attentional states (Burgess et al., 2007; Gilbert et al., 2005). Many of these high-level cognitive operations are intimately related to one another and likely constitute alternative conceptual framings of the same underlying phenomena. The involvement of RLPFC across a such a diverse array of cognitive task paradigms (for a meta-analysis, see (Gilbert et al., 2006)) thus begs the question of whether there are core computations shared across these paradigms, or whether anatomically circumscribed RLPFC subregions mediate distinct processes that only appear to be overlapping when one takes a bird's-eye view of the literature. Because many anterior prefrontal regions can be labeled as RLPFC, and because few studies have attempted to directly compare RLPFC involvement across different cognitive domains, such as memory and reasoning, it has been challenging to know whether the RLPFC effects that have been reported in these respective literatures are related to each other in a meaningful way. One previous study by Reynolds et al. (2006) jointly examined episodic retrieval and relational integration processes and found that these cognitive functions appeared to be supported by distinct RLPFC foci, although they did identify a right-lateralized RLPFC region that showed sensitivity to both retrieval and integration demands.

In the memory literature, RLPFC has been consistently implicated in episodic retrieval processes. Early positron emission tomography research showed that common RLPFC regions were engaged across four distinct memory retrieval tasks (Lepage et al., 2000). The authors theorized that RLPFC supports the enactment of a so-called "retrieval mode," involving the tonic specification of an internally-oriented attentional state in which one’s goal is to search one’s memory for relevant episodic content. Further research, using fMRI, confirmed that RLPFC is recruited in a temporally sustained manner during blocks of episodic retrieval trials, with the degree of activation modulated by the demands for cognitive control (Velanova et al., 2003). By incorporating a mixed block/event-related design, this study was also able to identify a separate RLPFC cluster that showed transient recruitment during trials with successful retrieval outcomes. Other studies have emphasized a role for RLPFC in the specification of retrieval strategies to recover specific contextual details about a past experience and/or the monitoring of the retrieved content (Dobbins & Han, 2006; Dobbins & Wagner, 2005; Ranganath et al., 2000; Reynolds et al., 2006; Simons et al., 2005; Simons et al., 2008). In meta-analyses of episodic retrieval, RLPFC consistently emerged as a core locus of activation (Cabeza & Nyberg, 2000; Gilbert et al., 2006; Wagner, Shannon, Kahn, & Buckner, 2005).

In the reasoning literature, a number of fMRI studies have demonstrated a role for RLPFC in relational reasoning, independent of task domain (for review, see Vendetti & Bunge, 2014). One early study presented participants with visuospatial reasoning problems adapted from the Raven’s Progressive Matrices test and found that RLPFC was preferentially activated on trials where two relations needed to be simultaneously considered and integrated (Christoff et al., 2001). A later study using word stimuli reported elevated RLPFC activity on trials where participants had to solve propositional analogies (requiring the comparison of two first-order semantics relationships) relative to trials that only demanded decisions about a single first-order semantic relationship

(Bunge et al., 2005). Although such findings might point one to the conclusion that RLPFC engagement is simply proportional to the cognitive demands of the task, carefully designed follow-up experiments have demonstrated that RLPFC activity cannot be attributed to task difficulty alone, but rather seems to track the complexity of the relational processing (Wendelken, Bunge, & Carter, 2008; Wendelken, Nakhabenko, et al., 2008) and/or the degree of representational abstractness (Christoff, Keramatian, Gordon, Smith, & Madler, 2009). In these studies, difficulty levels were either matched across conditions, or else it was the case that the most difficult condition was not the one that elicited the greatest RLPFC activity. Other work has ruled out an interpretation of RLPFC activity as being attributable to demands for interference resolution. In a study involving pairs of cartoon characters that either matched or mismatched on specific perceptual attributes, RLPFC was activated when an increasing number of visual characteristics needed to be compared but not when a visual characteristic needed to be inhibited (Cho et al., 2010). Further work has suggested that distinct RLPFC subregions may be preferentially recruited during separates phases of the analogical reasoning process, such as generating structured representations of the stimuli and performing the mapping/comparison process (Krawczyk, McClelland, Donovan, Tillman, & Maguire, 2010; Volle, Gilbert, Benoit, & Burgess, 2010). And it has been argued that left RLPFC is specifically involved in the abstract integration of multiple relationships (Bunge, Helskog, & Wendelken, 2009).

Clearly, RLPFC is recruited for both reasoning and memory processes, but how distinct are the functional roles for RLPFC regions in these two cognitive domains? One approach that has yielded some clues into the neurocognitive mechanisms supported by RLPFC has been to examine which brain regions RLPFC communicates with as individuals perform goal-oriented operations requiring the retrieval of task-specific content. RLPFC regions appear capable of flexibly adjusting their functional connectivity with distinct posterior brain regions depending on the goals of the task at hand. For instance, one study found that left RLPFC preferentially interacted with different task-specific processing areas in left frontal cortex according to whether one's task-set required preparation for an upcoming phonological task or semantic task (Sakai & Passingham, 2006). In a study of relational reasoning, Wendelken et al. (2012) found that the strength of coupling between left RLPFC and brain regions involved in either visuospatial or semantic processing is modulated based on the type of relations participants must consider to make their judgments. Although RLPFC can exhibit functional coupling with a range of content-specific processing regions, this area is thought to be a critical node in a core network sometimes referred to as the fronto-parietal control network (FPCN) (Dosenbach et al., 2007; Power et al., 2011). Indeed, RLPFC is often used as the "seed" region to identify the FPCN; this is typically done by looking for voxels throughout the brain whose spontaneous fluctuations in low-frequency blood-oxygen-level-dependent (BOLD) signal are correlated with those of the seed during the undirected resting-state (Power et al., 2011; Shirer, Ryali, Rykhlevskaia, Menon, & Greicius, 2012; Vincent et al., 2008). This was further verified by a meta-analysis examining co-activation of RLPFC areas, showing that they tend to co-activate with FPCN areas (Gilbert, Gonen-Yaacovi, Benoit, Volle, & Burgess, 2010).

Although patterns of correlated resting-state BOLD fluctuations can be used to subdivide the brain into a set of discrete networks, these networks dynamically interact with one another during cognitive tasks. For instance, the FPCN has been found to show strong functional coupling with either the default mode network (DMN) or the dorsal attention network (DAN) depending on whether the task context requires orienting one's attention towards internally-generated information or external information in the environment, which are the respective cognitive domains associated with these brain networks (Spreng et al., 2010). The ability of RLPFC (and its associated FPCN structures) to flexibly interact with distinct neural systems depending on task goals may be one important factor in understanding its common engagement across such a wide range of higher cognitive processes.

We designed the present fMRI study in an effort to further elucidate the nature of the RLPFC involvement in memory and reasoning. By having the same cohort of subjects perform closely matched tasks of episodic memory retrieval and verbal analogical reasoning during the same scanning session, our experiment offers a unique opportunity to evaluate the degree to which common and/or distinct RLPFC regions are engaged during these two cognitive domains. Our use of a mixed block/event-related design allows us to separately model transient recruitment in response to the information processing demands posed by individual trials and temporally-sustained processes (Petersen & Dubis, 2012). We predicted that transient effects would dominate in RLPFC, as many prior memory and reasoning studies have reported trial type-specific activation here. To the degree that overlapping RLPFC activations are observed across the memory and reasoning tasks, we can use multivariate classification techniques (Rissman & Wagner, 2012b; Tong & Pratte, 2012) to examine whether the underlying BOLD activity patterns nonetheless contain subtle markers of task-set identity, indicating sensitivity to the distinct computational demands of two tasks. We also aimed to examine whether the functional connectivity profiles of commonly engaged RLPFC regions show task-dependent changes that might be emblematic of the different types of mental representations that RLPFC must access and operate upon to accomplish the goals for the respective tasks.

Materials and Methods

Participants

Twenty-two participants were recruited from UCLA and the surrounding community. Written informed consent was obtained in accordance with procedures approved by the UCLA Institutional Review Board, and participants received monetary compensation. Two participants were scanned and then excluded from analysis because of excessive head motion that led to data distortion and restricted brain coverage. The average age of the remaining 20 participants (10 female) was 21.1 years old (range: 19-25). All participants were right-handed native English speakers with normal or corrected-to-normal visual acuity and no history of mental illness, drug and alcohol dependence, or MRI contraindications.

Cognitive Tasks

During the fMRI experiment, participants alternated between performing three distinct cognitive tasks: analogical reasoning, episodic memory retrieval, and visuospatial perception. Although the reasoning and memory tasks were of principle interest to us, the perception task was included as a comparison condition. We designed this task such that it shared the same stimulus characteristics and response demands as the other two tasks, yet did not require participants to engage in abstract thinking or operate on internally-generated representations. All three tasks were structured such that on each trial participants viewed four words simultaneously displayed in the four quadrants of the screen. The tasks differed only with respect to the decision that participants had to make about a given 4-word array. Participants were informed that each task would have four response options and that they would use their right hand to indicate their response, with digits 2 through 5 corresponding to options 1 through 4. All words used in the experiment were trial unique and drawn from a set of 1,184 words, comprised of both concrete nouns (e.g., lobster) and abstract nouns (e.g., ethics). This set was divided into three separate word lists, and the assignment of lists to the three task conditions was counterbalanced across participants so as to eliminate the possibility that group-level differences in brain activity across tasks could be attributed to differences in the characteristics of the particular set of words appearing in each task.

Each block began with a task-set cue indicating which task should be performed on the ensuing four trials. The letter “R” cued the Reasoning task. Participants were to evaluate the top word-pair and bottom word-pair of each 4-word array to decide whether or not the two word-pairs had an analogical relationship. Analogical relationships—defined as the two word-pairs sharing the same “A is to B” semantic relationship—were present on 50% of trials. If participants believed that the two word-pairs did not constitute a valid analogy, they were to specify how many semantic relationships were present (non-analogy trials contained two, one, or zero semantic relationships in equal proportion). The four response options were: *1) Valid Analogical Relationship, 2) Two Valid Semantic Relationships, 3) One Valid Semantic Relationship, 4) No Semantic Relationships*.

When cued to perform the Memory task with the task-set cue “M”, the participants’ task was to evaluate each 4-word array and determine whether one of the words had been previously encountered during an earlier memory encoding session, and if so, to indicate their recollection of the source context of the recognized word. The memory encoding session took place one day prior to MRI scanning and involved the presentation of a series of 80 words on a computer display. Each word was preceded by a 3 s cue, instructing participants to either visualize themselves interacting with the word’s referent (“Self” cue) or visualize somebody else interacting with the word’s referent (“Other” cue). Participants were allotted 10 s to generate a memorable visualization, followed by a 3 s interval before the next cue appeared. Participants were informed that they would later be tested on their memory for the words and their associated visualization conditions (i.e., the source context). During the scanned Memory task, each trial included a maximum of one previously studied word appearing at a random location in the 4-word array, but 25% of trials consisted of all novel words.

Note that participants did not have to specify which of the four words they remembered, but only whether they had a memory for one of the four words. The four response options were: *1) Remember One of the Words from SELF Context, 2) Remember One of the Words from OTHER Context, 3) Recognize One Of The Words, But Don't Recall Source, 4) All Words Are Novel*.

When cued to perform the Perception task with the task-set cue "P", participants judged which of the four words contained the greatest number of straight lines in its printed form. Response options for this task included: *1) Top Left Word Has The Most Straight Lines, 2) Bottom Left Word Has The Most Straight Lines, 3) Bottom Right Word Has The Most Straight Lines, 4) Top Right Word Has The Most Straight Lines.* The main function of this task was to serve as a baseline comparison for the Reasoning and Memory tasks, since like the other two tasks, it also required careful analysis of the word array and the indication of one of four potential responses. However, unlike the other two tasks, performance depended largely on perceptual processing of the low-level features of the word stimuli rather than evaluation of internally retrieved representations (i.e., semantic knowledge in the Reasoning tasks or episodic content in the Memory task).

Experimental Procedure

The experiment consisted of two sessions on consecutive days. On the first day, participants received a detailed overview of the three cognitive tasks that they would be performing during the next day's scanning session. The participants then completed the memory encoding task (described above). Following this encoding session, further instruction was provided on the four response options associated with each task and participants began a computerized training regimen to help them gain fluency with the buttons that were mapped to each response option. Once they demonstrated mastery of the button mappings, participants performed one practice run of each of the three tasks. None of the stimuli used in this practice session were reused during the fMRI scanning session.

On the second day, participants underwent MRI scanning as they alternated between performing the Reasoning, Memory, and Perception tasks. Data were collected across eight scanning runs, each comprised of nine 52 s blocks (3 blocks of each task). The ordering of these blocks was counterbalanced with the constraint that two blocks of the same cognitive task were never presented in sequence. Each block began with a task-set cue (6 s) followed by a fixation cross (2 s). Participants then performed four trials of the specified task. Each trial consisted of a 4-word stimulus array (8 s) during which time participants were to evaluate the stimuli and indicate their response. A 2 s fixation interval followed each trial, with an additional 4 s following the fourth trial of each block (**Figure 1**). Across the entire experiment, participants completed a total of 288 trials (96 trials of each task).

In order to construct the three word lists that were counterbalanced across subjects, we first generated three independent versions of the Reasoning task. This involved creating 144 analogy trials and 144 non-analogy trials, with each trial consisting of a 4-word array. A trial was deemed to be a non-analogy if no reasonable second-order relationship existed between the upper and lower word-pairs. Similarly, a word-pair was deemed as having no semantic relationship if it contained no clear first-order relationship between the two words. We calculated first-order and pair-wise semantic distance ratings for each trial using latent semantic analysis (http://lsa.colorado.edu; for a full review of this procedure, see (Green et al., 2010)), and we divided the 288 trials into three lists of 96 trials each, equating for semantic distance in each list. For any given participant, one of these lists would be used for the Reasoning task, and the words from the remaining two lists would be used to populate the Memory and Perception tasks. To do this, words were sorted by length, with the middle 50% of words assigned to the Perception task and the short and long words assigned to the Memory task. We tested that the average word length in each task was matched within one letter for each list. Within the Memory task list, 75% of the words were randomly selected to be studied in the memory encoding task and were randomly assigned to the “Self” or “Other” source condition. Each memory retrieval trial was created by randomly assigning words to the four quadrants of the screen; thus, no analogical relationships were present on these trials. Words allocated for the Perception task were assessed for how many straight lines were present in each of the words (all words appeared in lowercase letters in Geneva font). This was achieved by counting the number of straight lines in each letter (e.g., “j” has one straight line and “m” has 3 straight lines). We then generated experimental trials (4-word arrays) by ensuring that the word with the greatest number of straight lines had at least 2 more straight lines than the next best answer and that the second best answer had at least 1 more straight line than the third best answer.

MRI Data Acquisition and fMRI Preprocessing

Whole-brain imaging was conducted on a Siemens 3.0 Tesla TIM Trio MRI scanner at the Staglin IMHRO Center for Cognitive Neuroscience at UCLA. Functional images were collected using a T2*-weighted echoplanar imaging (EPI) sequence (TR = 2.0 s; TE = 30 ms; flip angle = 75°; FoV = 19.2 cm, voxel resolution = 3.0 x 3.0 x 3.7 mm). Each functional volume consisted of 33 axial slices acquired in a temporally interleaved sequence. Functional data were collected across eight runs of 239 volumes each. The three initial volumes from each run were discarded to allow for T1 stabilization. A field map image was obtained to facilitate subsequent unwarping of anterior frontotemporal regions that are prone to susceptibility-induced distortion. To aid in spatial registration of the functional data, a coplanar T2-weighted anatomical image was also collected, along with a high-resolution (1 mm^3) magnetization prepared rapid gradient echo (MPRAGE) T1-weighed image.

Image preprocessing and univariate fMRI analysis were performed with SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). Functional images were corrected for differences in slice acquisition timing, unwarped based on the voxel-displacement field map to correct for distortions in static magnetic field, and motion-corrected using a six-parameter rigid-body realignment procedure. Image co-registration involved a two-part procedure where the coplanar anatomical image was registered to the mean functional image and the MPRAGE was registered to the coplanar anatomical. The MPRAGE was then segmented into gray matter, white matter, and cerebrospinal fluid (CSF), and the gray matter image was warped to the SPM8 MNI grey matter template. The resulting nonlinear warping parameters were in turn applied to the functional images, which were resampled to 3 mm isotropic voxels and then smoothed with a 6 mm full width at half maximum Gaussian kernel.

Univariate fMRI Analysis

At the subject-level, fMRI data were analyzed using the general linear model (GLM) framework with a mixed block/event-related design (Visscher et al., 2003). The GLM included transient effects regressors for each event type of interest; separate regressors were used to model correctly performed trials and error trials. Events were modeled as variable duration boxcars with the durations specified based on each trial's response time. Additional regressors were included to model the 6 s task-set cues that preceded each block. Sustained effects were modeled as 38 s boxcars beginning at the onset of the first trial and ending at the offset of the fourth trial of each task block. Task-related regressors were all convolved with a canonical hemodynamic response function. Several covariates of no interest were also entered into the model, including run means, 6-direction head movement parameters, and a variable number of stick-function regressors corresponding to artifact-prone volumes to censor from analysis. Censored volumes were flagged using ArtRepair (http://cibsr.stanford.edu/tools/human-brain-project/artrepair-software.html) as having translational movements exceeding 2 mm and/or global signal changes exceeding 6 SD from the mean. Serial autocorrelation and low-frequency drifts were accounted for using a first-order autoregressive model and a high-pass filter of 0.0042 Hz (cut-off period = 236 s, corresponding to half the duration of a scanning run). At the group-level, random effects t-tests for contrasts of interest were performed on each voxel within a 50,162-voxel brain mask, which excluded white matter, ventricles, and any voxels not shared by all participants. Using FMRISTAT (http://www.math.mcgill.ca/keith/fmristat/) to model the null hypothesis distribution as Gaussian random field taking into account the image smoothness and the search space (Worsley, Taylor, Tomaiuolo, & Lerch, 2004), it was determined that the combination of a voxel-level threshold of $t > 3.17$ ($p < .005$, two-tailed) and a cluster extent requirement of 486 mm^3 (18 voxels) was sufficient to correct for multiple comparisons at the $p < .05$ level. This was the common minimum statistical threshold that was used for all whole-brain analyses. For the univariate analyses contrasting Memory and/or Reasoning activity against Perception activity, we adopted a more stringent voxel-level threshold of $t > 4.19$ ($p < .0005$, two-tailed) while maintaining the 18 voxel extent requirement (use of a lower threshold in these contrasts would result in excessively diffuse activation throughout much of the brain). The Reasoning and Memory tasks were directly compared with the Perception task to subtract out the effects of perceptual processing and response demands. Specifically, transient effects parameter estimates from correct Perception trials were subtracted from correct source retrieval trials (Memory task) and correct valid analogy trials (Reasoning task). To aid in visualization of the resulting data, volumetric maps were projected onto the left and right hemisphere inflated PALS cortical surface templates using Caret software (Van Essen, 2005).

Multi-Voxel Pattern Analysis

fMRI data were further analyzed with multi-voxel pattern analysis (MVPA) to identify regions whose BOLD activity patterns could reliably differentiate trials from the

Memory and Reasoning tasks. Specifically, we adopted a spherical searchlight mapping approach (Kriegeskorte, Goebel, & Bandettini, 2006), in which a multivariate classifier model is trained and tested using only information represented within a small spherical cluster of voxels, with this process then being repeated thousands of times until the "searchlight" has been centered at every possible brain location. Since each searchlight contains the central voxels and its surrounding neighbors (here defined as any voxels within a 3-voxel radius of the center), it inherently contains some overlapping information with searchlights centered nearby, making this approach useful for mapping the spatial distribution of locally diagnostic information throughout the brain. This analysis was implemented using the Princeton MVPA toolbox (https://code.google.com/p/princeton-mvpa-toolbox/) and custom MATLAB code. For each trial, preprocessed but unsmoothed BOLD images corresponding to the 3rd, 4th, and 5th TRs following stimulus onset were averaged, yielding trial-specific brain activity maps ("patterns"). These three TRs (reflecting BOLD activity levels measured 4-10 s post-onset) were chosen a priori based on our intuitions regarding the temporal evolution of the hemodynamic response; we confirmed that these TRs were appropriate for MVPA decoding during our initial piloting. Also, owing to recent concerns about the susceptibility of searchlight MVPA to pick up on brain signals that scale with subtle, yet consistent, response time (RT) differences between conditions (Todd, Nystrom, & Cohen, 2013), we pre-emptively removed the effects of RT from each voxel's activity on a trial-by-trial basis with linear regression. Searchlight MVPA was then performed on the residuals. For each searchlight sphere, we trained a Gaussian Naïve Bayes (GNB) classifier algorithm to discriminate correct valid analogy trials from correct source memory trials. For participants who did not have equal numbers of trials in each condition, a random subset of trials from the more plentiful condition were randomly selected for exclusion prior to classification; in this way, the trials counts from the two conditions were always balanced. The average number of Reasoning and Memory trials included in this analysis was 29.10 per class (range: 10-40). The accuracy of the classifier, determined by a within-subjects 10-fold cross-validation procedure (i.e., using 90% of the available trials for training and the remaining 10% of the trials for testing in each cross-validation fold), was assigned to the voxel in the center of that sphere. This entire process was repeated 10 times for each participant to minimize the effects of random trial balancing. Group-level t-maps were generated by comparing the mean area under the curve (AUC) classification estimate for each voxel against a null-hypothesis value of 0.5 (for a thorough description of AUC, which is similar to classification accuracy, see Rissman et al. (2010)). The resulting maps were stringently thresholded using a whole-brain Bonferroni correction for multiple comparisons ($t > 6.73$) to aid in visualization of the peak effects.

Defining Regions of Interest (ROIs)

The region of peak decoding accuracy in RLPFC was identified from the searchlight MVPA analysis and was used to generate a spherical ROI (6 mm radius), which was then used as the seed in the task-related functional connectivity analysis described below. The sphere radius of 6 mm, which is twice the voxel width, was chosen to replicate that used in McLaren et al.'s (2012) paper introducing the generalized psychophysiological interactions approach. The anatomical localization of this region was assessed by querying the Harvard-Oxford Atlas (Kennedy et al., 1998) for the probability of it being in the frontal pole.

Task-Related Functional Connectivity Analysis

In order to assess the task-dependent connectivity of our RLPFC seed ROI, fMRI data were analyzed using the generalized psychophysiological interactions (gPPI) toolbox (http://www.nitrc.org/projects/gppi) (McLaren et al., 2012). This is done by performing multiple regression in the GLM framework with the constituent regressors being: (1) the physiology of the seed region (i.e., its BOLD timeseries), (2) the psychological regressors from the task (i.e., the sustained effects model, which coded for the onsets and duration of each task block), and (3) a psychophysiological interaction (PPI) term representing the interaction between the physiological and psychological regressors. The same regressors of no interest included in the univariate GLM were also included in the gPPI GLM. The sustained effects model was chosen instead of the transient effects model due to the increased power afforded by using all timepoints within each block. However, it was confirmed that re-running the gPPI analysis with the transient effects model produced nearly identical results. Task-dependent connectivity maps, based on the PPI regressor parameter estimates from each condition, were generated for each participant and subjected to group-level random effects t-tests. Contrast maps that compared condition-specific connectivity versus baseline (i.e., a null hypothesis value of 0) were stringently thresholded at the whole-brain Bonferroni level ($t > 6.73$) to aid in visualization of peak effects. Contrast maps that directly compared functional connectivity between tasks were thresholded at our standard minimum threshold ($t > 3.17$; cluster extent ≥ 18 voxels).

Seed-to-Network Connectivity Profiling

To quantify the strength of each seed ROI's coupling with distinct brain networks, we extracted connectivity parameter estimates from 264 individual nodes throughout the brain (each defined as a 5 mm radius sphere); the coordinates of these nodes were reported in a recent study that used resting-state connectivity and meta-analytic data to identify dissociable functional networks (Power et al., 2011). We chose to adopt the same 5 mm radius spheres used in that study in order to precisely replicate the networks and maintain sufficient distance between nearby spheres. Based on the nature of our tasks and our a priori hypotheses regarding their network connectivity profile, we chose to focus our analyses on 6 of the networks defined by that study: FPCN, DMN, DAN, salience network (SN), memory retrieval network (MRN), and visual network (VN). The relevance of the FPCN, DMN, and DAN has been discussed above. The SN was included due to its important role in coordinating attention towards salient stimuli and its interaction with brain networks involved in cognitive control (Menon & Uddin, 2010; Seeley et al., 2007). The MRN and VN were included due to their respective roles in the retrieval of memory and visual processing of task stimuli (Power et al., 2011). The nodes in these 6 networks constituted 148 of the 264 total regions. Each subject's connectivity parameter estimates were averaged across nodes within each network, and group-level effects were analyzed using repeated measures multivariate ANOVAs and post-hoc simple effects comparisons with Šídák correction for multiple comparisons.

Results

Behavioral Analysis

Response distributions for all three tasks are plotted in **Figure 2**, demonstrating that participants performed the three tasks accurately, with error responses following a predictable pattern for each task. In the Memory task, the overall hit rate was significantly higher than the overall false alarm rate (t(19) = 12.76, p < .001), and the source memory hit rate (i.e., probability of indicating the correct source, given an attempt to report the source) was significantly higher than the source false alarm rate (t(19) = 10.40, p < .001). Although participants only indicated having a memory for the source context on 60.00% of Old Word Present trials, when they did so they were highly accurate, selecting the correct source 82.34% of the time. In the Reasoning task, the hit rate for valid analogy trials was significantly higher than the false alarm rate (i.e., calling a non-valid analogy "valid") (t(19) = 16.93, p < .001). Overall accuracy (pooled across trial types) did not significantly differ between the Memory task and the Reasoning task (76.36% vs. 75.12%; p = .69). In our tabulation of overall accuracy for the Memory task, hits (including trials where participants reported recognition of an old word but either could not recall or incorrectly recalled its source context) and correct rejections (responding that "All Words are Novel" on Old Word Absent trials) were scored as correct responses, and misses (responding "All Words are Novel" on Old Word Present trials) and false alarms (reporting a memory on Old Word Absent trials) were scored as incorrect responses. For the Reasoning task, correct trials were those in which participants properly indicated whether the word array contained a valid analogy, 2 semantic relations, 1 semantic relation, or 0 semantic relations. Finally, in the Perception task, the probability of participants correctly reporting the word with the greatest number of straight lines was significantly greater than the probability of reporting the word with the second highest straight line count (t(19) = 13.86, p < .001). Participants' overall accuracy on the Perception task (66.89%) was somewhat lower than their overall accuracy for the other tasks (vs. Memory task: t(19) = 3.54, p = .002; vs. Reasoning task: t(19) = 3.21, p = .005). However, in designing the Perception task as a control condition, our aim was merely to engage participants with a challenging perceptual decision task, and thus we cared predominantly about participants' mental effort (reflected in their RTs) rather than their success per se.

We aimed to match the Memory, Reasoning, and Perception tasks as closely as possible to minimize potential confounds such as bottom-up perceptual input, number of response options, and RT. Mean (± SE) RTs were as follows: Memory = 5.04 s (.15), Reasoning = 4.72 s (.10), Perception 5.03 s (.19); the main effect of task, although trending, was not significant (F(2,18) = 3.45, p = .054). Importantly, mean RTs for the two primary trial types of interest (correct source responses in the Memory task and correct valid analogy responses in the Reasoning task) did not significantly differ (t(19) = 1.06, p = .304). When considering RTs to correctly performed Reasoning trials excluding valid analogies, the pattern of results was consistent with participants' use of a hierarchical process-of-elimination strategy. Specifically, trials with no semantic relations were faster than those with one semantic relation (t(19) = 3.78, p = .001), which in turn were faster than those with two semantic relations (t(19) = 2.28, p = .034). The fact that valid analogy trials showed RTs on par with one semantic relation trials (t(19) = 0.55, p = .59) and faster than two semantic relations trials (t(19) = 2.79, p = .012) suggests that participants terminated further processing once an analogy had been confidently identified, but continued futilely searching for an analogical relationship on two semantic relations trials (and possibly also continued searching for another first-order relationship on one semantic relation trials). A complete reporting of RT data across tasks and trial types is provided in **Supplemental Table I**.

Univariate fMRI Analysis

Activation parameter estimates from successful source retrieval trials from the Memory task and successful valid analogy trials from the Reasoning task were each contrasted with successful trials from the Perception task in an effort to control for bottom-up perceptual input, word reading, and motor response demands (**Figure 3; Supplemental Table II**). Memory trials in which participants successfully indicated the source context engaged a broad set of prefrontal regions including ventrolateral PFC (VLPFC), DLPFC, ventromedial PFC, DMPFC, and insular cortex; although these activations were seen in both hemispheres, activation was stronger and more extensive in the left hemisphere. Additional activations were observed in left lateral temporal cortex, PCC, precuneus, left angular gyrus, and left hippocampus. Reasoning trials in which participants successfully identified valid analogies engaged a largely overlapping set of prefrontal regions with a similar degree of left hemisphere bias. Additional activations were observed in bilateral lateral temporal cortex, angular gyrus, intraparietal sulcus (IPS), PCC, and early visual cortex. The common involvement of left lateral PFC, PCC, bilateral insula, and left angular gyrus suggests that both FPCN and DMN structures are utilized in these two tasks. We next performed a direct contrast of successful source memory retrieval trials vs. successful valid analogy trials (**Figure 4a; Supplemental Table II**). The analysis revealed no significant differences in the left lateral PFC and only minimal differences in the bilateral inferior parietal lobule. However, analogy trials did show increased involvement in the right lateral PFC, early visual cortex, left lateral occipital cortex, right IPS, and bilateral lateral temporal cortex, while source retrieval showed greater activations in the precuneus, PCC, left insula, left angular gyrus, left medial temporal lobe, and anterior cingulate cortex.

Multi-Voxel Pattern Analysis

The striking overlap of left lateral PFC recruitment during source memory retrieval and solving valid analogies, along with the lack of significant univariate activity differences between these conditions throughout this large swath of cortex, seems to suggest that memory and reasoning engage common left PFC-mediated control processes. However, given the inherently distinct types of mental representations that must be accessed and integrated in order for one to recall the contextual source of a memory or to evaluate the validity of an abstract verbal analogy, it seems plausible that neural processing in left lateral PFC might be reconfigured in some subtle yet predictable way when performing these respective tasks. To examine this possibility, we conducted a searchlight MVPA analysis, which can offer heightened sensitivity to detect condition-specific changes in local activity patterns, even when levels of mean BOLD activity are comparable across conditions.

As with the transient effects univariate contrast reported above, our searchlight MVPA analysis focused on the discriminability of Reasoning trials where participants correctly identified a valid analogy from Memory trials where they correctly reported the source context of a previously encountered item. This analysis revealed robust decoding performance throughout many brain areas. To identify the most consistently informative clusters within this map, we imposed secondary thresholding procedure requiring that at least 75% of participants showed decoding performance that surpassed a within-subject metric of significance at each sphere location (determined based on a binomial null hypothesis distribution, taking into account the number of trials included in the classification analysis for each subject (Pereira, Mitchell, & Botvinick, 2009)). For a voxel to be present in the resulting map, it thus was not only essential that decoding accuracy levels had low variance across subjects (yielding high t-values) but also that the accuracy levels were significantly above chance in most individual subjects. The resulting map (**Figure 4b**) showcased especially reliable decoding in left lateral PFC with a clearly demarcated peak in the posterior aspect of RLPFC. Other regions exhibiting reliable decoding included the left lateral temporal cortex, angular gyrus, and midline areas such as PCC and precuneus.

It is intriguing that some regions that showed significant univariate effects did not reach significance in the MVPA searchlight analysis. Such discrepancies between univariate and searchlight MVPA results are not uncommon and reflect the differential sensitivity of these techniques to distinct attributes of the BOLD data (Davis et al., 2014; Jimura & Poldrack, 2012). One possibility is that univariate effects in some regions were too variable at the level of individual trials to yield decoding accuracies surpassing our stringent thresholding procedure. Indeed, most of these regions do show some degree of Memory vs. Reasoning decoding at a more lenient threshold.

With any searchlight MVPA analysis there is always the possibility that classification performance in a given region might be heavily influenced by condition-specific differences in the mean activity level within that region rather than its local spatial pattern of activation. To assess the degree to which our decoding analysis was detecting information above and beyond that which could be gleaned from each sphere's mean signal, we ran a new searchlight analysis that forced the classifier to generate its predictions based only on a single feature for each sphere, its mean signal level. We then performed a paired t-test between the pattern-based searchlight maps and the mean-of-sphere (MoS) based maps to identify which sphere locations showed significantly improved decoding when provided with the pattern information. Of the 905 significant voxels in our original searchlight map, 866 (96%) survived this test, and the mean classification AUC across these 905 voxels diminished from AUC=0.70 in the pattern-based analysis to AUC=0.59 in the MoS analysis, indicating a marked advantage in decoding when the classifier was provided with multivariate pattern information.

Given our interest in understanding the nature of prefrontal contributions to memory and reasoning, we next identified the locus of maximal decoding performance within the frontal lobe. The top-performing sphere was localized to the posterior aspect of left RLPFC (MNI coordinates of central voxel: [-42, 42, 6]; mean classification AUC = .71; group t-value = 10.06). This region, which falls near the boundary of middle frontal gyrus and inferior frontal gyrus, constitutes the most caudal section of the lateral frontal pole (Kennedy et al., 1998); its RLPFC designation was assessed by cross-referencing the central coordinate against the Harvard-Oxford atlas, which assigns it a 68% probability of being "Frontal Pole" and only a 5% probability of being "Inferior Frontal Gyrus."

To further explore this left RLPFC region's involvement, we defined a spherical ROI around the top-performing voxel and examined both its univariate activity profile and its functional connectivity profile. Univariate parameter estimates (**Figure 5a**) revealed that this region showed activation that scaled both with the amount of mnemonic content retrieved on Memory task trials and with the amount of relational/semantic information accessed on Reasoning task trials. Specifically, during the Memory task, this region showed maximal activity on trials where participants reported remembering the source of a recognized item (regardless of whether this source report was accurate), marginally lower activity on trials where participants only reported item recognition (vs. correct source retrieval: t(19) = 1.94, p = .071; vs. incorrect source retrieval: t(12) = 1.78, p = .10), and substantially lower activity on Correct Rejection trials, where the participants correctly reported that no studied items were present (vs. item only recognition: t(16) = 3.30, p = .004). Note that data from participants with fewer than 5 trials of any given trial type are excluded from the respective statistical contrasts. During the Reasoning task, this area showed maximal activity on trials where participants correctly reported the presence of a valid analogy or two semantic relations (with no significant difference between these trial types: t(19) = 0.37, p = .709). Both of these trial types showed greater activity than trials with only one semantic relation (vs. analogy: t(19) = 3.05, p = .006; vs. two semantic relations: t(19) = 3.12, p = .005), and trials with one semantic relation elicited greater activity than trials with no semantic relations (t(19) = 3.81, p = .001). When the event-related activity estimates from the Reasoning and Memory task were directly contrasted, correct valid analogy trials showed greater activity than correct source retrieval trials (t(19) = 2.55, p = .019); an effect that only achieved significance in this ROI analysis but not in the whole-brain voxelwise contrast (e.g., **Figure 4a**). Activity during correct source retrieval was comparable with that measured during one semantic relation trials (t(19) = 0.36, p = .722). Additionally, 36 of 41 voxels in the left RLPFC ROI showed significant effects in the original searchlight analysis compared to MoS classification, showing that multivariate pattern information is critical for classifying between analogical reasoning and episodic memory retrieval in this region. Taken together, these data suggest that this left RLPFC region most strongly responds when participants attempt to integrate two semantic relationships (whether or not these two relationships are ultimately found to constitute a valid analogy), but that this region also exhibits notable involvement in attempting to retrieve the contextual source of a verbal memory. In contrast, activity in this region during correctly performed Perception task trials did not reliably exceed the fixation baseline level (t = 0.66, p = .516).

In addition to interrogating univariate activity levels within this MVPA-defined RLPFC ROI, we obtained activity parameter estimates from three additional ROIs defined based on peak foci reported by prior studies of analogical reasoning (Bunge et al., 2005; Cho et al., 2010; Green et al., 2010). Consistent with these prior reports, activity within each of these ROIs (**Figure 5b-d**) showed reasoning-related effects in our data set, such that activity was greater for reasoning trials necessitating the comparison between two semantic relationships (i.e., analogy and 2 semantic relations trials) than for trials with one or no semantic relationships (all p's < .05). Of particular interest, these three "reasoning-related" ROIs also showed clear memory-related effects in our study (e.g., significantly elevated activity during correct source retrieval trials relative to correct rejections, all p's < .001) suggesting the need for a broader interpretation of their functional role.

Task-related Functional Connectivity Analysis

We then performed a gPPI analysis to characterize task-dependent connectivity effects (Friston et al., 1997; McLaren et al., 2012) of the left RLPFC seed. A group-level map depicting regions that were significantly correlated with the RLPFC ROI during Memory, Reasoning, or both is presented in **Figure 6a**. The left RLPFC seed exhibited overlapping Memory and Reasoning connectivity effects in seed-adjacent left RLPFC areas, left VLPFC, left DLPFC, and DMPFC. Relative to the Memory task, the RLPFC seed's connectivity during the Reasoning task showed a broader spatial extent throughout left lateral PFC and exhibited unique regions of coupling in IPS, right DLPFC, and left lateral temporal cortex regions. A random effects paired t-test between the Reasoning and Memory conditions (**Figure 6b**), showed two significant clusters favoring Reasoning: one in left BA 45 (peak MNI coordinate: [-39, 23, 22]), partially overlapping with putative Broca's area (Anwander, Tittgemeyer, von Cramon, Friederici, & Knösche, 2007) and one in the right superior parietal lobule (peak MNI coordinate: [21, -70, 64]); a Reasoning > Memory effect was also present in the homologous left parietal region, but this cluster did not survive correction for multiple comparisons. During the Memory task, the RLPFC seed showed unique task-dependent coupling with many regions, including bilateral angular gyrus, left lateral temporal cortex, PCC, precuneus, right RLPFC, and right DLPFC (**Figure 6a**), with significant Memory > Reasoning effects emerging in all of these regions (**Figure 6b**).

Although whole brain maps provide one assay of a seed's connectivity, it can be informative to more directly evaluate the degree to which specific brain networks—documented based on prior work—show functional coupling with each seed. To this end, network connectivity parameter estimates were extracted from six previously described brain networks (Power et al., 2011), and the within-network means are presented in **Figure 6c** (note that the radar plot also includes estimates derived from the Perception task, to allow for comparison). These within-network means were entered into a multivariate ANOVA with the factors of network and task, and post-hoc simple effects comparisons were performed between the tasks for each network using the Šídák correction. This analysis revealed a significant main effect of network ($F(5,15) = 21.53$, $p < .001$), while the main effect of task was trending ($F(2,18) = 2.92$, $p = .080$). There was a highly significant network by task interaction ($F(10,10) = 12.11$, $p < .001$).

Simple effects comparisons showed that the RLPFC seed's connectivity with the DMN was significantly increased during Memory relative to Reasoning (t(19) = 4.59) and relative to Perception (t(19) = 4.34). The same was true for its coupling with the MRN, with a significant advantage seen for Memory over Reasoning (t(19) = 5.61) and marginally significant advantage for Memory over Perception (t(19) = 3.37, critical t-threshold = 3.42); although an apparent advantage exists for Perception over Reasoning, this effect was not significant (t(19) = 2.24). The RLPFC seed also showed a significant boost in its connectivity with the SN during Memory relative to Perception (t(19) = 4.65), but its connectivity with the DAN showed the reverse pattern, with a significant advantage for Perception over Memory (t(19) = 3.42). At the network-level, the RLPFC seed did not show any preferential coupling with the assessed brain networks during Reasoning, relative to Memory and Perception. These network analyses showcase the ability of this RLPFC region to dynamically modulate its functional communication with distinct cortical networks in accordance with the processing demands posed by each task context (e.g., favoring coupling with the DMN and MRN during Memory, which requires an internally-oriented focus on one's episodic recollections, and favoring coupling with the DAN during Perception, which requires externally-oriented attention to low-level perceptual attributes of the stimuli).

Discussion

The present fMRI study used a novel experimental paradigm, coupled with multivariate data analytic tools, to characterize the functional contribution of RLPFC regions to higher cognition. We focused our investigation on two relatively complex cognitive processes—episodic source memory retrieval and analogical reasoning—since these tasks have been strongly associated with RLPFC function (Badre & D'Esposito, 2009; Gilbert et al., 2006; Krawczyk, 2012; Ramnani & Owen, 2004; Vendetti & Bunge, 2014). Our third cognitive task was closely matched to the other tasks with respect to its perceptual attributes and response demands yet did not require participants to access and integrate semantic or episodic knowledge. This provided a baseline from which to compare fMRI effects during memory and reasoning.

Our results revealed remarkable overlap of episodic memory-related activity (trials with correctly retrieved source details) and analogical reasoning-related activity (trials with correctly identified valid analogies) across a large swath of left lateral PFC. This finding of shared prefrontal involvement across tasks requiring seemingly distinct cognitive operations is consistent with prior demonstrations that common lateral prefrontal regions exhibit domain-general recruitment across a wide range of complex cognitive tasks (Duncan & Owen, 2000; Fedorenko, Duncan, & Kanwisher, 2013). Although we found overlapping memory and reasoning effects in both left and right lateral PFC, the extent of recruitment was far broader in the left hemisphere, where it extended anteriorly into RLPFC. This left hemisphere dominance may reflect the verbal nature of our cognitive tasks.

Although our experiment is the first, to our knowledge, to directly compare brain activity during memory and reasoning tasks, our interest in the potential overlap of the RLPFC mechanisms that support these two cognitive processes is motivated by numerous prior studies that have independently identified similar RLPFC regions that activate either during episodic memory retrieval or analogical reasoning tasks (e.g., Bunge et al., 2005; Cho et al., 2010; Dobbins & Wagner, 2005; Ranganath et al., 2000; Wendelken, Nakhabenko, et al., 2008), in addition to Reynolds et al. (2006), which examined both retrieval and integration processes in the context of an episodic memory task. Considering the recent focus in the literature on the RLPFC mechanisms in relational reasoning, where RLPFC foci have been consistently and selectively linked to task conditions requiring relational integration (Krawczyk, 2012), we aimed to investigate whether these regions would show comparable effects in our data set. And, perhaps more importantly, our data set affords us the ability to also evaluate how these same regions respond during episodic memory retrieval. To this end, we defined ROIs based on peak coordinates reported in three prior studies; two left RLPFC foci were identified from analogical reasoning studies with verbal (Bunge et al., 2005) or nonverbal stimuli (Cho et al., 2010), and we also explored activity within a more anterior and dorsal prefrontal region that has been linked to verbal analogical reasoning (Green et al., 2010). Replicating prior work, all three areas generally activated more strongly for reasoning trials necessitating the comparison between two semantic relationships than for trials with one or no semantic relationships. But interestingly, activity in these very same regions also tracked aspects of episodic retrieval, such that trials where participants reported source retrieval (regardless of accuracy) showed greater activity than trials where participants correctly indicated that no studied items were present in the 4-word array. These data demonstrate that left RLPFC exhibits domain-generality for both reasoning and memory across areas that have been recently considered to be primarily involved in relational integration processes.

In striking contrast to left RLPFC, which showed comparable activation during analogical reasoning and episodic memory retrieval, its right hemisphere homologue showed a strong preference for reasoning. The involvement of right RLPFC in reasoning is consistent with many prior relational reasoning studies that have reported bilateral RLPFC effects (Cho et al., 2010; Christoff et al., 2001; Christoff, Ream, Geddes, & Gabrieli, 2003; Watson & Chatterjee, 2012; Wendelken et al., 2012; Wendelken, Nakhabenko, et al., 2008). In one prior effort to understand the differential contributions of left and right RLPFC, Bunge et al. (2009) concluded that only left RLPFC met their stringent criteria for a role in relational integration, whereas right RLPFC showed activity that scaled with task complexity in a graded manner, but was not selective for relational integration. Right RLPFC areas have also been implicated in attentional switching and subgoal processing (Braver & Bongiolatti, 2002; Braver, Reynolds, & Donaldson, 2003; Gilbert et al., 2005), so it is possible that these types of cognitive control processes may be the mechanism through which right RLPFC provides auxiliary support to left RLPFC in analogical reasoning tasks.

Although only right hemisphere prefrontal regions emerged as significant in our univariate contrast of reasoning vs. memory trials, we wanted to explore the possibility that left prefrontal regions also show differential neural responses across these two tasks, but in a manner that was perhaps too subtle to be detected by the simple assessment of mean BOLD signal levels. To this end, we used a whole brain searchlight MVPA approach to identify regions whose local BOLD activity patterns were sufficiently distinct so as to facilitate accurate classification of whether a given trial was involved in reasoning or memory operations. We specifically focused on trials from each task that constituted the pinnacle of successful information processing in their respective domains. Specifically, we trained our classifier to discriminate reasoning trials with correctly identified valid analogies from memory trials with correctly reported source contexts. Perhaps unsurprisingly, this analysis revealed significant decoding effects in right RLPFC, putatively driven by this region's differential univariate engagement between tasks. More noteworthy was our finding that even stronger decoding effects were observed in left-lateralized prefrontal regions, with the peak effect emerging in RLPFC. The fact that local activity patterns within left RLPFC are reliably dissociable during memory and reasoning trials, despite roughly comparable activity levels, could reflect that this region is performing similar cognitive control processes (e.g., relational integration/comparison) on distinct forms of information that it gains access to via its functional communication with content-representing regions. In other words, RLPFC activity patterns may be modulated by the nature of the inputs that this area is receiving (e.g., semantic vs. episodic knowledge representations). Alternatively, the dissociable BOLD patterns in RLPFC could be indicative of underlying neural codes that are linked to the engagement of distinct cognitive control processes. According to this view, a subtle reconfiguration of RLPFC activity may reflect the specification and enactment of domain-specific task goals, or the implementation of distinct computations performed on activated knowledge representations. In the reasoning task, participants must assess the second-order relationship of two first-order relationships, whereas in the memory task they must evaluate the relationship between a present stimulus and a past experience. With respect to the latter, it is plausible that participants arrive at their episodic source judgments by quickly generating a mental image of themselves and/or someone else interacting with the recognized item (i.e., re-simulating the encoding task) and then assessing the relative familiarity of the resulting mental image(s). The nature of this episodic comparison process shares fundamental elements with the relational comparison process inherent in analogical reasoning, perhaps explaining the shared left RLPFC recruitment. Yet differences in specific types of representations being compared and the dissociable neural networks providing this information may account for the decodable RLPFC activity patterns uniquely associated with each task.

We reasoned that a thorough assessment of how rostral prefrontal regions communicate with other brain networks during different cognitive states might offer additional insight into the nature of their functional contributions. To this end, we examined the task-dependent connectivity profile of the RLPFC node that emerged in our analysis of trial-type specific MVPA decoding. This RLPFC seed showed pronounced differences in the strength and anatomical distribution of its connectivity across these two tasks. Specifically, during the Memory task the RLPFC seed's coupling with the DMN, MRN, and SN was significantly elevated above the level observed during the Reasoning and Perception tasks. We hypothesize that RLPFC plays a role in monitoring and integrating self-referential episodic source details represented within DMN and MRN regions. RLPFC's heightened coupling with the SN during Memory was a less expected finding. Although this network is thought to be involved in the bottom-up monitoring of salient environmental stimuli, this network may also help facilitate the orienting of one's attention towards salient episodic information retrieved from memory (Ciaramelli, Grady, & Moscovitch, 2008; Menon & Uddin, 2010). Also somewhat surprising was the fact that none of our six networks-of-interest showed stronger coupling with the RLPFC seed during Reasoning than Memory or Perception. However, in a mapwise contrast two individual brain regions did show reliably stronger coupling during Reasoning. One of these areas was a left lateral prefrontal region (BA 45) that was posterior and dorsal to the seed, putatively corresponding to Broca's area. We suspect that this region likely contributes to controlled semantic retrieval demands (e.g., Bunge et al., 2005; Goldberg, Perfetti, Fiez, & Schneider, 2007; Wagner, Paré-Blagoev, Clark, & Poldrack, 2001) posed by the Reasoning task. The other area was a superior parietal lobe region potentially involved in the top-down attentional demands of the task, which could include rapid shifting of attention between the word pairs and visuospatial imagery of the analogical relationships (e.g., a useful strategy for solving some of the analogies, e.g., "jacket : zipper :: wound : suture"). The task-dependent flexibility of the RLPFC seed's coupling was further illustrated by the finding that it showed significantly heightened coupling with the DAN during the Perception task, relative to the Memory task (its advantage over Reasoning was not significant). Thus, when the task demands exclusively required externally-focused visuospatial attention to facilitate the goal of identifying which word's printed form contained the greatest number of straight lines, the RLPFC region strengthened its connectivity with the brain network whose functions are most well-aligned with the information processing demands of the Perception task. Thus, the task-dependent connectivity analysis demonstrate that RLPFC can flexibly adjust its coupling with distinct brain regions and networks to enact task goals in all three tasks.

Given the diversity of functional roles that prior studies have ascribed to this RLPFC area, it is challenging to specify what overarching principles may best account for the present data. It is likely that there is considerable functional heterogeneity within RLPFC, and additional experimentation and meta-analytical investigations may help elucidate the contributions of distinct subregions. That said, we believe that our findings points to at least one common theme. A common left-lateralized posterior RLPFC area appears to play a particularly important role whenever two or more highly structured representations (e.g., semantic relationships, episodic memory traces, etc.) need to be compared or integrated. That this area showed overlapping engagement across two very different cognitive tasks suggests that its functional contribution should not be characterized in terms of memory retrieval or analogical reasoning-related processes, per se, but rather by a more general role in operating upon two or more retrieved declarative knowledge representations in the service of an impending decision. This account of the role of RLPFC in analogical reasoning and episodic memory retrieval is consistent with the mechanisms described by Bunge and Wendelken (2009) in these task contexts. The ubiquitous involvement of RLPFC across such a diverse array of cognitive paradigms in the fMRI literature is likely due to this region's ability to flexibly interact with whichever posterior regions/networks process and represent information relevant to one's current behavioral goals.

It is important to note that the left RLPFC region highlighted in our analyses falls at the posterior aspect of the territory that can be fairly referred to as "rostral" PFC. This relatively posterior localization raises the question of how our findings relate to prior work concerning RLPFC contributions to higher cognition. Although the central coordinate of our region of interest is approximately 1 cm anterior to the peak RLPFC focus identified by Koechlin et al. (2003a) as being responsible for the most abstract form of task-set control, our region is approximately 1 cm posterior to the RLPFC area that Badre & D'Esposito (2007) implicated as the apex of the control hierarchy. Our region is also 1 cm posterior to foci reported in some prior studies of episodic retrieval (e.g., Dobbins & Wagner, 2005) and relational reasoning (e.g., Christoff et al., 2001). That said, many other studies of memory and reasoning have used the label "rostral PFC," "anterior PFC," or "frontal pole" to refer to foci whose y-coordinates, like that of our present RLPFC ROI, fall between +40 and +42 (e.g., Cho et al., 2010; Krawczyk et al., 2010; Kroger et al., 2002; Ranganath et al., 2000; Wendelken, Nakhabenko, et al., 2008). Further work will be needed to better characterize the differential functional contributions of more anterior RLPFC regions, such as those that fall squarely within BA10, versus more posterior RLPFC regions, such as those featured in our study, which fall near the boundary of BA10 and BAs 46 and 47.

More work will also be needed to clarify whether the left RLPFC region identified in our study is preferentially engaged by verbal tasks, such as the tasks used in our experiment, or whether its seemingly domain-general properties extend to other information processing modalities. To this end, future experiments should compare memory and reasoning tasks that use visuospatial stimuli or auditory stimuli. Although it may be challenging to design non-verbal memory and reasoning task paradigms that appropriately equate the level of bottom-up perceptual stimulation across tasks, such studies could provide additional insight into the relative contributions of left and right hemisphere RLPFC regions. Furthermore, fMRI studies with superior temporal resolution and/or the use of effective connectivity modeling techniques may help better characterize the timing of RLPFC involvement relative to information processing operations occurring in other prefrontal and posterior cortical regions. Such work could also shed light on which regions communicate directly with RLPFC and which apparent interactions are mediated through one or more intermediate relays. Finally, the use of targeted brain stimulation techniques, such as transcranial magnetic stimulation or transcranial direct current stimulation, could valuably weigh in on the still under-specified causal relationship between RLPFC function and memory and reasoning task performance.

Figures

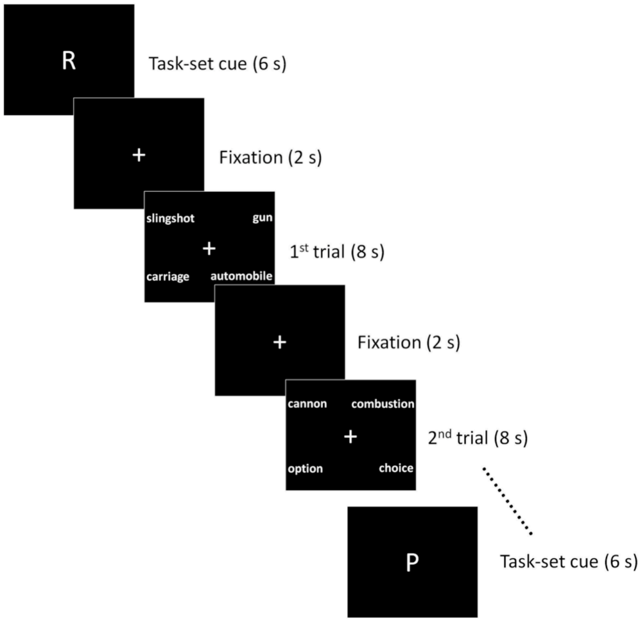


Figure 2.1.1: Schematic depiction of task paradigm. Each block starts with a task-set cue (R, M, or P) indicating which task should be performed during the upcoming four trials. Trials consist of 4-word arrays, and participants have 8 s to indicate a response. All events were separated by a brief fixation interval. After a four-trial block ends, a new block with a different task-set begins. In this example, the first trial represents a valid analogy and the second trial features two non-analogous semantic relationships.

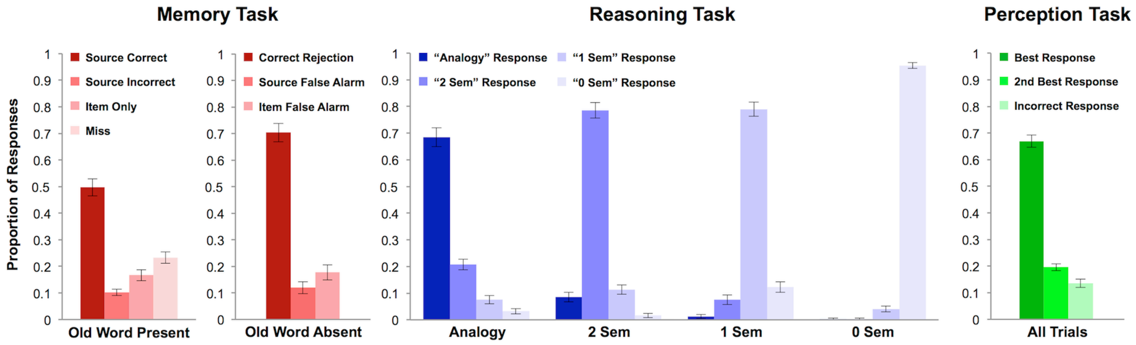


Figure 2.1.2: Distribution of behavioral responses for the Memory, Reasoning, and Perception tasks. For the Memory task, trial types are split up according to whether the 4-word probe array contained a word that had been studied (Old Word Present) or whether all four words were novel (Old Word Absent). For the Reasoning task, trials are split up according to whether the 4-word array included a Valid Analogy, 2 Semantic Relations, 1 Semantic Relation, or No Semantic Relations. For the Perception task, data from all trials are analyzed according to whether participants correctly indicated which word contained the greatest number of straight lines (Best Response), or whether they produced a suboptimal response that was either the close runner-up (2nd Best Response) or one of the other two words (Incorrect Response).

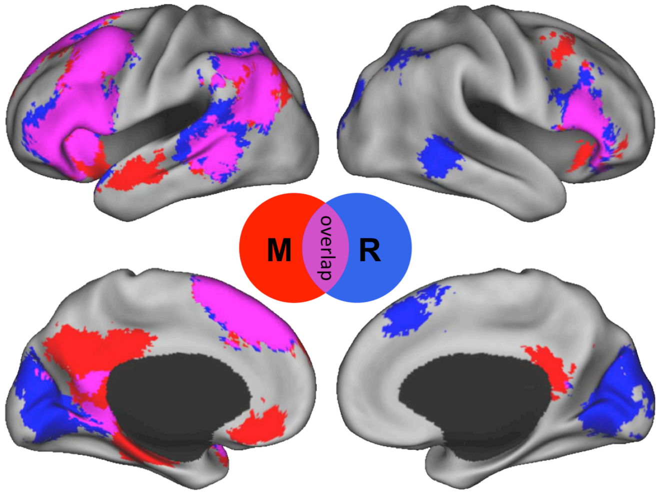


Figure 2.1.3: Univariate BOLD activity during memory and reasoning. Regions exhibiting transient activation during Memory trials with correctly retrieved source details (red), Reasoning trials with correctly identified valid analogies (blue), or overlapping activity for both trial types (purple). Memory and Reasoning effects are shown relative to activity

levels from the Perception task, which served as a common control condition and has been contrasted out of each map. Maps are thresholded at $t > 4.19$ ($p < .0005$, two-tailed; cluster extent ≥ 18 voxels).

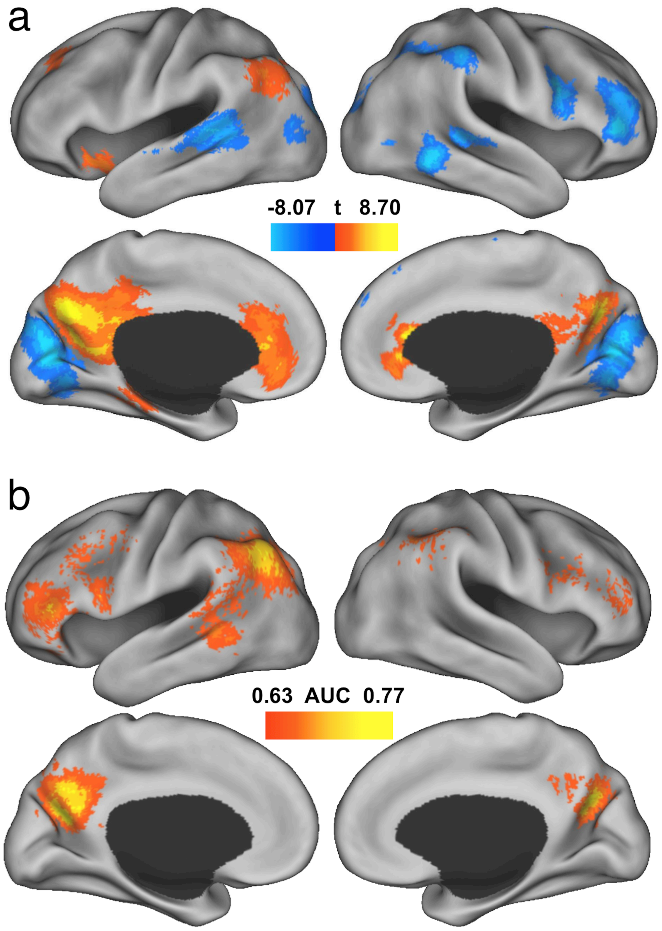


Figure 2.1.4: Univariate and multivariate comparisons of transient memory and reasoning effects. (*a*) Random effects paired t-test of univariate activity parameter estimates from correct source retrieval trials and correct valid analogy trials. Warm colors represent regions with significantly greater activity during memory and cool colors represent regions with significantly greater activity during reasoning; maps thresholded at $p < .05$ (corrected). (*b*) Results of whole-brain searchlight-mapping MVPA, illustrating

regions whose local BOLD patterns (within a 3-voxel radius sphere) could facilitate reliable classification of these two trial types. Voxel intensities represent the classifier's area under curve (AUC) at each sphere center; only effects achieving group-level significance at $p < .05$ (whole-brain Bonferroni corrected; $t > 6.73$) and individual subject-level significance in at least 75% of subjects are depicted.

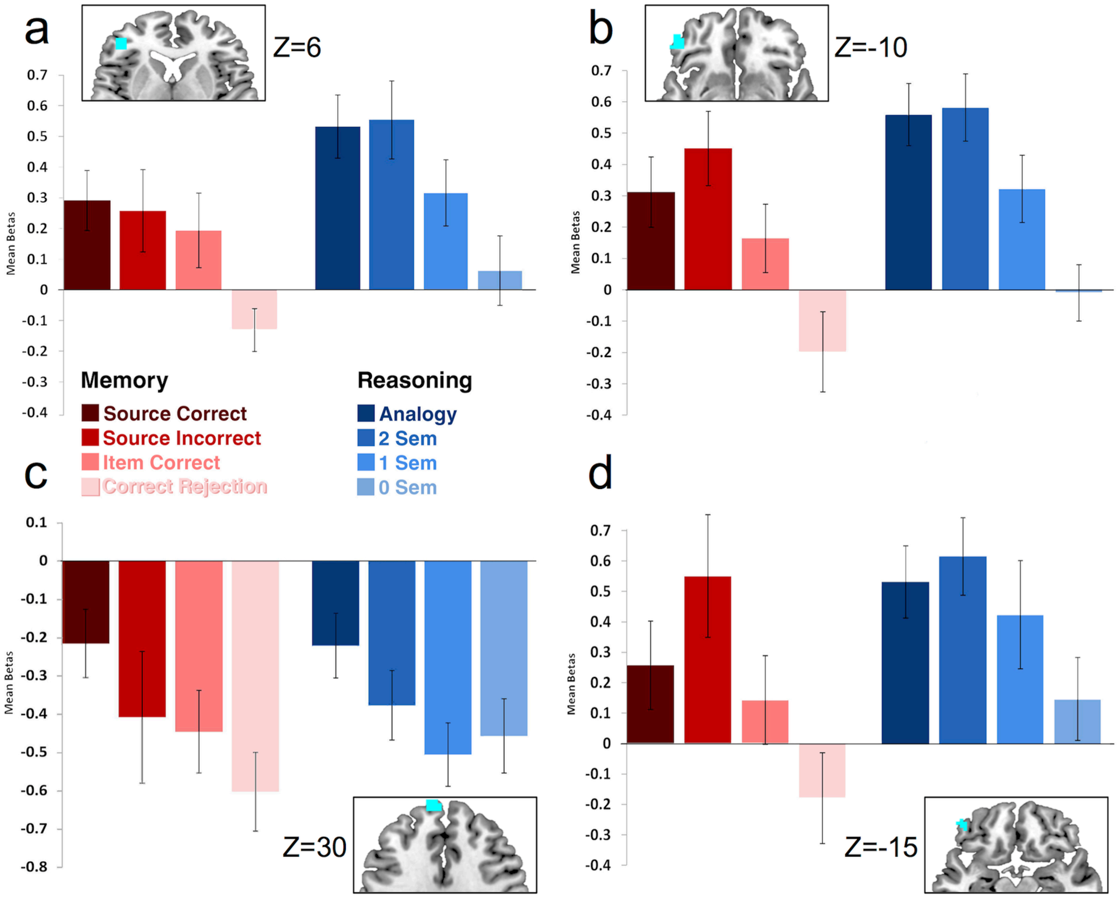


Figure 2.1.5: Univariate activity parameter estimates extracted from our left RLPFC seed ROI and three additional ROIs derived from previous studies of analogical reasoning. All four ROIs exhibited trial type-dependent activity changes during both the Memory and Reasoning tasks, suggestive of functional contributions to both cognitive

domains. Inlay images depict locations of ROIs (cyan clusters) on a template brain. (*a*) Our left RLPFC seed ROI, centered on the peak searchlight MVPA decoding effect; MNI coordinates: [-42, 42, 6]. (*b*) Left RLPFC ROI, defined based Cho et al. (2010); MNI coordinates: [-50, 42, -10]. (*c*) Left dorsal frontopolar ROI, defined based Green et al. (2010); MNI coordinates: [-8, 62, 30]. (*d*) Left RLPFC ROI, defined based Bunge et al. (2005); MNI coordinates: [-42, 48, -15].

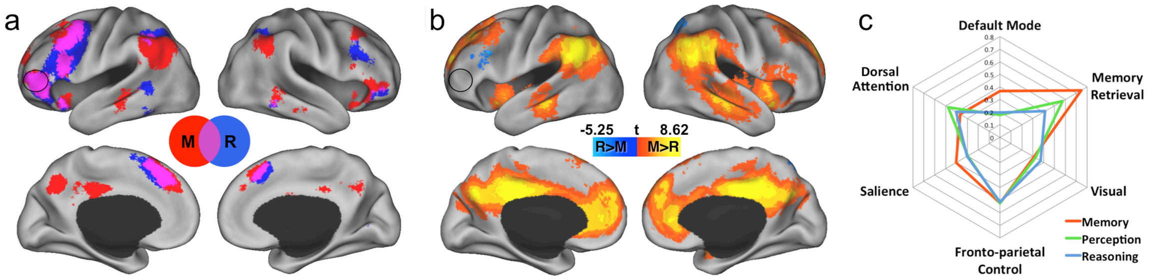


Figure 2.1.6: Task-dependent functional connectivity. Group-level t-maps representing the gPPI analysis depict regions showing significantly positive functional coupling with the RLPFC (*a*) seed during Memory (red) and Reasoning (blue), with overlapping effects shown in purple. This single-condition map is stringently thresholded at p < .05 (whole-brain Bonferroni corrected; t > 6.73). A direct contrast between Memory and Reasoning is shown in panel (*b*), with warm colors indicating Memory>Reasoning and cool colors indicating Reasoning>Memory. This contrast map is thresholded at p < .05 (cluster corrected; t > 3.17; extent ≥ 18 voxels). Mean network-level connectivity parameter estimates for the RLPFC seed (*c*) are represented on a radar plot, with data from the Perception task (green) included.

Memory Task Old Word Present			
	Combined	Self	Other
Source Correct	4.37 (0.15)	4.25 (0.15)	4.53 (0.18)
Source Incorrect	4.88 (0.21)	N/A	N/A
Item Only	5.70 (0.17)	5.56 (0.23)	5.45 (0.18)
Miss	5.74 (0.16)	5.64 (0.20)	5.75 (0.17)

Memory Task Old Word Absent	
Correct Rejection	5.49 (0.18)
Source False Alarm	N/A
Item False Alarm	N/A

Reasoning Task				
	Analogy	2 Sem	1 Sem	0 Sem
Analogy	4.52 (0.12)	N/A	N/A	N/A
2 Sem	5.52 (0.17)	5.02 (0.19)	N/A	N/A
1 Sem	N/A	N/A	4.60 (0.11)	N/A
0 Sem	N/A	N/A	N/A	4.09 (0.13)

Perception Task	
Best Response	4.88 (0.19)
Second Best Response	5.33 (0.20)
Incorrect Response	5.46 (0.23)

Supplemental Table 2.1.1: Mean response times (± SE) as function of task-set and trial type. Rows indicate the categorization of the response from participants, while multiple columns represent different task conditions (e.g., in the Reasoning Task, the row labeled "2 Sem" and the column labeled "Analogy", represents Analogy trials where participants responded that the trial was a Two Semantic Relations trial). Trials from the Memory task are subdivided based on whether an old word was present or absent. Cells only include data from subjects with at least 5 trials of that type. Empty cells indicate trial types for which fewer than 10 subjects had a sufficient number of trials.

Transient Effects Univariate Analysis

Task Contrast	Brain Region	BA	x	y	z	Voxels	*t*-value
Source Memory Retrieval vs. Correct Perception	Frontal Operculum Cortex	47	-45	23	-2	1816	10.59
	Frontal Operculum Cortex	45	-45	20	7	-	10.44
	Inferior Frontal Gyrus	44	-57	20	19	-	10.10
	Precuneus Cortex	30	-9	-55	13	579	9.18
	Parahippocampal Gyrus	30	-27	-25	-20	-	8.12
	Cingulate Gyrus	23	-3	-52	22	-	7.80
	Lateral Occipital Cortex	39	-42	-61	22	414	8.77
	Lateral Occipital Cortex	39	-45	-64	31	-	8.15
	Lateral Occipital Corte	19	-39	-70	40	-	7.14
	Thalamus	27	-3	-13	10	347	8.31
	Pallidum	25	9	2	1	-	8.20
	Caudate	48	-12	2	19	-	7.49
	Inferior Frontal Gyrus	45	54	29	4	155	7.54
	Inferior Frontal Gyrus	45	57	29	15	-	7.06
	Frontal Orbital Cortex	47	48	29	-5	-	6.57
	Occipital Fusiform Gyrus	18	12	-85	-35	89	6.79
	Occipital Fusiform Gyrus	18	12	-76	-29	-	6.20
	Middle Temporal Gyrus	21	-57	-46	-2	127	6.53
	Middle Temporal Gyrus	21	-63	-49	7	-	6.05
	Frontal Medial Cortex	11	-6	38	-14	52	6.43
	Subcallosal Cortex	11	-6	23	-17	-	5.44
	Insular Cortex	47	30	20	-8	26	6.34
	Middle Temporal Gyrus	21	-57	-1	-17	52	6.02
	Middle Temporal Gyrus	21	-69	-13	-14	-	5.48

	Middle Temporal Gyrus	20	-57	-10	-17	-	5.11
	Middle Frontal Gyrus	9	45	14	46	23	5.80
Reasoning Analogy vs. Correct Perception	Superior Frontal Gyrus	9	-6	41	46	953	12.95
	Superior Frontal Gyrus	8	-9	23	55	-	9.99
	Middle Frontal Gyrus	9	-39	17	46	-	7.46
	Inferior Frontal Gyrus	45	-54	23	19	959	11.56
	Inferior Frontal Gyrus	45	-51	20	4	-	11.05
	Frontal Orbital Cortex	47	-45	23	-5	-	10.82
	Caudate	25	-12	8	13	62	9.55
	Middle Temporal Gyrus	22	-66	-46	7	655	9.40
	Lateral Occipital Corte	39	-48	-64	25	-	7.41
	Angular Gyrus	39	-39	-58	43	-	6.67
	Lingual Gyrus	18	-9	-70	4	927	9.18
	Intracalcarine Cortex	17	-12	-85	1	-	8.00
	Lingual Gyrus	30	-15	-46	-5	-	7.44
	Occipital Fusiform Gyrus	18	15	-73	-29	167	7.71
	Occipital Fusiform Gyrus	19	33	-64	-32	-	6.77
	Occipital Fusiform Gyrus	18	15	-82	-38	-	6.07
	Inferior Frontal Gyrus	45	60	29	7	230	6.14
	Inferior Frontal Gyrus	45	54	23	22	-	6.00
	Frontal Pole	47	36	35	-17	-	5.99
	Middle Temporal Gyrus	21	60	-46	-5	71	6.09
	Middle Temporal Gyrus	20	72	-43	-11	-	4.72
	Occipital Fusiform Gyrus	18	-12	-82	-32	32	5.93
	Caudate	25	9	14	7	41	5.62
	Pallidum	25	9	2	1	-	4.96
	Lateral Occipital	39	42	-58	43	23	4.84

	Lateral Occipital Cortex	39	42	-67	46	-	4.64
Source Memory Retrieval vs. Reasoning Analogy	Precuneus Cortex	7	-9	-73	37	308	8.70
	Precuneus Cortex	18	-3	-70	31	-	8.09
	Precuneus Cortex	23	-9	-61	28	-	7.48
	Cingulate Gyrus	25	-6	35	7	44	6.45
	Paracingulate Gyrus	32	-9	35	22	-	5.21
	Precuneus Cortex	23	6	-64	34	21	5.37
Reasoning Analogy vs. Source Memory Retrieval	Intracalcarine Cortex	18	-6	-85	13	723	8.07
	Cuneal Cortex	18	-3	-82	22	-	7.02
	Occipital Pole	18	-15	-91	19	-	6.56
	Supramarginal Gyrus	40	57	-37	49	115	7.47
	Superior Parietal Lobule	40	33	-49	40	-	7.28
	Superior Parietal Lobule	7	33	-52	49	-	4.75
	Middle Temporal Gyrus	37	60	-49	-8	88	7.19
	Middle Temporal Gyrus	37	55	-58	4	-	4.84
	Supramarginal Gyrus	22	-57	-46	10	149	7.12
	Superior Temporal Gyrus	22	-66	-40	7	-	6.68
	Superior Temporal Gyrus	21	-57	-22	-2	-	6.06
	Frontal Pole	45	51	41	-2	158	6.92
	Frontal Pole	45	45	44	13	-	6.18
	Frontal Pole	45	45	38	4	-	5.56
	Precentral Gyrus	44	54	11	28	101	6.26
	Precentral Gyrus	44	45	5	22	-	5.12
	Inferior Frontal Gyrus	44	60	17	10	-	4.93
	Superior Temporal Gyrus	22	54	-34	4	39	5.72
	Superior Temporal Gyrus	21	63	-22	-2	-	5.14

Supplemental Table 2.1.2: Peak activation foci from the transient effects univariate analysis. The Reasoning and Memory tasks are separately contrasted with the

Perception task, which is used as a baseline condition. The Reasoning and Memory tasks are directly compared as well. Brodmann areas (BA), MNI coordinates, and Harvard-Oxford Atlas labels (brain region) are presented in addition to number of voxels and peak t-values.

SECTION 2.2.

Anodal transcranial direct current stimulation to left rostrolateral prefrontal cortex selectively improves source memory retrieval

Abstract

Background: Left rostrolateral prefrontal cortex (RLPFC) has been shown to consistently activate in neuroimaging studies investigating cognitive control in memory and reasoning and to participate in larger-scale cortical networks involved in these processes. Transcranial direct current stimulation (tDCS) can be used to modulate the excitability of targeted brain regions and thus can be applied to left RLPFC to determine the benefits of stimulating this region during memory and reasoning.

Objectives: We aimed to assess whether targeted anodal stimulation to RLPFC would lead to augmentation of episodic memory retrieval and analogical reasoning tasks in comparison to cathodal stimulation or sham stimulation.

Methods: Seventy-two healthy adult participants were evenly divided into three experimental groups. All participants performed continuously alternating tasks of episodic memory retrieval, analogical reasoning, and visuospatial perception. Participants always received sham stimulation for the first session of the experiment and then underwent sham again or either anodal or cathodal tDCS to RLPFC for 30 minutes at 1.5 mA during the second session.

Results: The experimental group that received anodal tDCS to RLPFC during the second session demonstrated significantly improved episodic memory source retrieval

performance, relative to both their first session performance, and relative to performance changes observed in the other two experimental groups. Performance on the analogical reasoning and visuospatial perception tasks did not exhibit reliable improvements from tDCS.

Conclusions: Our results demonstrate that anodal tDCS to RLPFC leads to a selective and robust improvement in episodic source memory retrieval.

Introduction

Rostrolateral prefrontal cortex (RLPFC) has been theorized to be the highest order cognitive control center in the reputed rostro-caudal hierarchy of the lateral prefrontal cortex (Badre & D'Esposito, 2009; Koechlin & Hyafil, 2007; Ramnani & Owen, 2004) and has been implicated in functional neuroimaging studies examining cognitive control processes in episodic memory (Lepage et al., 2000; Ranganath et al., 2000; Simons et al., 2005; Simons et al., 2008) and relational reasoning (Cho et al., 2010; Green et al., 2010; Wendelken & Bunge, 2010). More generally, RLPFC appears to be critical for the integration or comparison of highly structured representations, regardless of domain (Bunge & Wendelken, 2009; Westphal et al., 2016). In order for RLPFC to perform its role in goal-directed cognition across a diverse set of cognitive tasks, it needs to be able to flexibly couple with neural systems that process the domain-specific information relevant to the behavioral goals of each task. Indeed, research from Westphal and colleagues (2016) showed that RLPFC exhibited particularly robust coupling with domain-specific brain regions for each task, as it coupled with the internally-oriented default mode network (DMN) during episodic source memory retrieval, while also exhibiting connectivity with the externally-oriented dorsal attention network (DAN) during visuospatial perception and Broca's area during verbal analogical reasoning.

RLPFC is composed of brain regions that belong to two major neural systems, the fronto-parietal control network (FPCN) and the DMN. The DMN system is critical for memory tasks as it has an important role in the retrieval of episodic and semantic memories, in addition to activating for other internally-oriented tasks such as prospection into future scenarios (Andrews-Hanna, 2012). The FPCN primarily consists of the lateral prefrontal regions implicated in the rostro-caudal hierarchy (Badre & D'Esposito, 2009; Power et al., 2011; Vincent et al., 2008) and has been shown to be able to flexibly couple as a system with either the DMN or DAN, depending on whether the goal-directed task required attention to internal or external attributes (Spreng et al., 2010). FPCN regions are spatially distributed in such a way to promote flexible coupling, as they are typically spatially juxtaposed between DMN and DAN regions (Spreng et al., 2010). However, in RLPFC, the FPCN regions are not spatially proximate to any DAN regions but are primarily spatially positioned next to neighboring DMN regions (Power et al., 2011). Moreover, the FPCN component of left RLFPC is relatively close to the anterior aspect of Broca's area, which we previously found to be functionally connected to RLPFC during analogical reasoning (Westphal et al., 2016). Therefore, RLPFC appears to be a sensible target for brain stimulation aimed at improving memory and reasoning performance as it contains task-relevant FPCN and DMN regions that can be simultaneously stimulated using transcranial direct current stimulation (tDCS).

Although tDCS stimulates a relatively large patch of cortex, a series of studies have shown that tDCS is "activity-selective" (Bikson & Rahman, 2013), such that tDCS preferentially augments neural systems that are already endogenously activated by cognitive tasks. This property may make the effects of tDCS more focal than previously assumed (Lapenta, Minati, Fregni, & Boggio, 2013). Albeit the neurophysiological effects of anodal and cathodal stimulation are complex and still not fully understood, one prominent model suggests that the region underlying the anode will typically experience enhanced excitability and plasticity, whereas the region underlying the cathode will typically experience decreased excitability and plasticity (De Berker, Bikson, & Bestmann, 2013). However, this simple model appears to only be true for the radial currents that run inward through the cerebral cortex, which are more highly concentrated beneath the electrodes than the surrounding areas and produce the excitability changes primarily in the neuron somas (Rahman et al., 2013). Therefore, we hypothesize that anodal tDCS to left RLPFC will exhibit activity selectivity under the electrode for task-relevant FPCN and DMN areas in the RLPFC, which should result in improved episodic memory retrieval. We also hypothesize that anodal tDCS to RLPFC has the potential to improve analogical reasoning performance due to the role of RLPFC in integration processes in relational reasoning (e.g., Bunge et al., 2009; Cho et al., 2010), and the presence of the nearby Broca's area (Westphal et al., 2016), which may be close enough to the electrode to exhibit net depolarization effects. We furthermore predict that anodal tDCS will not affect visuospatial perception, as RLPFC has not been shown to be particularly active during a perceptual judgment task (Westphal et al., 2016). As with our previous fMRI study, we here too included a stimulus-matched visual spatial perception task as control task; this will allow us to evaluate the possibility that anodal tDCS leads to generalized cognitive improvement. Importantly, our experimental protocol always begins with a sham stimulation session for each subject to establish baseline performance and allow for within-subject examination of stimulation effects. This sham stimulation session was immediately followed by either anodal stimulation, cathodal stimulation, or additional sham stimulation of left RLPFC (a between-subject manipulation). The group receiving sham stimulation during both the first and second sessions provides an assay of how task performance changes over time, and the group receiving cathodal stimulation provides an important test of whether the general application of electrical brain stimulation leads to task improvements, or whether the polarity of stimulation is a critical factor.

Materials and Methods

This study is a follow-up to a previous fMRI study. For a more comprehensive report on how the cognitive tasks were designed and created, please refer to Westphal and colleagues (2016). Important features of the paradigm are described below.

Participants

Eighty-one subjects were recruited from UCLA and the greater Los Angeles community. Data from four participants were excluded due to extremely poor performance in the Memory task, indicative of a lack of understanding of the task instructions (i.e., their false alarm rate equaled or exceeded their hit rate). One subject was excluded for failure to understand and/or comply with task instructions during the Memory encoding task, while another subject was removed due to an inability to master the button responses to the cognitive tasks. Two subjects had to be removed from the study due to problems with the tDCS device and one more subject had to be excluded due to finding the tDCS stimulation to be unpleasant. In the end, 72 subjects were included across three stimulation groups, with each group averaging 20 years of age and consisting of 23 females and 21 males. Participants were required to be 18-30 years old, be native English speakers, be right-handed, have normal or corrected-to-normal vision, have no neurological or psychiatric disorders, have no history of brain damage, and not consume illegal drugs or alcohol use of more than four drinks per day. All subjects provided written informed consent in accordance with operations approved by the UCLA Institutional Review Board and participants received monetary compensation.

Procedure

The experiment consisted of two experimental sessions on consecutive days. During the first session, participants completed a memory encoding task and were notified that they would be tested for their memory for both the word and the encoding context. The task consisted of the presentation of a sequence of 80 words with each word being preceded by a mental imagery context cue specifying whether the participants should visualize themselves ("Self") or another person ("Other") interacting with the word. Words from the first and second halves of the memory encoding task were evenly split into the first and second sessions of the Memory task. Afterwards, the participants learned the button responses for the Memory, Reasoning, and Perception tasks (see Figure 1) utilizing a computerized training program. Participants then completed a practice run of these three tasks prior to performing the full version of these tasks during the second session.

On the second day, participants performed the three cognitive tasks while undergoing the tDCS procedure. Each cognitive task was split into two sessions with equal task conditions tallies. Task order was pseudo-randomized, as the same cognitive task was never presented twice in a row and all three tasks were always presented in each set of three task blocks. The tDCS procedure consisted of 4 runs in each session, with each run consisting of nine 49 s blocks (three blocks of each task). Each block included the presentation of a task-set cue indicating the task to be performed, followed by a fixation cross for 2 s, 4 task trials, and a final 5 s fixation cross. Each trial had a 7 s presentation of a 4-word stimulus array and was followed by a 2 s fixation cross. Participants were allowed to respond at any point throughout the trial. Each session lasted approximately 30 minutes and consisted of 144 trials, with 48 trials for each cognitive task.

The cognitive tasks each used 4-word stimulus arrays to equate visual input, yet required distinct cognitive processing to perform each task and had independent response options. The words were all displayed in lower-case Geneva font. In the Memory task ("M" cue), participants were instructed to scan the words and identify if they had studied one of the words in the first day memory encoding task (75% of trials had a word from the memory encoding task, while 25% of trials had all novel words). Participants were told to specify the encoding context, if possible. The response options were: *1) Remember One of the Words from SELF Context, 2) Remember One of the Words from OTHER Context, 3) Recognize One of the Words, But Don't Recall Source, 4) All Words are Novel*. In the Reasoning task ("R" cue), participants were instructed to evaluate if the top and bottom word-pairs constituted an analogical relationship (50% of trials contained analogies). If not, they were told to specify how many semantic relationships were presented (50% of trials were equally divided into 2, 1, or 0 semantic relationship trials (16.7% each)). The response options were: *1) Valid Analogical Relationship, 2) Two Valid Semantic Relationships, 3) One Valid Semantic Relationship, 4) No Semantic Relationships*. In the Perception task ("P" cue), participants were instructed to determine which word had the most straight lines within the letters and the correct answer always had two more straight lines than the next best answer. The response options were: *1) Top Left Word has the Most Straight Lines, 2) Bottom Left Word has the Most Straight Lines, 3) Bottom Right Word has the Most Straight Lines, 4) Top Right Word has the Most Straight Lines.*

Transcranial Direct Current Stimulation

TDCS was applied using a 9-volt battery-powered, constant direct current 1x1 stimulator (Soterix Medical Inc., New York, NY) through two separate conductive carbon rubber electrodes inside of 5 x 7 cm (35 cm^2) sponges. Sponges were immersed in a saline solution (.9%) and were attached to the scalp by plastic straps. During conditions with active tDCS at 1.5 mA, the maximum current density was .043 mA/cm^2, which is comfortably in the safe range for tDCS in human subjects (Nitsche et al., 2003). The international 10-20 EEG system was used to identify the stimulation sites. The primary stimulation site was left RLPFC (see Figure 2a), which was defined from a previous fMRI study using this task paradigm (Westphal et al., 2016). In that study, we identified a left RLPFC cluster (MNI coordinates = -42, 42, 6) that not only showed elevated BOLD activity during correctly performed trials of the Reasoning and Memory tasks, relative to the Perception task, but also contained sufficient representational information within its local BOLD activity patterns to facilitate robust decoding (using a multi-voxel pattern classification approach) between trials of the Reasoning and Memory tasks. Right motor cortex was used as the reference site as this area is commonly paired with supraorbital stimulation and is not thought to be important for these cognitive tasks as the right motor cortex projects to left side of the body and participants used their right hands to respond to the task (2014; Nitsche et al., 2008). Based on projections of 10-20 EEG sites into MNI space, the left RLPFC area was defined as being the midpoint between the Fp1 and F7 sites (Vitali et al., 2002) while right motor cortex was specified as the C4 site (see Figure 2b). Visualization of the targeted left RLPFC region on the cortex and scalp region was done using MRIcroGL (http://www.mccauslandcenter.sc.edu/mricrogl/), and visualization of the 10-20 EEG sites was done using a figure adapted from Malmivuo and Plonsey (1995).

The first session always involved sham stimulation as a baseline performance condition, while the immediately ensuing second session included either anodal stimulation of RLPFC (“Anode group”), cathodal stimulation of RLPFC (“Cathode group”), or further sham stimulation (“Sham group”); see Figure 3 for a schematic of the group design. Real stimulation was never performed in the first session, as a recent study demonstrated that tDCS facilitation effects in a visual search task may persist for up to 90 minutes (McKinley et al., 2013), and thus a group receiving real stimulation during the first session would likely still be influenced by the stimulation during the second session. Stimulation sessions began with 30 s of ramping up to 1.5 mA followed by 30 minutes of stimulation at 1.5 mA, and ending with 30 seconds of ramping down. Sham stimulation matches the real stimulation timing, but only ramps up to 1.5 mA and back down, at the beginning and end of the session.

Item Analysis

After the collection of data from all eligible subjects, an item analysis was performed in order to screen for and remove any problematic trials. Trials were removed if more than 50% of subjects showed poor performance for that specific trial. Poor performance was defined as misses or false alarms in the Memory task, choosing an incorrect response in the Reasoning task, and failing to identify the best or second best response in the Perception task. This analysis flagged 8 trials in the Reasoning task and 2 trials in the Perception task, and these trials were removed from all subjects' data prior to statistical analysis.

Statistical Analysis

Performance in the Memory task was assessed by calculating the source retrieval hit rate (defined as the proportion of trials containing a studied item for which participants reported the correct source context), as well as the source retrieval false alarm rate (defined as the proportion of trials not containing a studied item for which participants erroneously reported a source context). Subtraction of the false alarm rate from the hit rate yielded a corrected recognition (“Pr”) measure that inherently adjusts for potential response biases (Snodgrass & Corwin, 1988). Performance in the Reasoning task was assessed by calculating the analogy hit rate (defined as the proportion of trials containing a valid analogy for which participants correctly reported the presence of an analogy), as well as the analogy false alarm rate (defined as the proportion of non-analogy trials for which participants erroneously reported the presence of an analogy). Here too the false alarm rate was subtracted from the hit rate to yield a Pr measure. Performance in the Perception task was assessed by calculating the proportion of trials for which participants correctly identified which word contained the most straight lines. Pr scores were not calculated for the Perception task as there was no equivalent of a false alarm rate for that task.

Results

Effects of Experimental Group on Task Performance

The effects of tDCS were examined on performance metrics for each of the cognitive tasks using mixed model ANOVAs with session (first session vs. second session) as the within-group factor and experimental group (Anode vs. Cathode vs. Sham) as the between-group factor (see Figure 4). The mixed model ANOVA for the Perception task did not result in a significant main effect of session (F(1,69) = 2.41, p = .125), effect of experimental group (F(2,69) = .17, p = .84), or the interaction between them (F(2,69) = .79, p = .46). The mixed model ANOVA for the Reasoning task Pr scores resulted in a significant main effect of session (F(1,69) = 18.53, p < .001), a non-significant effect of experimental group (F(2,69) = .57, p = .57), and a significant interaction (F(2,69) = 4.41, p = .016). The mixed model ANOVA for the Memory task source retrieval Pr scores produced a significant main effect of session (F(1,69) = 15.28, p < .001), a non-significant effect of group (F(2,69) = .79, p =.46), and a significant interaction (F(2,69) = 4.06, = .022). The significant interactions for the Reasoning and Memory tasks were followed up by post-hoc Student-Newman-Keuls (SNK) tests examining the effect of session between experimental groups. In Reasoning, the increase in Reasoning Pr scores from the first to second session was significant for the Cathode group over the Anode group (p < .05), but was only trending for the Cathode group over the Sham group (p = .071). No further analysis was performed, as the improvement in Reasoning for the Cathode group was not reliably better than the practice effects in the Sham group. In Memory, the increase in source retrieval Pr scores from the first to second session was significant for the Anode group over the Cathode group (p < .05) and Sham group (p < .05), showing that source retrieval performance was reliably improved from anodal stimulation.

Change in Memory Task Performance for Anode Group

After finding that the Anode group showed a reliable improvement in Memory source retrieval, measured by Pr scores, we aimed to identify how participants' responses to studied Memory items changed as a result of left RLPFC anodal stimulation. Responses to these items can be categorized as incorrect source retrieval, item recognition, or miss, in addition to correct source retrievals. Post-hoc paired t-tests, with the Bonferroni correction, between first session (sham stimulation) and second session (anodal stimulation) showed that source retrieval hits ($p < .001$; $\alpha_{\text{crit-Bonferroni}} = .0125$) were significantly elevated while misses ($p = .001$; $\alpha_{\text{crit-Bonferroni}} = .0125$) were significantly reduced, while source incorrect responses ($p = .076$) and item recognition ($p = .566$) were unchanged (see Figure 5) although it is worth mentioning that these tests are non-independent due to fewer misses necessarily increasing the proportion of responses in the other conditions. These results show that anodal tDCS to RLPFC in comparison to sham stimulation appears to increase source retrievals, which simultaneously reducing misses.

Discussion

Our study examined the effects of tDCS to left RLPFC during episodic memory retrieval and analogical reasoning in comparison to visuospatial perception in three distinct experimental groups. We obtained data from sham stimulation as a baseline session for all three groups and then applied anodal stimulation to RLPFC, cathodal stimulation to RLPFC, or sham stimulation again. We did not observe any noticeable placebo effects from tDCS in the experimental group solely receiving sham stimulation, nor did we observe reliable task performance enhancements from cathodal tDCS to RLPFC paired with anodal tDCS to right motor cortex. The group that received anodal stimulation to RLPFC exhibited a reliable increase in source memory retrieval performance in comparison to the other two experimental groups, but did not exhibit any improvements during the analogical reasoning task. Furthermore, when assessing the memory performance of subjects who received anodal stimulation to RLPFC in comparison to sham stimulation, there was a clear increase in the amount of source memories retrieved but there was also a noteworthy reduction in the amount of missed items. This suggests that the increase in source memories retrieved may be coming from subjects recollecting items that would have otherwise been forgotten entirely without the tDCS intervention. Previous studies have been able to manipulate memory performance using tDCS, although to our knowledge no study has been able to improve source retrieval performance directly during retrieval itself or while using RLPFC as the target region. Anodal tDCS to nearby left DLPFC (typically paired with a right RLPFC cathode) has led to mixed results during memory tasks, as stimulation during retrieval reduced reaction time but interfered with concrete word recognition in one study (Manenti, Brambilla, Petesi, Ferrari, & Cotelli, 2013) and did not improve retrieval of words in a separate study, but did exhibit improved recognition after tDCS was applied during encoding (Javadi & Walsh, 2012). In contrast, a separate study showed that anodal stimulation to DLPFC actually impaired associative encoding based on a subsequent recognition test (Gaynor & Chua, 2016). Anodal tDCS to left DLPFC during retrieval improved monitoring accuracy for semantic knowledge questions while not improving performance in another study (Chua & Ahmed, 2016), while a separate study exhibited improved source memory retrieval performance after stimulating during a post-encoding/pre-retrieval consolidation period (Gray, Brookshire, Casasanto, & Gallo, 2015). In another study, stimulation during a reconsolidation period where subjects performed a recognition task for verbal material previously encoded, resulted in memory improvements in a second recognition session, but no acute retrieval improvements were seen in the recognition memory task during anodal stimulation (Javadi & Cheng, 2013). Considering that anodal tDCS to left DLPFC during the retrieval period has not led to consistent mnemonic improvements, what mechanisms could make such a spatially proximate region like RLPFC able to exhibit the improvements in source memory retrieval demonstrated in this study?

RLPFC may be an ideal brain region to stimulate for episodic memory retrieval augmentation due to the simultaneous enhancement of active brain regions in the FPCN and DMN, also known as activity selectivity (Bikson & Rahman, 2013). This may lead to increased functional connectivity in the task-relevant DMN and FPCN networks, which was previously demonstrated to improve memory task performance in prior work with the cognitive task used in this study (Westphal et al., 2017). A recent study by Amadi and colleagues (2014) examined the resting state functional connectivity of anodal stimulation of the right RLPFC and concurrent cathodal stimulation of the left motor cortex and discovered that the functional connectivity in the DMN was increased, while also showing further strengthened functional connectivity in a large cluster which included motor areas and extended into FPCN and DAN regions (Power et al., 2011). Considering that our electrode montage was the inverse of electrode montage used by Amadi and colleagues (2014) and left and right RLPFC areas exhibit strong functional connectivity with each other (e.g., Vincent et al., 2008), it is likely that our left RLPFC anodal stimulation will similarly result in increased functional connectivity in the DMN and FPCN systems. This is supported by another study examining functional connectivity changes due to tDCS, which had an electrode montage with the anode near our left RLPFC area on left dorsolateral prefrontal cortex and the cathode on right RLPFC, which showed strengthened connectivity during the resting state within and between the DMN and FPCN, especially near the left DLPFC anode (Keeser et al., 2011). However, two other studies with this electrode montage have had mixed effects, as one showed increased connectivity within the FPCN, but not DMN (Peña-Gómez et al., 2012), while another showed increased FPCN and DMN connectivity but solely in the right hemisphere (Park et al., 2013). Although these electrode montages have the cathode placed on right RLPFC, a functional near-infrared spectroscopy study examining the effects of tDCS on hemodynamic responses of underlying cortex with a left RLPFC anode and right RLPFC cathode electrode montage demonstrated a significant increase in oxyhemoglobin near the anode but only a negligible effect from the cathode (Merzagora et al., 2010). Functional networks are simply brain regions that demonstrate correlated hemodynamic responses (e.g., Fox et al., 2005; Vincent et al., 2008), so this may suggest that increasing the hemodynamic response from anodal, as opposed to cathodal, stimulation is potentially producing the observed increases in fMRI functional connectivity in these studies. Considering that anodal tDCS appears to significantly strengthen functional connectivity across task-relevant systems during the resting state, it is possible that activity selectivity from tDCS could potentially further enhance functional coupling between these task-relevant systems, which may explain the strength of the memory augmentation effects in this study. This may also explain why reasoning performance was not improved, as previous neuroimaging work with this cognitive task did not show increased coupling between the FPCN and DMN during analogical reasoning (Westphal et al., 2016; Westphal et al., 2017). These data suggest that analogical reasoning heavily relies upon prefrontal circuitry and the Broca's region that did couple with RLPFC during reasoning may have been too far from the RLPFC sponge electrode to receive net depolarization or activity selectivity effects. These results suggest that improving behavioral performance may be more effective when simultaneously stimulating multiple behaviorally relevant nodes and/or neural systems.

An alternative explanation for how anodal tDCS improved source memory retrieval in this study was demonstrated in a recent study by Barron and colleagues (2016), where tDCS was used to reduce GABA concentrations underneath the anode at right occipital-temporal cortex (cathode at left RLPFC), measured by magnetic resonance spectroscopy, which led to a correlated re-expression of dormant associative memories between visual shape stimuli, one day after encoding. The associative memories in this study were already becoming dormant after 24 hours, which is the same window between sessions in our study, but anodal tDCS was able to reduce inhibitory masking of these dormant memories to facilitate recall. It is possible that anodal tDCS to RLPFC in our study is also altering this balance between excitatory and inhibitory connections, although this would certainly be in different brain regions in our study as the visual shape stimuli associations were stored in occipital-temporal cortex in the study by Barron and colleagues (2016).,The source memories in this study that appeared to be retrieved during anodal tDCS to RLPFC but forgotten in the other conditions, are likely to be stored in distributed regions accessible by the DMN, which has nodes in RLPFC, and the hippocampus (e.g., Andrews-Hanna, 2012; Geib, Stanley, Wing, Laurienti, & Cabeza, 2015). Another explanation for the memory effects in our study is referred to as stochastic resonance, which is the concept that in non-linear systems that the introduction of small amounts of noise, such as that from tDCS, can improve performance when the signal is small (De Berker et al., 2013). This may explain why fewer memories were forgotten while undergoing anodal tDCS, as some of these memories are likely to be associated with smaller amounts of signal than the robust memories that are retrieved with or without tDCS.

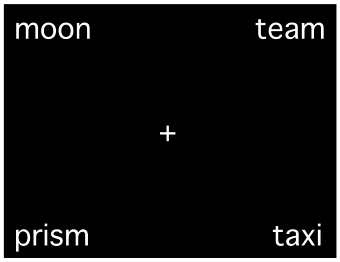
Our study was limited by not having neuroimaging data on the study participants to further investigate the causal mechanisms resulting in improved source memory retrieval from anodal tDCS to RLPFC. Potential studies could examine fMRI functional connectivity during the performance of a memory task immediately after anodal tDCS to RLPFC to conclusively determine if more widespread connectivity between the DMN and FPCN is responsible for the improved memory effects seen in this study. This could also be done at rest for the left RLPFC site, as this area could potentially boost coupling between the DMN and FPCN without needing endogenous activation.

Figures

Cognitive Tasks

- **Memory (M)**: identify if any of the 4 words had been previously encountered during the memory encoding task and indicate the context of the memory, if possible
- **Reasoning (R)**: judge whether the top and bottom word pairs constitute an analogical relationship or specify how many semantic relationships were present
- **Perception (P)**: identify which of the 4 words contained the greatest number of straight lines

Trial Example



Response Options		
Memory Task	**Reasoning Task**	**Perception Task**
1) Remember word from SELF context	1) Analogical relationship	1) Top left word
2) Remember word from OTHER context	2) Two semantic relationships	2) Bottom left word
3) Remember word but don’t recall source	3) One semantic relationship	3) Bottom right word
4) All words are novel	4) No semantic relationships	4) Top right word

Figure 2.2.1: Schematic of the cognitive tasks. Memory, Reasoning, and Perception tasks all had unique cognitive goals, used 4-word arrays, and had 4 distinct response options. A task block involves showing a task cue (“M”, “R”, or “P”), which informs the subject of which task to perform and is followed by 4 trials before switching to the next cognitive task.

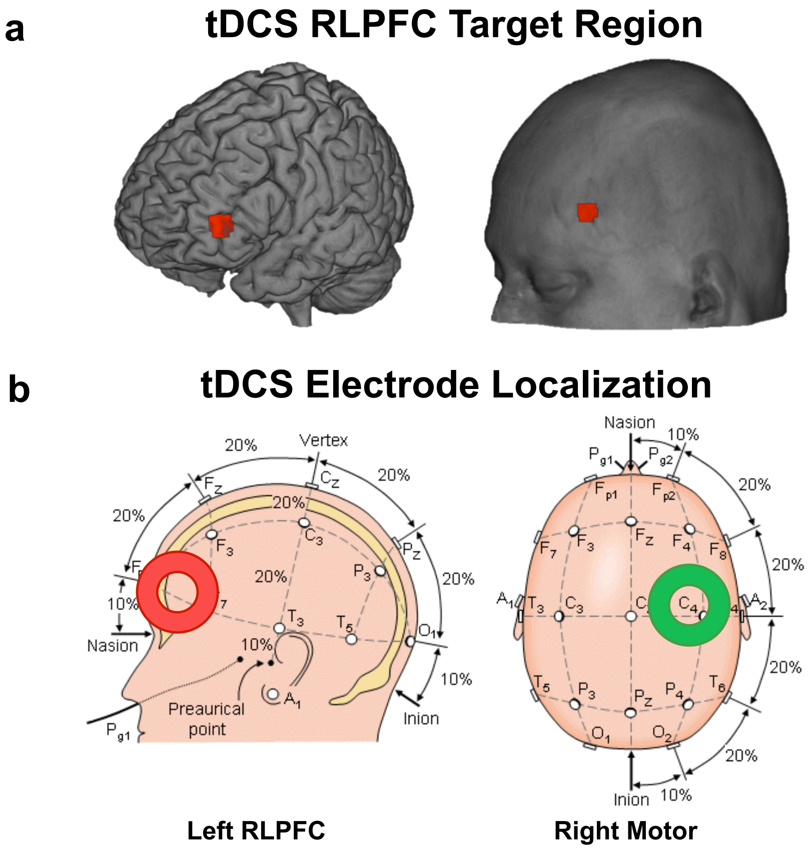


Figure 2.2.2: Representations of the tDCS stimulation sites. (*a*) Depiction of the left RLPFC target location from Westphal and colleagues (2016) rendered on a template brain and then projected onto a template head, that was approximately the midpoint of where the sponge electrode was placed. (*b*) Illustration of the sponge electrode locations on a schematic of the 10-20 EEG system. This shows a representation of the Anode group, with the red circle showing anodal stimulation of the left RLPFC site, which was in between the Fp1 and F3 locations, and the green circle demonstrating cathodal stimulation of the right motor cortex site, situated on C4.

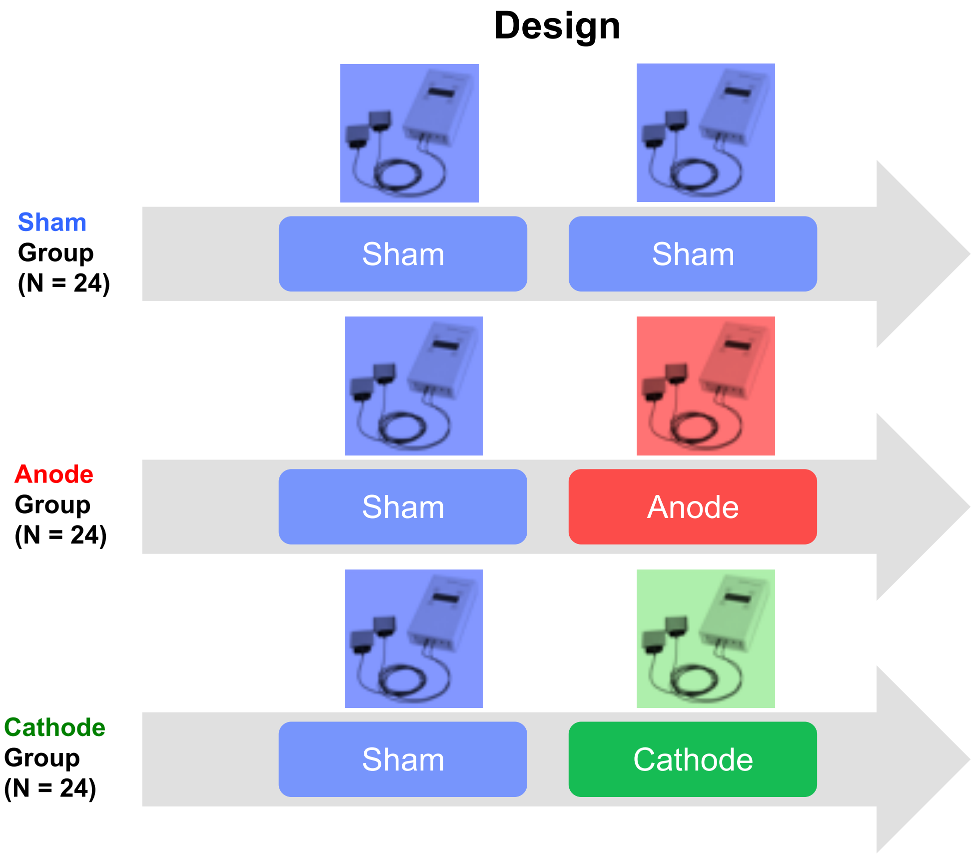


Figure 2.2.3: Portrayal of the tDCS experimental group design. Each experimental group began with sham stimulation (shown in blue) for the first session, while the second session varied depending on stimulation group. The Sham group had another sham stimulation for the second session, while the Anode group had anodal stimulation (shown in red) and the Cathode group had cathodal stimulation (shown in green) of RLPFC during the second session.

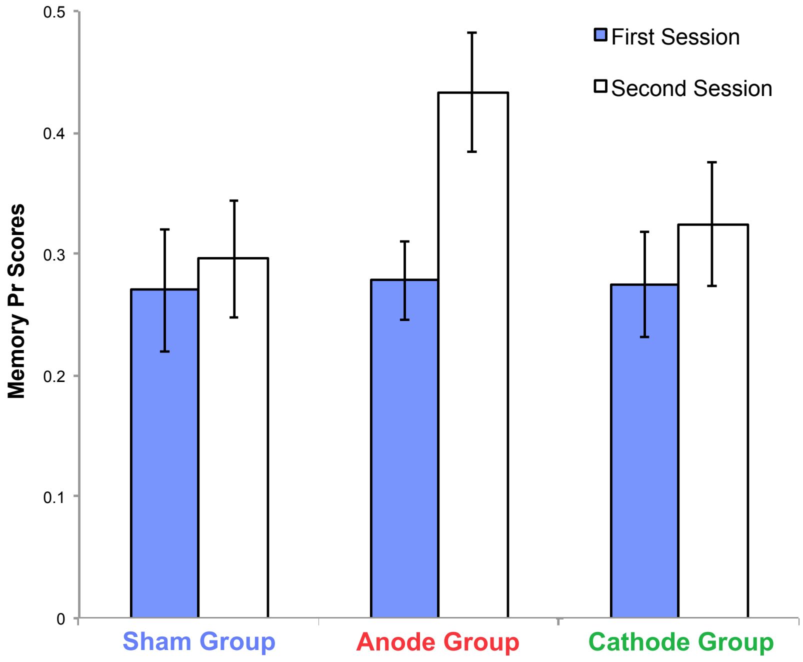


Figure 2.2.4: Memory source retrieval Pr scores across experimental groups. The first session was sham stimulation for each group, while the stimulation of the RLPFC in the second session depended upon experimental group. The Anode group demonstrated improved source memory retrieval above the Cathode ($p < .05$) and Sham ($p < .05$) groups, demonstrating that anodal stimulation to left RLPFC improved source memory retrieval.

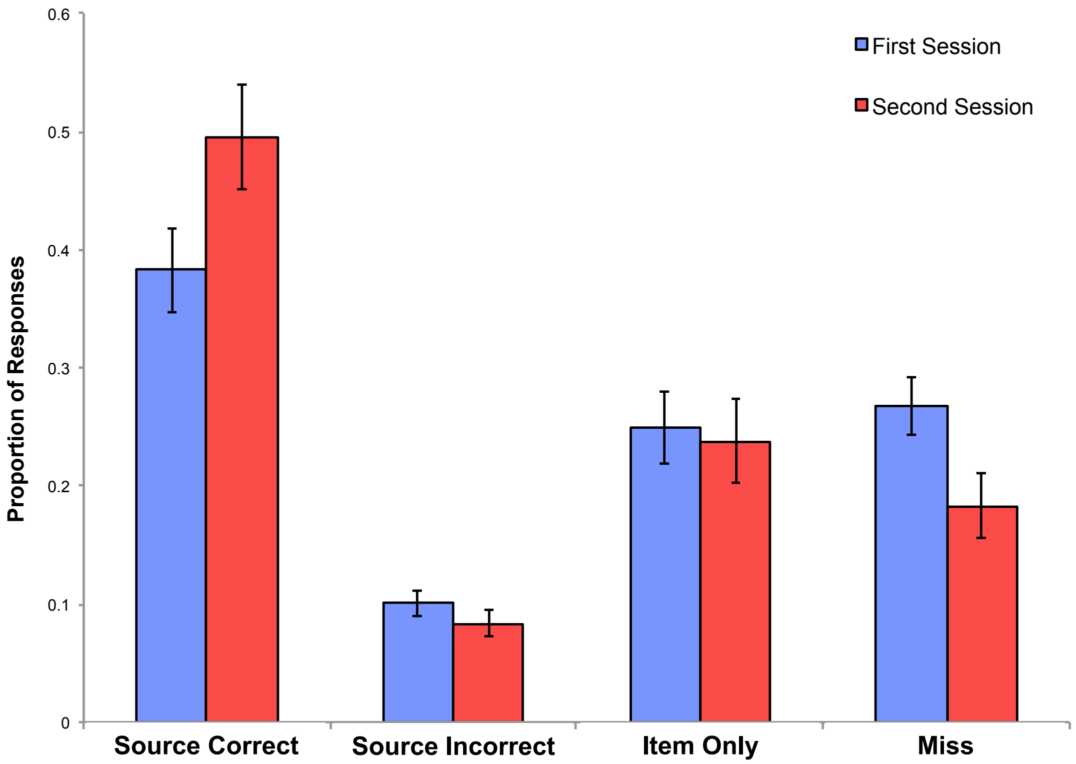


Figure 2.2.5: Change in memory performance between sham and RLPFC anodal stimulation in the Anode group. All responses were to trials where a studied word from the memory encoding task was encountered during either sham stimulation (shown in blue) in the first session or anodal stimulation to RLPFC (shown in red) during the second session. Post-hoc paired t-tests comparing between sessions showed that source memory retrieval significantly improved ($p < .001$), while misses significantly reduced ($p = .001$) during RLPFC anodal stimulation.

CHAPTER 3

Network Dynamics

SECTION 3.1.

Episodic memory retrieval benefits from a less modular brain network organization[2]

Abstract

Most complex cognitive tasks require the coordinated interplay of multiple brain networks, but the act of retrieving an[2] episodic memory may place especially heavy demands for communication between two networks that do not strongly interact with one another in many task contexts: the fronto-parietal control network (FPCN) and default mode network (DMN). We applied graph theoretical analysis to task-related fMRI functional connectivity data from twenty human participants and found that global brain modularity—a measure of network segregation—is markedly reduced during episodic memory retrieval relative to closely matched analogical reasoning and visuospatial perception tasks. Individual differences in modularity were correlated with memory task performance, such that lower modularity levels were associated with a lower false alarm rate. Moreover, these two networks showed significantly elevated coupling with each other during the memory task, which correlated with the global reduction in brain modularity. Both networks also strengthened their functional connectivity with the

---

[2] This section was previously published as: Westphal, A.J., Wang, S. and Rissman, J. (2017) Episodic memory retrieval benefits from a less modular brain network organization. *Journal of Neuroscience*, 37(13), 3523-3531.

hippocampus during the memory task. Taken together, these results provide a novel demonstration that reduced modularity is conducive to effective episodic retrieval, which requires close collaboration between goal-directed control processes supported by the FPCN and internally-oriented self-referential processing supported by the DMN.

Significance Statement

Modularity, an index of the degree to which nodes of a complex system are organized into discrete communities, has emerged as an important construct in the characterization of brain connectivity dynamics. We provide novel evidence that the modularity of the human brain is reduced when individuals engage in episodic memory retrieval, relative to other cognitive tasks, and that this state of lower modularity is associated with improved memory performance. We propose a neural systems mechanism for this finding where the nodes of the fronto-parietal control network and default mode network strengthen their interaction with one another during episodic retrieval. Such across-network communication likely facilitates effective access to internally-generated representations of past event knowledge.

Introduction

Given the highly distributed nature of memory representations in the brain (Rissman & Wagner, 2012a), the act of retrieving a past episode requires the coordinated engagement of a broad set of cortical and medial temporal lobe regions (Jeong, Chung, & Kim, 2015). Recent neuroimaging work has highlighted the particular importance of two large-scale neural networks in facilitating the process of episodic retrieval. The fronto-parietal control network (FPCN), which predominantly consists of regions along the lateral prefrontal cortex (PFC) and intraparietal sulcus (Power et al., 2011; Vincent et al., 2008), is thought to aid in the memory search process by representing one's retrieval goals and prioritizing the processing of relevant environmental cues that might help trigger the retrieval of the desired mnemonic content, as well as monitoring the details that come back to mind in the service of an impending decision or action (Donaldson, Wheeler, & Petersen, 2010; Nyhus & Badre, 2015; Spreng et al., 2010). The default mode network (DMN), which includes regions of the medial PFC, posterior cingulate cortex, angular gyrus, and medial temporal lobes, is thought to play a key role in the introspective processes needed to attend to and transiently represent self-generated information, such as memories about one's involvement in a past event (Andrews-Hanna, 2012; Raichle, 2015). Indeed, most DMN regions have been implicated as components of a "core recollection network" (Rugg & Vilberg, 2013), highlighting the close correspondence between DMN function and episodic retrieval. It was initially believed that the DMN did not collaboratively interact with neural systems involved in cognitive control, as its activity is typically anti-correlated with the FPCN and other components of the “task-positive system” during cognitive tasks (Gusnard, Raichle, & Raichle, 2001; Weissman, Roberts, Visscher, & Woldorff, 2006) as well as during the resting state (Fox et al., 2005; Fransson, 2005; but see Spreng, Sepulcre, Turner, Stevens, & Schacter, 2013 for evidence that these networks can show positive coupling during rest). However, further fMRI work has revealed that communication between the FPCN and DMN may indeed be quite important during the execution of tasks requiring controlled access to internally-generated self-referential representations (Cocchi, Zalesky, Fornito, & Mattingley, 2013; Smallwood, Brown, Baird, & Schooler, 2012), such as recollecting the context of past memories (Fornito et al., 2012) or simulating future autobiographical plans (Gerlach, Spreng, Madore, & Schacter, 2014; Spreng et al., 2010). Such cross-talk between these two large-scale networks raises the possibility that the interplay between goal-directed control and introspective monitoring needed for episodic retrieval may push the brain into a more globally integrated state, allowing greater fluidity of information transfer. This notion is supported by recent demonstrations that functional connectivity levels throughout much of the brain are elevated during successful episodic retrieval (Geib et al., 2015; King, de Chastelaine, Elward, Wang, & Rugg, 2015; Schedlbauer, Copara, Watrous, & Ekstrom, 2014; Westphal et al., 2016). However, no prior study has explored the relationship of global brain connectivity and network-specific interactions during episodic retrieval.

In the present fMRI study, we use the graphical theoretical construct of modularity (Newman, 2006; Sporns & Betzel, 2016) to index the degree to which the brain exhibits segregation into discrete communities, or modules, during episodic memory retrieval. While a highly modularized brain network organization likely confers advantages for the efficiency of information processing (Meunier, Lambiotte, & Bullmore, 2010), complex cognitive operations require an appropriately calibrated balance between modular and integrative processing (Bertolero, Yeo, & D'Esposito, 2015). By comparing modularity measured during an episodic memory task with that measured during the performance of two comparably demanding non-memory tasks that share identical stimulus and response characteristics, we aim to test the hypothesis that the brain should exhibit a lower level of modularity during episodic retrieval. To the extent that lower modularity is conducive to the type of inter-network communication that we believe is critical for episodic retrieval, we further predict that modularity levels should be correlated with memory performance. Finally, we will test whether the FPCN and DMN show elevated inter-network coupling with each other, as well as with the hippocampus, during episodic retrieval.

Materials and Methods

This report presents a new analysis of fMRI data previously analyzed using univariate general linear models, multi-voxel pattern classification, and seed-based connectivity methods focused on rostrolateral PFC regions (Westphal et al., 2016). The present study is motivated in part by our prior result that rostrolateral PFC showed elevated functional connectivity with much of the brain during episodic memory retrieval relative to closely matched tasks of analogical reasoning and visuospatial perception. Key features of the paradigm are described below.

Participants

Twenty healthy adult (mean age = 21.1 years) participants (10 female) from UCLA and the surrounding community participated in this study and had sufficient data for analysis purposes. Written informed consent was obtained in accordance with procedures approved by the UCLA Institutional Review Board, and participants received monetary compensation for their time. All were fluent English speakers with normal or corrected-to-normal vision and no history of drug or alcohol dependence, mental illness, or contraindications to MRI.

Procedure

The experiment required participation in two sessions conducted on consecutive days. On the first day, participants performed a memory encoding task, where they were presented with a series of 80 words, each preceded by a mental imagery context cue indicating whether they should mentally visualize themselves (“Self”) or another person (“Other”) interacting with the referent of the ensuing word. Participants were informed that they would later be tested on their memory for both the word and the associated imagery context. The participants then performed a computerized task where they gained proficiency in understanding the button response options for the Memory, Reasoning, and Perception tasks that they would be performing in the scanner the next day. Lastly, they performed a practice run of the three cognitive tasks.

On the second day, fMRI data were acquired as participants performed the three cognitive tasks, which were counterbalanced such that two blocks of the same task were never consecutively presented, and all three tasks had to be presented in each set of three blocks. The total session consisted of eight scanning runs, which each included nine 52 s blocks, with three blocks of each task. Blocks consisted of the presentation of a task-set cue for 6 s, indicating which task was to be performed, followed by a 2 s fixation cross, and then 4 trials of the specified task. Each trial consisted of the presentation of a 4-word stimulus array for 8 s, during which time participants indicated their response, followed by a 2 s fixation cross. An extra 4 s of fixation was included the end of each 4-trial task block. A schematic of the three-task paradigm is presented in Figure 1a. The experiment included 288 total trials, with 96 trials of each task.

The Memory, Reasoning, and Perception tasks all used 4-word stimulus arrays to equate bottom-up input to the visual system and only differed in the cognitive processes required to evaluate the stimuli and arrive at an appropriate decision. The Memory task (cued by an "M") required participants to scan the 4-word array and identify if one of the words had been encountered during the memory encoding task on the previous day (75% of trials contained a studied word; 25% contained all novels words). Participants were encouraged to specify the associated encoding context, if they remembered it. The response options were: *1) Remember One of the Words from SELF Context, 2) Remember One of the Words from OTHER Context, 3) Recognize One of the Words, But Don't Recall Source, 4) All Words are Novel*. The Reasoning task (cued by an "R") required participants to assess whether the top word-pair and bottom word-pair formed an analogical relationship, or if not, to indicate how many semantic relationships were present (50% of trials contained a valid analogical relationship; 16.7% contained two non-analogous semantic relationships; 16.7% contained one semantic relationship;

16.7% contained no semantic relationships). The response options were: *1) Valid Analogical Relationship, 2) Two Valid Semantic Relationships, 3) One Valid Semantic Relationship, 4) No Semantic Relationships*. The Perception task (cued with a "P") required participants to judge which word, printed in lower-case Geneva font, contained the greatest number of straight lines within its letters. The words in each array were chosen such that one always had at least two more straight lines than any of the others. The response options were: *1) Top Left Word has the Most Straight Lines, 2) Bottom Left Word has the Most Straight Lines, 3) Bottom Right Word has the Most Straight Lines, 4) Top Right Word has the Most Straight Lines.*

MRI Data Acquisition and fMRI Preprocessing

Whole-brain MRI was administered on a 3.0 Tesla Siemens TIM Trio scanner at the UCLA Staglin IMHRO Center for Cognitive Neuroscience. Functional images were acquired using a T2*-weighted echoplanar imaging sequence (TR = 2.0 s; TE = 30 ms; flip angle = 75°; FoV = 19.2 cm; voxel resolution = 3.0 x 3.0 x 3.7 mm; 33 interleaved axial slices). The first three volumes of each 239-volume run were discarded to ensure T1 stabilization. To facilitate the spatial registration of the functional images, we acquired a high-resolution (1 mm^3) T1-weighted anatomical scan and a co-planar T2-weighted anatomical scan. Additionally, to aid in unwarping of anterior regions of the frontal and temporal lobes, we collected a field map scan representing magnetic field inhomogeneities.

Image preprocessing was performed with SPM8 (RRID: SCR_007037; http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) and custom MATLAB

(RRID: SCR_001622) code. Preprocessing included slice time correction, motion correction, unwarping, co-registration, anatomical segmentation, spatial normalization to the MNI template, spatial smoothing (6 mm FWHM), and high-pass filtering (cut-off period = 236 s). The head motion estimates were then used as regressors and the residuals were saved for further analysis. Lastly, each voxel's timecourse was demeaned for each scanning run.

Task-specific Functional Connectivity Estimation

After the functional data were preprocessed, task-specific timecourses were extracted for each task and each subject from a set of 264 nodes identified in a meta-analysis and resting state parcellation study by Power and colleagues (2011). To create task-specific timecourses, we excised 38 s (19 TRs) of data from each task block (beginning 10 s after cue onset and ending 2 s after the offset of the fourth trial) and concatenated these segments across the 24 blocks of each task condition, resulting in 456 TRs of data for each task (Figure 1b). We then averaged the timecourses within all voxels of each node, and then correlated these mean timecourses across all pairs of nodes to yield a 264x264 correlation matrix for each task and each subject (Figure 1c). Note that because all three tasks had identical stimulus characteristics and event timing parameters, functional connectivity differences between tasks are unlikely to be due to differences in bottom-up perceptual stimulation. However, to further protect against the possibility of our graph theoretic metrics for each task being systematically influenced by the properties of the generic task model, we regressed out the timecourse of all task events and performed the functional connectivity analysis on the residuals. This procedure for obtaining estimates of task-dependent connectivity that are independent of signal fluctuations driven by the onset/offset of stimulus events is sometimes referred to as “background connectivity” analysis (Al-Aidroos, Said, & Turk-Browne, 2012; Cordova, Tompary, & Turk-Browne, 2016). The task timecourse model was specified by convolving a boxcar model for all task events (with durations of 6 s for cues and 8 s for word arrays) with SPM8’s canonical hemodynamic response function. Although we report the findings after the task-related timecourse was regressed from the data, we note that all of the results below are replicated without this analysis step. To improve normality and facilitate statistical testing, each subject’s matrix of Pearson r-values was Fisher-transformed prior to further analysis.

Graph Theoretic Analysis

We used the Brain Connectivity Toolbox (RRID: SCR_004841; https://sites.google.com/site/bctnet/; Rubinov & Sporns, 2010) to estimate several graph theoretic metrics of interest from each correlation matrix. The graph theory metrics were measured at a range of sparsity levels for each task, ranging from a lower bound of the top 4% of correlation strengths to an upper bound of the top 20% of correlation strengths, in 2% intervals (including 6%, 8%, 10%, 12%, 14%, 16%, and 18%). The upper bound of 20% was selected as this was the most dense graph where each task had small-worldness levels significantly above 1 for each task with small-worldness defined as normalized clustering divided by normalized path length. The lower bound of 4% was chosen due to this being the sparsest graph where small-worldness was computable for each subject and task. Clustering and path length were normalized by dividing the obtained metric with the average metric obtained in 10 randomly initialized networks. All graph theory metrics were aggregated across the different sparsity thresholds by calculating the area under the curve (AUC) for each metric (Bassett & Lynall, 2014).

Modularity, which reflects how effectively community detection algorithms (Fortunato, 2010) can partition the correlation matrices into communities of nodes that demonstrate primarily within-module connectivity, was calculated for all three tasks and all subjects using the Louvain algorithm (Blondel, Guillaume, Lambiotte, & Lefebvre, 2008). In addition to comparing modularity across tasks, we tested our hypothesis that individual differences in modularity scores might be related to Memory task performance. To this end, we correlated modularity with three behavioral performance metrics (mnemonic discriminability (*d'*), hit rate, and false alarm rate). The *d'* measure is calculated by subtracting the false alarm rate from the hit rate, with both measures normalized using the inverse of the cumulative standardized normal distribution. The hit rate was defined as the proportion of trials containing a studied word for which the participant correctly indicated that a studied word was present (regardless of source accuracy). The false alarm rate was defined as the proportion of trials not containing a studied word for which the participant falsely reported recognition (with or without source details).

We directly calculated the mean correlation strength between the nodes of the FPCN and DMN in order to assess the degree to which the interaction between these two large-scale networks can be linked to global modularity levels. The average transformed correlation between all 25 FPCN nodes and 58 DMN nodes was computed for each task. Given the critical role of the hippocampus in memory, we also examined the mean strength of FPCN and DMN coupling, with the hippocampus, which was treated as a network consisting of two nodes (because the 264-node parcellation used in our analyses did not include hippocampal nodes, we defined nodes in left and right hippocampus using the Harvard-Oxford atlas (RRID: SCR_001476) with a probability threshold of 50%).

Results

Behavioral Results

The distribution of responses across trial types within each task condition, as well as the associated response times, has been previously reported in full (Westphal et al., 2016); key summary statistics are reproduced here. Overall accuracy for the Memory task (i.e., proportion of trials on which participants correctly indicated whether or not the word array contained a studied word) was 75.1% (mean hit rate = 0.77; mean false alarm rate = 0.30; mean d' = 1.37). Although participants only reported a memory for the source context on 60.0% of trials containing an old word, when they did so they were highly accurate, selecting the correct source 82.3% of the time. Overall accuracy for the Reasoning task (i.e., proportion of trials on which participants correctly indicated whether the word array contained a valid analogy, or two, one, or no semantic relationships) was 76.4%. Overall accuracy for the Perception task (i.e., proportion of trials on which participants correctly indicated which word contained the greatest number of straight lines) was 66.9%. Mean response times (± SE) across all task trials were as follows: Memory = 5.04 s (.15), Reasoning = 4.72 s (.10), and Perception = 5.03 s (.19).

Task-dependent Changes in Global Connectivity

Modularity is a global graph theoretic measure that indexes how well functional connectivity of the brain can be partitioned into distinct communities (groups of nodes that interact more strongly with each other than with the rest of the network). A high modularity value indicates that distinct communities, or modules, interact minimally with one another, whereas a lower modularity value suggests stronger inter-modular interactions. Our graph analysis results found that brain connectivity during the Memory task exhibited significantly lower modularity than during both the Reasoning and Perception tasks (Figure 2a); paired *t*-tests confirmed this result at every sparsity level (all *p*'s < 0.05 after Benjamini-Hochberg FDR correction for 18 tests, with the exception one test (Reasoning > Memory at 4% sparsity) that only showed trend level significance ($p = .068$). Modularity estimates were aggregated across the nine sparsity thresholds using an area under the curve (AUC) metric and compared across tasks (Figure 2b). A repeated measures ANOVA demonstrated a significant effect of task using the modularity AUC measure ($F_{(2,18)} = 5.64$, $p = .013$). Post-hoc tests showed that the Memory task exhibited reduced modularity compared to the Reasoning ($p = .008$) and Perception ($p = .003$) tasks, with the latter two conditions showing no difference from each other ($p = .844$); $\alpha_{\text{crit-Bonferroni}} = .017$. Although mean modularity levels showed task-dependent changes, we note that individual differences in modularity were strongly correlated across tasks ($r_{\text{(Reasoning, Memory)}} = .821$, $p < .001$; $r_{\text{(Reasoning, Perception)}} = .904$, $p < .001$; $r_{\text{(Memory, Perception)}} = .841$ $p < .001$, indicating that overall brain modularity may be a trait characteristic whose magnitude can systematically increase or decrease across cognitive task states.

Given our finding that modularity was significantly reduced during the Memory task, we next examined whether modularity levels were related to participants' behavioral performance on this task. Memory modularity scores were negatively correlated with memory *d'* scores, although this trend narrowly failed to reach significance ($r = -.426$, $p = .061$). When *d'* was dissected into its hit rate and false alarm rate components, there was no correlation observed between Memory modularity and hit rates ($r = .120$, $p = .616$), but false alarm rates showed a significant positive correlation with modularity ($r = .551$, $p = .012$; $\alpha_{\text{crit-Bonferroni}} = .017$; 95% confidence interval (bootstrapped): .145 – .794). This brain-behavior relationship, shown in Figure 2c, demonstrates that individuals with higher modularity tend to make more false alarm errors on the memory task (i.e., reporting recognition or recollection of a word on trials where no studied words were present in the array).

Across-Network Correlations

We next aimed to determine if the connectivity strength between our networks of interest, the FPCN and DMN, would be elevated in the Memory task. We assessed this by computing the average connectivity strength (Fisher-transformed correlation coefficient) between all pairs of FPCN and DMN nodes, excluding all intra-network connections, during each task condition (Figure 3a). A repeated measures ANOVA revealed a significant effect of task on FPCN-DMN connectivity ($F_{(2, 18)} = 21.76$, $p < .001$); all post-hoc paired comparisons were significant (Memory>Reasoning, $p = .008$; Memory>Perception, $p < .001$; Reasoning>Perception, $p < .001$; $\alpha_{\text{crit-Bonferroni}} = .017$). To determine if this effect was specific to connectivity between the FPCN and DMN, we examined the connectivity properties of two additional large-scale networks: the cingulo-opercular network (CON), implicated in the maintenance of stable cognitive task-sets (Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008), and the dorsal attention network (DAN), implicated in the top-down control of visuospatial attention (Corbetta & Shulman, 2002). The CON did not show any task-dependent changes in its connectivity strength with the other networks (CON-FPCN, $F_{(2, 18)} = 2.22$, $p = .138$; CON-DMN, $F_{(2, 18)} = 1.79$, $p = .195$; CON-DAN, $F_{(2, 18)} = 0.40$, $p = .678$). The DAN did show task-dependent changes in connectivity with the FPCN ($F_{(2, 18)} = 13.10$, $p < .001$) and DMN ($F_{(2, 18)} = 23.63$, $p < .001$), but these effects were driven by its connectivity levels during the Perception task. Specifically, the DAN showed increased coupling with FPCN during Perception relative to both Memory ($p < .001$) and Reasoning ($p = .003$), whereas DAN showed decreased coupling with DMN during Perception relative to both Memory ($p < .001$) and Reasoning ($p < .001$); in neither case did its mean connectivity level during Memory numerically exceed nor statistically differ from that of Reasoning (all p's > 0.1).

Given our finding of heightened inter-network connectivity between the FPCN and DMN during the Memory task, we were interested in whether this effect was related to our earlier finding of decreased global brain modularity during Memory. To examine whether these effects were related, we correlated individual differences in the degree to which FPCN-DMN connectivity was increased during Memory (relative to its mean value during Reasoning and Perception) with the degree to which modularity was decreased during Memory (relative to its mean value during Reasoning and Perception). The correlation between these change scores was significantly negative ($r = -.718$, $p < .001$; 95% confidence interval (bootstrapped): -.153 – -.893); Figure 3b. Inspection of the scatter plot led to the identification of an outlier in the lower right quadrant; however, the correlation remained significant when this data point was removed ($r = -.526$, $p = .021$).

FPCN and DMN Coupling with Hippocampus

While our core hypotheses have focused on connectivity effects within large-scale networks rather than individual brain regions, we were interested in examining the degree to which these networks modulated the strength of their coupling with the hippocampus as a function of participants' cognitive task set. Because the Power et al. (2011) 264-node parcellation used in our analyses did not include hippocampal nodes, we explored hippocampal connectivity by defining ROIs in left and right hippocampus using the Harvard-Oxford atlas. We then computed the mean pairwise connectivity between each hippocampal node and all FPCN and DMN nodes and submitted the results to a network x task repeated measures ANOVA (Figure 4). Consistent with prior resting state connectivity results showing that the hippocampii are closely linked with the DMN (Andrews-Hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010; Vincent et al., 2006), we found a main effect of network ($F_{(1, 19)} = 19.91$, $p < .001$), whereby hippocampal connectivity was significantly greater with DMN nodes than with FPCN nodes. We also found a main effect of task ($F_{(2, 18)} = 7.66$, $p = .004$), driven by elevated activity during the Memory task relative to its mean level during Reasoning and Perception. And finally, we found a significant network x task interaction ($F_{(2, 18)} = 4.12$, $p = .034$), such that Memory advantage in hippocampal connectivity with the FPCN was more pronounced relative to Reasoning ($p = .011$) than relative to Perception ($p = .057$), whereas the Memory advantage in hippocampal connectivity with the DMN was more pronounced relative to Perception ($p < .001$) than relative to Reasoning ($p = .059$). We also examined the specificity of the FPCN and DMN interactions with the hippocampus by comparing them to the effects obtained when running the same analysis using the CON and DAN. Repeated measures ANOVAs assessing task-related connectivity were not significant for the connectivity between the hippocampus and the CON ($F_{(2, 18)} = 2.03$, $p = .161$) or DAN ($F_{(2, 18)} = 0.92$, $p = .418$).

Discussion

Our study used graph theoretic modeling to evaluate the whole-brain fMRI functional connectivity properties associated with episodic memory retrieval. Importantly, our unique experimental protocol allowed us to compare these properties to those measured when the same participants performed two non-episodic tasks with identical stimulus presentation characteristics and highly comparable response demands. We found that global brain modularity, an index of network segregation, was markedly reduced during episodic retrieval relative to the reasoning and perception tasks and was associated with improved memory performance. Further analysis indicated that this reduction in modularity was strongly associated with increased connectivity between the FPCN and DMN networks.

Although several recent fMRI studies have examined how brain modularity is impacted by changes in memory-related task demands, such as comparisons of load levels of an N-back working memory task (Liang, Zou, He, & Yang, 2016; Stanley, Dagenbach, Lyday, Burdette, & Laurienti, 2014; Vatansever, Menon, Manktelow, Sahakian, & Stamatakis, 2015), our study is the first to directly compare how modularity differs between memory and other complex cognitive tasks. Our finding that modularity was consistently lower during episodic retrieval than during analogical reasoning or visuospatial processing suggests that the act of retrieving an episodic memory requires a highly integrated brain state where the nodes of seemingly distinct modules are more likely to interact with nodes outside their own designated modules. At first glance it might seem surprising that a complex cognitive task like analogical reasoning did not elicit a comparably integrated brain state, given its demands for deriving and comparing abstract semantic relationships. However, the present findings are consistent with a prior seed-based connectivity analysis of these data, which also indicated that analogical reasoning engaged a more anatomically circumscribed network than that engaged during episodic retrieval (Westphal et al., 2016). Specifically, when directly comparing functional connectivity during reasoning and memory, Westphal et al. (2016) found that left rostrolateral PFC, a region commonly used as a seed for identifying the FPCN (e.g., Vincent et al., 2008), showed significantly heightened connectivity with only two brain regions during reasoning: a nearby prefrontal region (left BA 45) putatively involved in semantic processing and a region of the superior parietal lobule. In contrast, dozens of large clusters throughout the FPCN and DMN showed elevated connectivity with left rostrolateral PFC during memory relative to reasoning. Thus, while it unquestionable that analogical reasoning requires the interactivity of multiple brain systems (Knowlton, Morrison, Hummel, & Holyoak, 2012), our data suggest that the demands for across-network communication are even greater during episodic retrieval. It is possible that many of the challenging computations needed to solve analogies can be accomplished by neural circuits within PFC, and thus globally enhanced brain connectivity need not necessarily be a hallmark of analogical reasoning.

The enhancement of large-scale network connectivity associated with episodic retrieval was clearly evident in our follow-up analysis examining the connectivity between our two principal networks-of-interest. Not only did the nodes of the FPCN and DMN strengthen their connectivity with each other during memory, but the magnitude of this increased inter-network coupling correlated with the magnitude of the modularity reduction effect. Although increased FPCN-DMN coupling is unlikely to be the sole factor underlying the global modularity reduction, the strong correlation between these respective metrics suggests that it may be a major contributor to this phenomenon. The heightened interactivity between the FPCN and DMN during episodic retrieval is consistent with prior fMRI findings from Spreng and colleagues (2010), who used a partial least squares analysis approach to reveal greater coactivation of these two networks during an autobiographical planning task than during similarly structured tasks involving visuospatial planning or counting. Our finding is also consistent with the results of Fornito and colleagues (2012), who compared connectivity during episodic retrieval to connectivity during a pseudo-resting state condition. They found that while the DMN interacted minimally, if not antagonistically, with FPCN regions during rest, its nodes became more tightly coupled with FPCN nodes during episodic retrieval.

While such cooperative interactions between FPCN and DMN appear to be a hallmark of episodic retrieval, the interplay between these networks may be more broadly conceptualized as facilitating the controlled generation and maintenance of an internally-oriented train of thought (Smallwood et al., 2012). According to this view, the FPCN may function as something akin to a ‘global workspace’ (Dehaene, Kerszberg, & Changeux, 1998), capable of augmenting or suppressing inputs from other networks in accordance with one’s current goals, and in so doing, specifying which representations will dominate the contents of conscious processing. When processing is focused on information in the sensory environment, connectivity between the FPCN and the externally-oriented dorsal attention network will dominate. However, when the demands of a task require the monitoring of self-generated information (i.e., information that cannot be readily extracted from the immediate sensory environment), the FPCN will strengthen its coupling with the DMN.

In addition to our finding of strengthened FPCN-DMN coupling, we found that both networks showed increased connectivity with the hippocampus during episodic retrieval. Although the hippocampus is often considered a component region of the DMN (Andrews-Hanna et al., 2010; Raichle, 2015; Vincent et al., 2006), hippocampal connectivity with DMN regions has been found to be task-dependent, with high coupling observed during episodic retrieval and resting state conditions, but minimal coupling detected during encoding (Huijbers, Pennartz, Cabeza, & Daselaar, 2011). Our analyses showed that while the hippocampus interacted more strongly with the DMN during all three cognitive tasks, its interactions with both the DMN and FPCN were significantly stronger during the memory task. This finding is generally consistent with recent graph-theoretical demonstrations that the hippocampus fulfills a hub-like role, flexibly interacting with nodes of multiple cortical networks to facilitate successful episodic retrieval (Geib et al., 2015; Schedlbauer et al., 2014).

Another noteworthy result from the present investigation was the correlation between participants' modularity levels and their behavioral performance on the memory task. Specifically, participants with lower modularity tended to make fewer false alarms on the memory task (i.e., they were less likely to report the presence of a studied word on trials featuring word arrays with all novel words). It is unclear why this brain-behavior relationship was most strongly manifest in the false alarm rate data, as we would have also predicted an effect on participants' ability to correctly retrieve memories for trials containing old items (i.e., increased hit rate). Future work with larger samples may be need to determine whether reduced modularity confers a generalized advantage for retrieval task performance (we note that we did find a nearly significant negative correlation between modularity and overall memory *d'*), or whether the advantage is indeed selective to false alarms, perhaps by bolstering the mnemonic control processes necessary to correctly reject the novel foils. That said, our finding that lower modularity was beneficial for memory performance is largely consistent with several recent reports.

Meunier and colleagues (2014) examined functional connectivity across a smaller network of 36 regions during an olfactory recognition memory task, and they too observed a negative correlation between modularity and performance. Another recent study compared modularity across load levels in an n-back working memory task and found that increased memory load was associated with lower modularity, which in turn was associated with faster reaction times for correct responses (Vatansever et al., 2015). An N-back working memory study by Stanley and colleagues (2014) found no overall change in modularity as a function of load, yet did find that subjects who performed best on the more challenging 2-back condition tended to show reduced modularity during that condition. Intriguingly, several other studies that have measured participants' modularity levels during resting state fMRI scans have found the opposite relationship between modularity and performance on memory tasks (performed outside the scanner). Two such studies found that *higher* modularity was associated with better performance on visuospatial working memory tasks (Alavash, Doebler, Holling, Thiel, & Gießing, 2015; Stevens, Tappon, Garg, & Fair, 2012), and one study, which used a graph theoretical metric of network segregation, found that higher segregation of association networks predicted improved performance in verbal episodic memory (Chan, Park, Savalia, Petersen, & Wig, 2014).

Further work will be needed to evaluate whether this apparent divergence in the relationship between task-related and resting state modularity levels and memory performance is a meaningful phenomenon. Our results suggest that, at least when measured during cognitive task performance, modularity levels may reflect a trait characteristic, in that participants' modularity scores were highly correlated across the three tasks. In this sense, the reduction in modularity associated with episodic retrieval represents a transient modulation of one's network properties from its 'baseline' state. However, it remains unclear how the task-related 'baseline' (putatively indexed by the reasoning and perception tasks in our experiment) may differ from a resting baseline state, or from other cognitive task states. Although our three tasks were carefully structured so as to share a common set of stimulus and responses characteristics, other cognitive tasks may be difficult to constrain in this way, making comparisons challenging. Still, we believe that our results provide a valuable foundation for future research, showcasing the potential of a graph theoretical analysis approach to provide valuable insights into the brain network properties that underlie complex cognition.

Figures

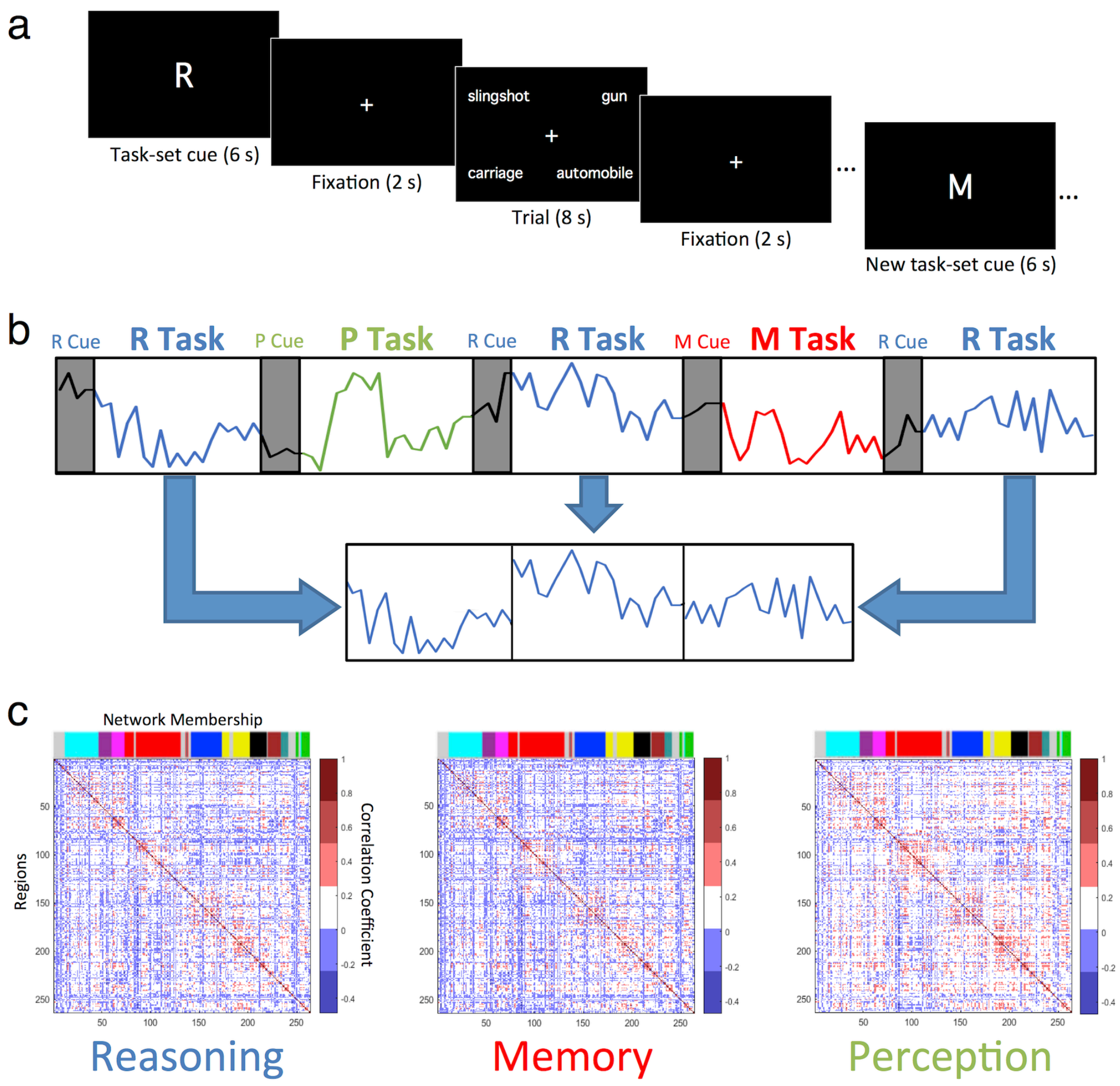


Figure 3.1.1: Schematic representation of cognitive task paradigm, procedure for creating task-specific timecourses, and mean task-specific correlation matrices. (*a*) Task blocks begin with the presentation of a task-set cue (M, R, or P) specifying which task (Memory, Reasoning, or Perception) should be performed during the following four trials. Each trial consists of a 4-word array, and participants have 8 s to respond with a button press. Trials were separated by brief periods of resting fixation. After the end of each 4-trial task block, a new task-set cue appears, followed by 4 trials of the new task. (*b*) Task-specific timecourses were created by concatenating task blocks (twenty-four 38-s blocks per task) for each node, excluding cue period activity. In this schematic example, three Reasoning task blocks were concatenated. (*c*) Mean correlation

matrices illustrate the pairwise correlations between all 264 nodes for each task, averaged across participants. The colored bands along the top of each plot indicate the network membership of the 264 nodes, as specified by Power et al. (2011).

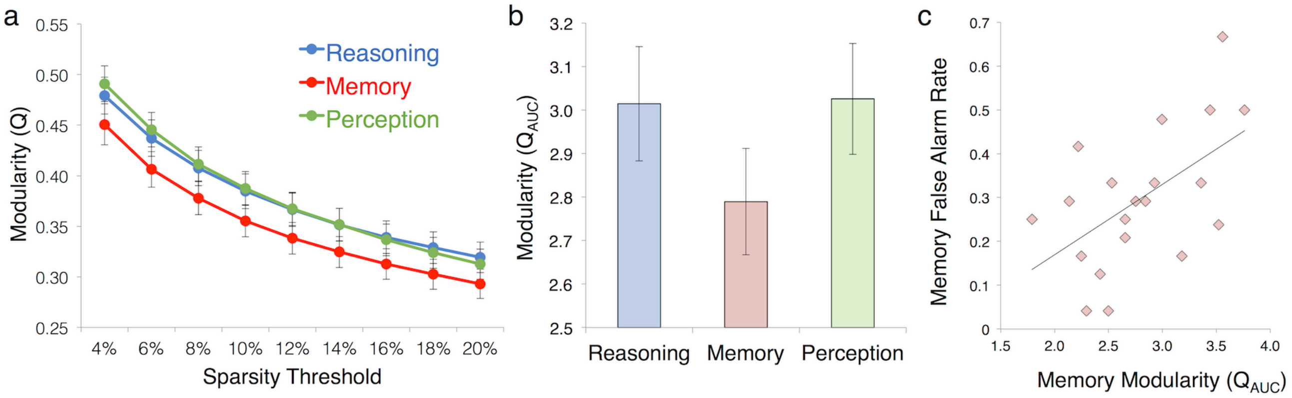


Figure 3.1.2: Modularity is reduced during Memory and related to task performance. (*a*) Modularity levels for each task and threshold demonstrate that modularity during Memory is significantly and consistently reduced compared to Reasoning and Perception at each sparsity threshold. (*b*) Comparison of mean modularity across tasks, revealing a significant reduction during Memory relative to Reasoning and Perception. (*c*) Scatter plot showing the correlation between brain modularity and false alarm rates during the Memory task ($r = .551$, $p = .012$).

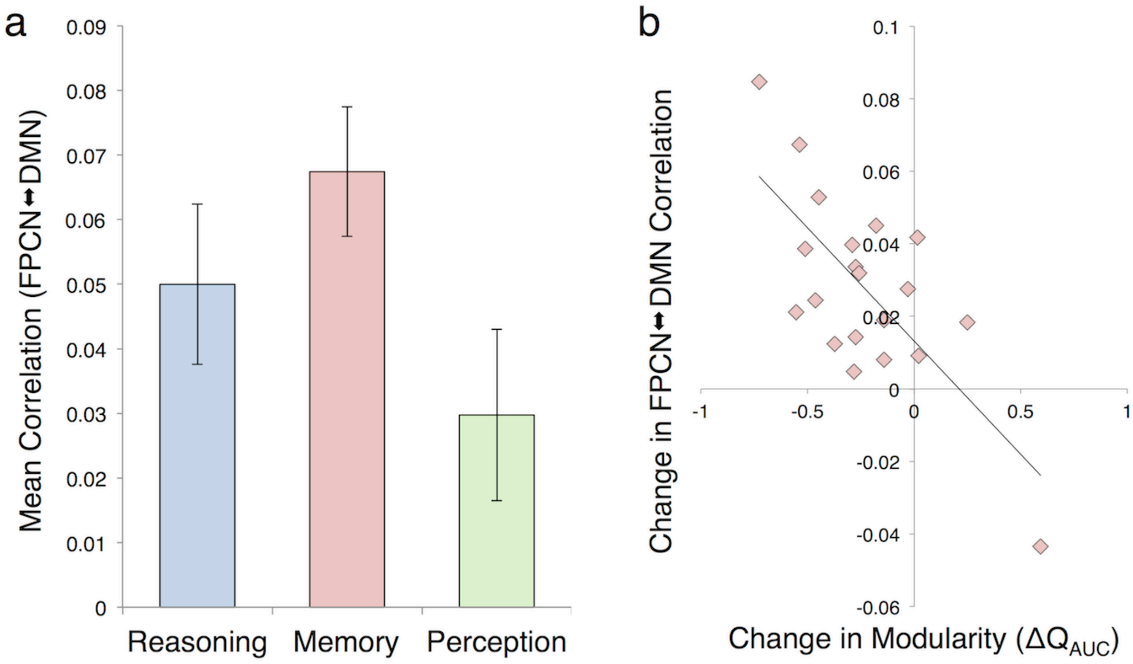


Figure 3.1.3: FPCN and DMN strengthen their coupling with each other during Memory, and the magnitude of this inter-network strengthening correlates with decreased modularity during Memory. (*a*) The FPCN and DMN show higher coupling during the Memory task than during the Reasoning and Perception tasks. (*b*) The scatter plot shows that those individuals whose brains showed larger increases in across-network connectivity between FPCN and DMN during Memory (relative to the average level observed during Reasoning and Perception) showed a correlated reduction in modularity during Memory (relative to the average level observed during Reasoning and Perception) ($r = -.718$, $p < .001$).

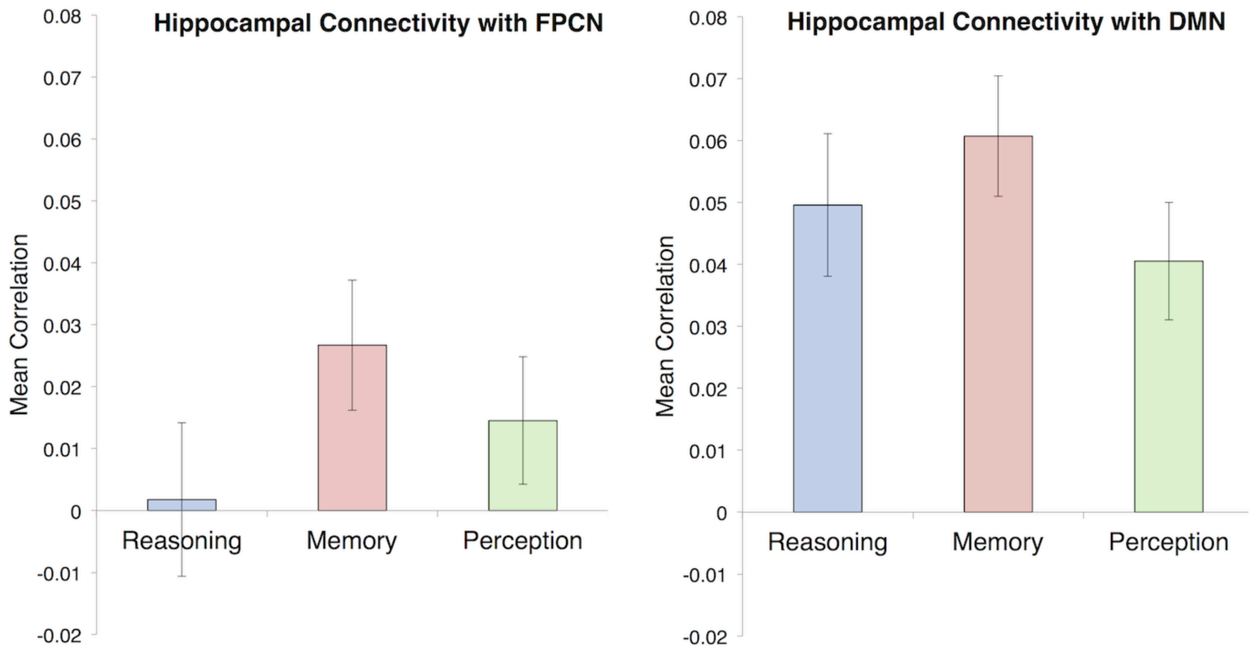


Figure 3.1.4: Hippocampal connectivity with FPCN and DMN is strengthened during Memory. The main effect of task demonstrates that the hippocampus exhibits increased coupling with the FPCN and DMN in the Memory task in comparison to the Reasoning and Perception tasks, consistent with a potential hub-like role in memory retrieval (e.g., Geib et al., 2015). Additionally, the main effect of network shows that the hippocampus exhibits preferential coupling with the DMN relative to its connectivity strength with the FPCN, consistent with resting state connectivity studies (e.g., Vincent et al., 2006).

SECTION 3.2.

Cued retrieval of negatively-valenced autobiographical memories results in impaired performance on the ensuing working memory task

Abstract: The ability to control declarative memory processes is a critical ability in daily life and is a process that appears to be dysfunctional in major depressive disorder (MDD) patients, who have difficulty breaking away from cycles of negative rumination by engaging executive control processes to reorient their focus towards the task at hand. Using a novel experimental paradigm, we examined how people's ability to perform a goal-directed visual working memory (WM) task would be impacted by a preceding instruction to briefly direct their attention to their internally generated thoughts. Using cued autobiographical memory retrieval as a means to promote self-referential thinking, we tested whether the emotional valence of the cued memory (either negative or neutral) would affect their performance on the ensuing 2-back WM task. Performance on WM task blocks that followed the retrieval of negative memories was significantly impaired relative to those that followed the retrieval of a neutral memory or a brief period of wakeful resting. Participants were aware of this, as their metacognitive ratings of interference from the negative memories were correlated with WM performance. We also found that participants' ratings of the valence and vividness of their negative memories were correlated with their emotion regulation style, such that higher levels of emotion suppression were associated with experiencing less vivid retrieval of negative autobiographical memories. Taken together, these findings demonstrate that, even in

cognitive healthy subjects, the act of recalling a negative autobiographical memory can transiently induce a rumination-like attentional state that is challenging to disengage from and thus interferes with ongoing cognition.

Introduction

Executive control processes are needed to regulate the balance between attending to events in one's external environment and attending to introspective processing, including the reliving of past memories and the associated emotions that they evoke (Mitchell & Johnson, 2009). The ability to control declarative memory processes is a critical ability in daily life and is a process that appears to be dysfunctional in major depressive disorder (MDD) patients, who have difficulty breaking away from cycles of negative rumination (Hamilton et al., 2011; Nolen-Hoeksema, 1991). MDD is characterized by an overwhelming tendency to become consumed with self-referential thoughts and memories, usually of an emotionally negative nature. This tendency has been hypothesized to be driven in part by an imbalance between large-scale neural systems involved in executive control and internally-oriented cognition (Marchetti et al., 2012). Whereas the healthy brain can use executive control processes to flexibly shift between brain states favoring internally-oriented mentation and externally-oriented information processing, the depressed brain may be overly prone to settle into the internally-oriented state, and once in this state, may struggle to re-orient attention back to the external environment (Hamilton et al., 2011; Rive et al., 2013). When MDD patients have been trained to improve executive control with a cognitive training intervention focused on augmenting selective attention and working memory, they exhibited improved symptomology over and above standard treatment using medication and psychotherapy (Siegle, Ghinassi, & Thase, 2007).

MDD patients exhibit impairment on flexibly allocating attentional resources under conditions of high interference encountered while multi-tasking, where rerouting of attention is required (Levens, Muhtadie, & Gotlib, 2009). Patients that exhibit more ruminative brooding were also more impaired by the high interference condition in this executive control task, suggesting that MDD patients may be continuously distracted by negative intrusive memories that interfere with ongoing tasks in daily life. It as if MDD causes the brain's default mode network (DMN), which supports introspective cognition, to become a 'sticky' attractor state, leading to excessive rumination (Marchetti et al., 2012). An inability to disengage from ruminative brooding can prevent depressed individuals from being fully engaged with their daily activities, which often require dynamically shifting one's focus from internal to external representations (e.g., recollecting past memories to facilitate the selection of appropriate behaviors in the present).

We are specifically interested in evaluating whether the retrieval of a negatively-valenced autobiographical episode will induce an internally-oriented brain state that may obstructively linger when changing task demands require a shift towards prioritizing the processing of incoming sensory stimuli. This may in turn exert a cost on the performance of goal-directed cognitive operations that depend on monitoring external stimuli and limiting distraction. It is essential that we better understand how the healthy brain enacts executive control to efficiently shift between internally- and externally-focused states, especially in the context of negative affect. In our task paradigm, participants are cued to either rest or vividly recall a negatively-valenced or neutral autobiographical memory and shortly thereafter are tasked with performing an externally-oriented visual working memory task. Since we are studying this paradigm with healthy subjects, we hypothesize that only the induction of negatively-valenced memories, as opposed to resting or retrieving neutral memories, will lead to impairment on the following visual working memory task.

Methods

Participants

Seventy-one research subjects from UCLA community participated in this study and received course credit in compensation. Two subjects were screened out due to indicating major depressive disorder symptoms, five subjects were removed from the subject pool due to computer problems during the experiment, and three subjects were removed due to subject noncompliance. The remaining sixty-one subjects consisted of 16 males and 45 females, with an average age of 20.33 years (SD = 1.54). Requirements for participation in this study were that the subjects were between 18 and 35 years old, native speakers of English, right-handed, had normal or corrected-to-normal vision, had no history of or current psychiatric disorders, had no history of traumatic memories, had no first-degree relatives with psychiatric disorders, had no neurological trauma, and had no drug or alcohol abuse within the previous 3 months.

Cognitive task

In our task paradigm, subjects were successively cued to shift between extended periods of introspective, episodic recollection and the performance of a goal-directed, visuospatial working memory 2-back task. Although we acknowledge that by its nature a 2-back working memory task inherently requires some attention to be allocated to internally maintained mnemonic representations of recently encountered stimuli, 2-back working memory tasks are known to engage frontoparietal brain regions involved in executive control and regions involved in external visual search while deactivating the DMN (Tomasi, Ernst, Caparelli, & Chang, 2006); thus we feel comfortable characterizing it as a task set that heavily taxes externally-oriented attention.

The general structure of the cognitive task paradigm is presented in **Figure 1**. Two thirds of the trials began with the presentation of a cue phrase for the memory retrieval task indicating which autobiographical episode they should attempt to vividly recall over the next 16 s. Half of the cued memories were negative and half were neutral. One third of the trials began with the word “rest,” instructing the participant to rest their mind for the next 16 s. Collectively, we will refer to the retrieval of autobiographical memories, in addition to spontaneous cognition during rest, as the introspective task. At the end of each recall period, there was a 2 s delay before subjects were cued to rate the emotional valence and vividness of their recollection, each on a 4-point scale. After rest, participants were instructed to rate the emotional valence and retrieval vividness of any spontaneous memory recollection that occurred during the resting period. Each rating probe was presented for 3 s, followed by an interval of 1 s. There was one more 2 s delay and then subjects performed the 2-back working memory task for 34 s with the presentation of 17 fractal images, each presented for 1.5 s with a 500 ms interval. Fractals are complex geometric stimuli that exhibit repeating patterns at different scales and are mathematically generated. Fractals were chosen as the 2-back stimuli instead of other stimuli, such as letters, to avoid subjects using a sub-vocal strategy for working memory maintenance (Juvina & Taatgen, 2007). The 20 fractal stimuli in this experiment were generated and chosen by Ragland and colleagues (2002) during their stimuli development procedure because the images were difficult to name and were used in this study with permission. The 2-back working memory task required subjects to indicate a target response if the current fractal stimulus was the same as the fractal stimulus presented two items previously. 1-back and 3-back lures were included where the fractal stimuli were the same as the fractal stimulus presented one item or three items back, respectively. The working task blocks had an average of 4 correct hits, 1 1-back lure, and 2 3-back lures. Each task trial ended with one final metacognitive judgment where participants were instructed to rate on a 4-point scale how much interference they experienced from the preceding introspective task (i.e., whether lingering thoughts about explicitly recalled life events, or events spontaneously recalled during rest, popped back into mind during the fractal working memory task and disrupted the ability to focus on the task). Over the course of 8 task runs, subjects performed a total of 48 such trials (16 beginning with the retrieval of negative memories, 16 beginning with neutral memories, and 16 beginning with undirected resting). The order of conditions was randomized, with the constraint that negative autobiographical memory, neutral autobiographical memory, and resting state must all be presented in each three item sequence. Each trial lasted a total of 66 s, including introspective, working memory, and metacognitive components.

Procedure

The study was a one-day experiment and subjects were given general instructions on how to perform the cognitive task before choosing memories for the memory retrieval task (shown in Appendix). Participants were given a worksheet on which they listed memories for notable life events that were associated with negative or neutral emotional valence. The worksheet contained 28 prompts for the selection of appropriate autobiographical memories, and each episode was rated for emotional valence, vividness, personal significance, and retrieval frequency on a 4-point Likert scale. Participants selected 8 neutral memories and 8 negative memories and provided a 2-3 word label for each memory (e.g., "walked dog", "painted room", "failed exam", "broke ankle") so that we could later cue the retrieval of these specific memories during the cognitive task. Each individual memory was cued twice over the course of the experiment. Subjects practiced the task with generic memories prior to starting the full version of the task with the memories chosen by the individual participants. Participants were given the Emotion Regulation Questionnaire (ERQ) to assess emotion regulation abilities after the cognitive task was finished and items were summed to get scores for cognitive reappraisal and expressive suppression coping styles (Gross & John, 2003).

Data analysis

Metacognitive ratings for valence, vividness, and perceived interference from the introspective task were averaged within and across subjects for negative memory retrieval, neutral memory retrieval, and resting conditions. Performance in the 2-back working memory task was also assessed separately after negative memory retrieval, neutral memory retrieval, and resting conditions. Specifically, we calculated corrected recognition scores (“Pr”) by subtracting the false alarm rate from the hit rate (Snodgrass & Corwin, 1988). The hit rate was calculated as the proportion of the 2-back targets where participants correctly made a target response. The false alarm rate was calculated as the proportion of non-targets where participants made a target response. Response times were calculated for the working memory task after each introspective condition by averaging all responses to fractal stimuli. All metrics were tested for significance through repeated measures ANOVAs across the negative memory retrieval, neutral memory retrieval, and resting introspective task conditions. Direct post-hoc comparisons between conditions were corrected for multiple comparisons with the Bonferroni correction.

Results

Working Memory Performance

The average response time for the working memory task after negative memory retrieval was 697 ms (SD = 99 ms), after neutral retrieval was 701 ms (SD = 103 ms), and after resting was 700 ms (SD = 98 ms). The repeated measures ANOVA was not significant (F(2,59) = 1.02, p = .37). Performance in the 2-back working memory task was assessed using corrected recognition scores. The average corrected recognition score after negative memory retrieval was .61 (SD = .20), after neutral memory retrieval was .64 (SD = .19), and after rest was .64 (SD = .19). The repeated measures ANOVA was significant (F(2,59) = 5.49, p = .007), and corrected recognition performance was significantly worse after negative retrieval than after neutral retrieval (p = .003) and after rest (p = .005). There was no significant difference between neutral retrieval and rest (p = .52). Furthermore, we tested if subjects' perceived interference from the negative retrieval task was correlated with corrected recognition performance after negative retrieval, and this indeed showed a significant negative correlation (r = -.32, p = .012), which is shown in **Figure 2**, in addition to corrected recognition scores across introspective task conditions. Lastly, we examined if there was a gender effect for corrected recognition performance after the retrieval of a negative memory, by performing an independent samples t-test between genders. This test was not significant (t(59) = .56, p = .58), suggesting that gender was not a determining factor for working memory performance after the retrieval of negatively-valenced autobiographical memories.

Metacognitive Ratings

Average valence ratings across subjects for each condition were 1.58 (SD = .30) for negative memory retrieval, 2.76 (SD = .34) for neutral memory retrieval, and 2.38

(SD = .57) for resting. The repeated measures ANOVA for valence across conditions was significant ($F(2,57) = 176.24$, $p < .001$) and all post-hoc comparisons were significant. Specifically, negative retrieval had lower valence ratings than neutral memory retrieval ($p < .001$) and rest ($p < .001$) and rest exhibited lower valence than during neutral memory retrieval ($p < .001$). Average vividness ratings across subjects for each condition were 3.00 (SD = .55) for negative memory retrieval, 2.65 (SD = .66) for neutral memory retrieval, and 2.44 (SD = .75) for resting. The repeated measures ANOVA for vividness across conditions was significant ($F(2,58) = 17.24$, $p < .001$). Vividness for negative retrieval was significant above neutral memory retrieval ($p < .001$) and resting ($p < .001$). Vividness for neutral memory retrieval and rest did not exhibit a significant difference that passed multiple comparisons correction ($p = .035$; $\alpha_{\text{crit-Bonferroni}} = .017$) although neutral memories were trending towards being more vivid. Average perceived interference from the introspective task on the working memory task ratings across subjects for each condition were 2.27 (SD = .55) for negative memory retrieval, 2.02 (SD = .64) for neutral memory retrieval, and 2.02 (SD = .62) for resting. The repeated measures ANOVA for perceived interference from the introspective task on working memory was significant ($F(2,59) = 13.12$, $p < .001$). Perceived interference from the negative memory retrieval was significant above neutral memory retrieval ($p < .001$) and resting ($p < .001$) while neutral memory retrieval and rest exhibited no significant difference ($p = .96$). The metacognitive ratings are shown in **Figure 3**.

Emotion Regulation

Emotion regulation abilities were measured with the ERQ and the average reappraisal score in this study was 29.93 (SD = 4.94) and the average suppression score was 13.95 (SD = 4.65). We examined if these measures were related to the metacognitive experience of valence and vividness of negative memory retrieval. Reappraisal scores were strongly trending towards being negatively correlated with emotional valence for negative memories (r = -.25, p = .052), while suppression scores were significantly negatively correlated with vividness of negative memory retrieval (r = -.27, p = .036). Scatterplots for both findings are presented in **Figure 4**.

Discussion

This study examined the effects of cued autobiographical negative memory retrieval on performance of a subsequent 2-back working memory task. Indeed, as predicted, negative memory retrieval led to impaired performance on the ensuing visual working memory task. Interestingly, participants were also aware of how much interference was being experienced on the task, as this metacognitive measure correlated with objective working memory task performance. Previous studies investigating the effects of negative mood induction on task performance have found that cognitive tasks that actively distract subjects from the induced negative mood state tends to reduce expression of the negative valence (Erber & Tesser, 1992; Morrow & Nolen-Hoeksema, 1990), although a study that induced disgust prior to performing a 2-back working memory task showed that purposeful down-regulation of negative valence resulted in worse working memory performance compared to when participants were not given explicit instructions (Scheibe & Blanchard-Fields, 2009). A study by Siegle and colleagues (2002) alternated between a valence identification task using words of negative, positive, or neutral valence followed by the Sternberg working memory task in MDD patients and control subjects undergoing fMRI scanning. There was no effect of negatively-valenced words on working memory performance for either group, although the fMRI data showed elevated and sustained amygdala responses to negative words for the MDD patients during the performance of the working memory task, which was correlated with self-reported rumination and negatively correlated with dorsolateral prefrontal cortex activation. Further work examining negative valence during working memory found that amygdala activity in response to negative emotional distractors during the working memory maintenance period predicted worse performance and reduced prefrontal cortex activation (Anticevic, Barch, & Repovs, 2010). A study by Young and colleagues (2012) examined the effects of alternating between retrieving autobiographical memories generated in response to words of negative, neutral, or positive valence with performance on subsequent cognitive tasks. Negative memory retrieval impaired performance on a simple visual perception task, but trended towards actually improving performance on a mathematical subtraction task that participants endorsed as being more difficult. Although it is not entirely clear why the 2-back working memory task in the current study resulted in diminished performance after retrieving negatively-valenced autobiographical memories, it may because the fractal 2-back task used in this study represents a medium difficulty task that can be easily disrupted. The 2-back working memory task does not appear to be difficult enough to strongly distract from the retrieved mnemonic contents from the introspective task, but it does require substantial attentional resources from the prefrontal cortex for maintaining and updating the list of ordered fractal stimuli (Ragland et al., 2002). If attention is drawn away from the working memory task by the introspective task, it would be quite difficult to both reorient to the fractal stimuli and bring back to mind the order information in the task. A recent fMRI study supported that the medium difficulty 2-back task may also represent a challenging level of difficulty for MDD patients, who suffer from intrusive self-referential thoughts. This study had participants perform a verbal n-back task with 3-back, 2-back, and 1-back conditions and used machine learning algorithms on these data to classify between MDD patients and control subjects (Marquand, Mourão-Miranda, Brammer, Cleare, & Fu, 2008). When the classifier was used on the data from the 2-back condition of the task, the classification performance was highest with 68% accuracy diagnosing between control and patient groups, while data from the 1-back and 3-back conditions did not lead to significant classification, showing that the medium difficulty 2-back was most robust diagnostically. The brain regions important for the machine learning classification were primarily within the internally-focused DMN along with prefrontal cortex regions involved in dynamic cognitive control (Dosenbach et al., 2008).

Unsurprisingly, negative memories in our study were experienced by participants as being more negative in affect and more vivid than neutral memories or spontaneous cognition during rest, consistent with research showing that participants experience negative memories more vividly (Comblain, D'Argembeau, & Van der Linden, 2005). However, individuals in our study who reported higher amounts of emotional suppression experienced less vivid negative autobiographical memories. This is consistent with prior research showing that emotional suppression leads to memory deficits, but reappraisal strategies have generally been shown to reduce negative emotional experience (Gross, 2002). However, in our sample, there was a strong trend towards individuals who reported higher amounts of emotional reappraisal experiencing more negative affect during the reliving experience. This is consistent with a study comparing emotion regulation after sadness mood inductions in recovered MDD patients and healthy control subjects, that showed that the spontaneous use of reappraisal strategies in both groups were also associated with increased experience of negative mood from the mood induction, although the instructed use of reappraisal strategies reduced negative emotional experience in both groups (Ehring, Tuschen-Caffier, Schnülle, Fischer, & Gross, 2010). As our study did not explicitly instruct subjects on how to regulate their emotions, it appears that individuals who tend towards spontaneously using reappraisal strategies experience the negative valence from autobiographical memories more in the moment but did not suffer from worse performance as a result. This may be a more healthy strategy emotionally as MDD patients tend towards spontaneous use of suppression strategies (Ehring et al., 2010). While emotional reappraisal involves changing the self-relevant meaning of emotional stimuli, a number of studies have examined conceptually similar emotion regulation strategies while participants dealt with negative affect. A behavioral study examined the effects of decentering, an emotional regulation strategy involving observing and accepting negative feelings, in addition to rumination tendencies on working memory task performance after receiving interpersonal criticism (Kaiser, Andrews-Hanna, Metcalf, & Dimidjian, 2015). Higher rumination tendencies resulted in slower 1-back reaction times after criticism, while higher decentering tendencies led to faster 1-back reaction times after criticism, suggesting that decentering may be another emotion regulation style that could reduce the experience of negative emotion. One recent fMRI study had participants retrieve negative autobiographical memories and instructed subjects change attentional focus towards the non-emotional context of the memory, which was compared to having participants focus on emotional aspect of the memory (Denkova, Dolcos, & Dolcos, 2014). Having subjects focus on the context of the situation reduced the experience of negative emotion, along with reduced amygdala activation, while focusing on the emotional aspect of the memory led to more emotional intensity and greater activation of the amygdala. Another fMRI study examining emotion regulation in response to negative affect from viewing picture stimuli in MDD patients and healthy control subjects examined a reappraisal strategy where participants were instructed to reinterpret the negative stimulus to being less personally relevant and more generally positive (Sheline et al., 2009). While control subjects showed reduced activation for DMN regions during emotion regulation, MDD patients were not able to down-regulate DMN activity with this strategy. More work will need to be done to identify emotion regulation strategies that work for MDD subjects in addition to healthy subjects.

This study was limited by not having neuroimaging data available to investigate the neural mechanisms causing healthy subjects to experience interference from retrieving negative autobiographical memories and identify how healthy subjects are able to use emotion regulation strategies to halt continued processing of negative memories and orient attention back to the task at hand. Although emotional reappraisal strategies did appear to influence the experience of retrieving negative autobiographical memories, more emotion regulation strategies should be examined in future research. Furthermore, we were potentially limited by having a majority female sample, although we did not find a gender effect in our study sample. Future studies should further examine interactions between the DMN and prefrontal cortex regions in ecologically valid situations that confront MDD patients, such as encountering intrusive memories during goal-directed tasks, while further investigating neural mechanisms that allow subjects to regain focus away from negative emotional intensity towards volitional cognition for daily activities. Future studies should also examine the consequences of retrieving highly vivid memories with positive emotional valence, as this could help to dissociate the relative contributions of vividness and valence.

Figures

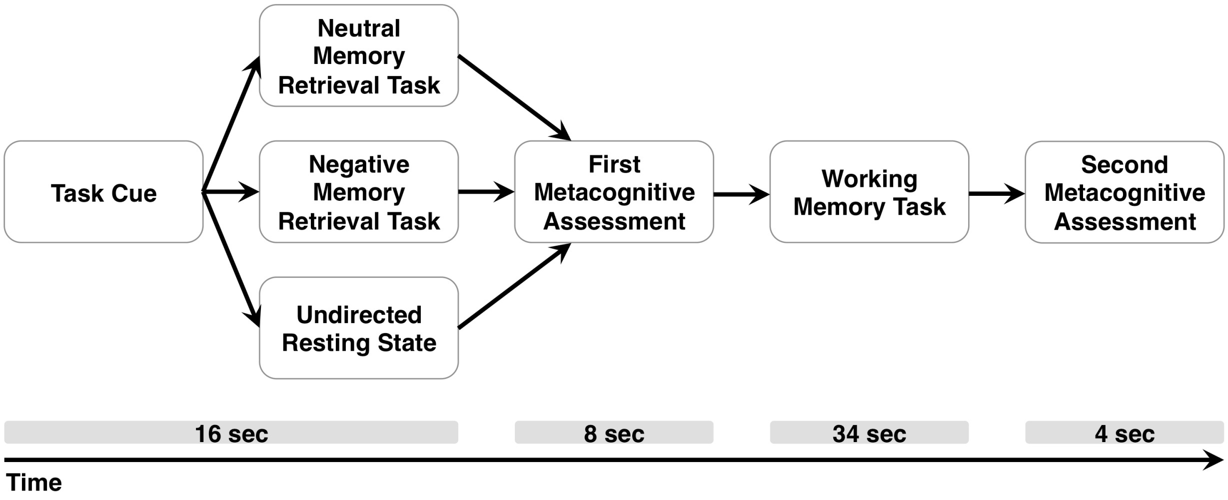


Figure 3.2.1: Schematic showing the cognitive task design and timing information. The task begins with a task-cue (16 s) showing specific memories to be retrieved in the negative or neutral autobiographical memory task or “Rest” for the undirected resting task, followed by the first metacognitive assessment. This assessment directs participants to rate the vividness and valence of the preceding cued memory or spontaneous memory (8 s). The participants then perform the fractal working memory task (34 s) and then rate how much perceived interference they had during working memory performance from the cued or spontaneous memories during the second metacognitive assessment (4 s).

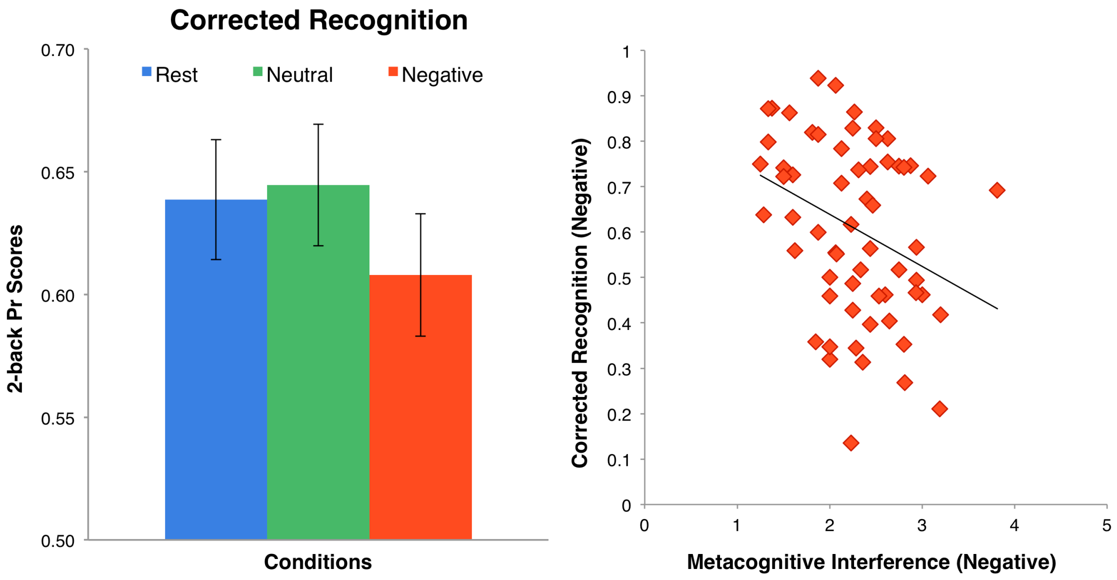


Figure 3.2.2: Corrected recognition performance across task conditions and metacognitive awareness. Performance in the working memory task, measured by corrected recognition scores, after the retrieval of negative memories was significantly impaired compared to performance after neutral memory retrieval ($p = .003$) and rest ($p = .005$). Participants were aware of this decreased performance as corrected recognition performance after negative retrieval was negatively correlated with ratings of perceived interference from the negative autobiographical retrieval task ($r = -.32$, $p = .012$).

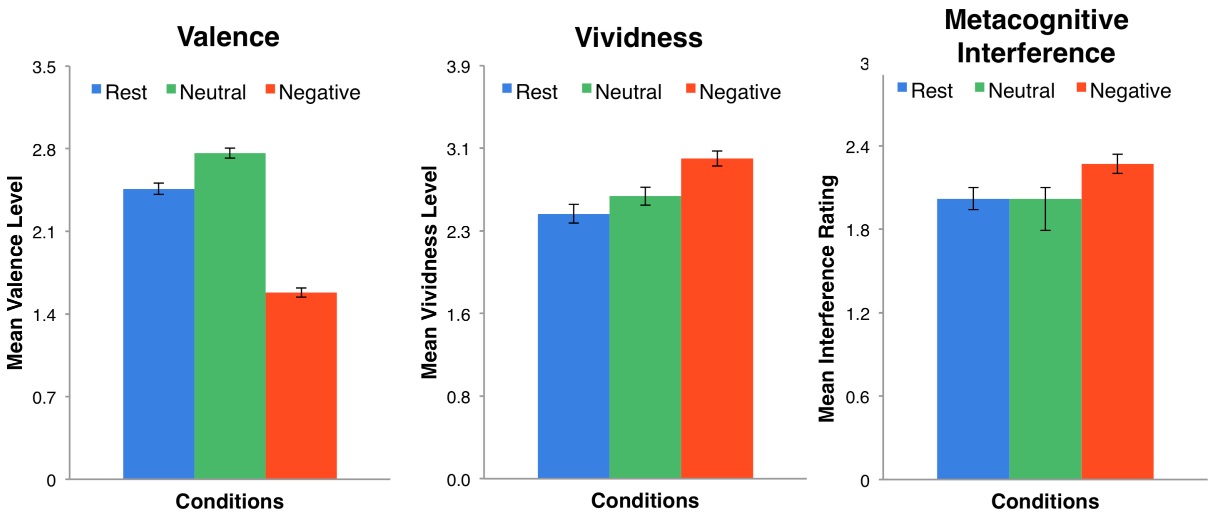


Figure 3.2.3: Metacognitive ratings across task conditions. Valence ratings were significantly lower from the negative autobiographical task, compared to neutral autobiographical retrieval (p < .001) and rest (p < .001). Vividness for negative autobiographical memories was increased compared to neutral autobiographical retrieval (p < .001) and rest (p < .001). Additionally, metacognitive interference from negative memories was greater than the inference from neutral memories (p < .001) or rest (p < .001).

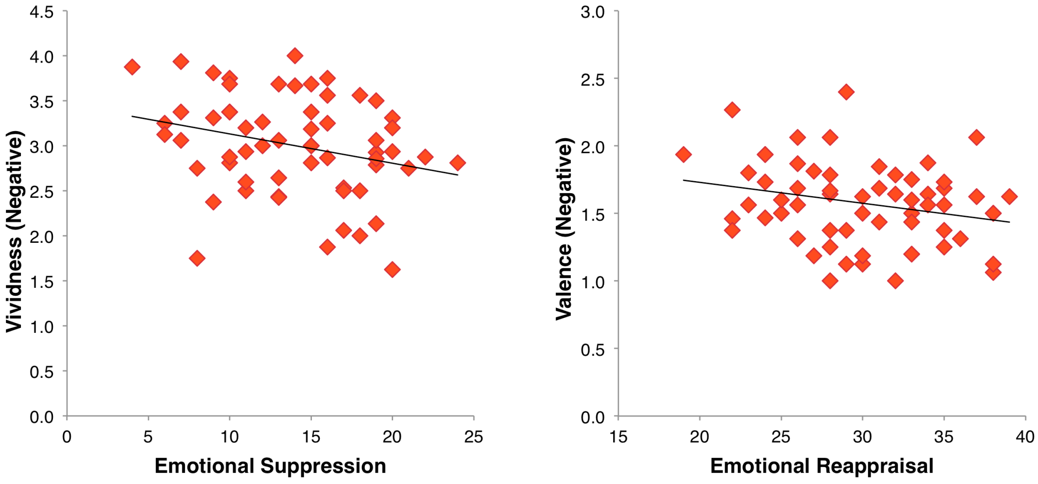


Figure 3.2.4: Emotion regulation and negative autobiographical memory experience. Participants who rated their emotion regulation as being more suppressive experienced less vivid negative autobiographical memories (r = -.27, p = .036), while participants who endorsed emotion regulation styles that were higher in reappraisal experienced lower-valenced negative autobiographical memories (r = -.25, p = .052).

Appendix

Autobiographical Memory Selection Instructions

Thank you for participating in this autobiographical memory study. This form will help guide you through filling out the text file that will be used to help you relive memories from your past in this experimental task.

We ask that you provide 8 events for both negative memories and neutral memories. You will list a total of 16 memories. A list of potential memory prompts is provided below. You may list more than one memory for each prompt. Please make sure that each of the events you provide is a specific instance that you can remember well.

One component of this experiment will involve thinking back to specific events from your past that were either emotionally negative or emotionally neutral. In order for this to work, we must begin by requesting that you provide us with a list of 16 unique event memories – 8 negative events and 8 neutral events (by "neutral" we are referring to any memorable event that was neither sad nor especially happy). To help you retrieve enough memories, we have provided a series of prompts below. If one of the prompts happens to trigger the recall of several distinct memories, you should feel free to list each of them as separate entries. Please use the provided Excel text file on your screen to provide information about your memories.

Once you have selected a memory based on the prompts below, please think of 2 words that you can use to succinctly describe the memory. For instance, "15th birthday" or "museum trip." If the memory you are reporting is negative, please place your memory with the negative memories under **the "Condition" column. If the memory is neutral, please place your memory with the neutral memories, specified in the** "Condition" **column**. Once you matched the correct valence of the memory with the condition, please write your keywords in that same row.

Then, under the appropriate columns:

- Rate the valence of the memory (1 being very negative, 2 being slightly negative, 3 being slightly positive, and 4 being very positive)
    - Rate the vividness of recollection
      (1 being very low, 2 being slightly low, 3 being slightly high, and 4 being very high)

- Rate the personal significance of the experience
  (1 being very low, 2 being slightly low, 3 being slightly high, and 4 being very high)
- Rate the frequency of how often you think of it
  (1 being very rarely, 2 being slightly rare, 3 being slightly often, and 4 being very often)

Memory prompts

If you have any of the following types of negative memories, please preferentially use these**:**

1. When you discovered that you were excluded from a social event.
2. When you or a loved one moved away.
3. When you experienced the death of a loved one or attended a funeral.
4. When you experienced the end of a romantic relationship.
5. When you were made fun of, teased, or harassed by others.
6. When you embarrassed yourself in front of others.

If you have any of the following types neutral memories, please preferentially use these**:**

1. When you recently took a trip to the grocery store.

2. When you ran into an acquaintance or briefly stopped to talk to them.
3. When you went to the first session of a course.
4. When you attended a study group or studied with a friend.
5. When you made small talk with a cashier at a store.
6. When you took public transportation.
7. When you talked to your teacher about course material.
8. When you helped a friend move in to a new apartment or house.
9. When you met your new classmates or neighbors.
10. When you worked on a group project.

If you do not have 8 events each from the previous negative and neutral memory conditions, please use the following prompts so that you have enough.

If you have any of the following types of negative memories, please use these:

1. When you were rejected by a romantic interest.
2. When your friends or family disappointed you.
3. When you realized that people were gossiping about you.
4. When you had an argument with a member of your family.

5. When you disappointed yourself by performing poorly.
6. When you lost a job or were suspended from school.

If you have any of the following types neutral memories, please use these:

1. When you went to get a haircut.
2. When you received an ID card.
3. When you ordered fast food.
4. When you visited the library.
5. When you go to the gym to exercise.
6. When you took an airplane flight.

Please make sure that you have a total of 8 negative memories and 8 neutral memories listed on the Excel text file and that all of the requested information about each memory is filled out. Please inform the experimenter that you are finished with this part of the experiment. Thank you for your help.

CHAPTER 4

Conclusion

The studies presented in this dissertation examine the complex and critical relationship between the executive control and declarative memory systems, thought to be supported in the human brain by the fronto-parietal control network (FPCN) and default mode network (DMN), respectively. The DMN has been demonstrated to broadly support internally-oriented cognition and is important for the retrieval of both episodic and semantic information (Andrews-Hanna, 2012). The FPCN has been implicated in enacting dynamic cognitive control (Dosenbach et al., 2008) and has been shown to have domain-general properties in goal-directed cognition, as it is able to flexibly couple with either the internally-oriented DMN or the externally-oriented dorsal attention network (DAN), dependent on whether the task required both cognitive control and access to internal or external feature information (Spreng et al., 2010). The FPCN system primarily consists of lateral prefrontal cortex regions, but also includes the intra-parietal sulcus (Power et al., 2011). The lateral prefrontal cortex regions that constitute the FPCN have been proposed to operate on a rostro-caudal axis, where representations are generally more concrete closer to motor areas and become much more abstract near the frontal pole (Badre & D’Esposito, 2009; Christoff & Gabrieli, 2000; Koechlin, Ody, & Kouneiher, 2003b).

Left rostrolateral prefrontal cortex (RLPFC) is considered to be the most abstract and highest order control center in this rostro-caudal axis and has been implicated in a diverse range of tasks requiring abstract cognitive control such as relational reasoning and integration (Bunge et al., 2005; Cho et al., 2010; Green et al., 2010; Wendelken & Bunge, 2010; Wendelken et al., 2012), initiating episodic memory search and evaluating information generated in episodic memory retrieval (Lepage et al., 2000; Ranganath et al., 2000; Simons et al., 2005; Simons et al., 2008), and shifting between external and internal attentional states (Burgess et al., 2007; Gilbert et al., 2005). The second chapter of this dissertation sought to understand the relationship between the RLPFC and its roles in reasoning and memory. The first section of Chapter 2 aimed to further understand if RLPFC contributes to reasoning and memory tasks with separate, domain-specific regions or if it contributed to these tasks in a domain-general way using fMRI. I created a cognitive task that continuously alternated between analogical reasoning, episodic memory retrieval, and visuospatial perception control tasks. RLPFC showed shared activation for analogical reasoning and episodic memory retrieval, yet a searchlight multi-voxel pattern analysis classifier was able to use the pattern information in RLPFC to decode between the two tasks (Westphal et al., 2016). I assessed the functional connectivity between RLPFC with the rest of the brain during these two cognitive tasks and identified that it communicated with quite distinct networks, specifically with the DMN during episodic memory retrieval and with a small network of left Broca's area and right superior parietal lobule during analogical reasoning. We concluded that RLPFC appears to engage for both tasks in a domain-general way and uses flexible connectivity with other neural systems to process the domain-specific information necessary for each task (Westphal et al., 2016). It appears that

RLPFC is needed for when multiple structured representations need comparing or integrating (Bunge & Wendelken, 2009). The structured representations were episodic memory features in the memory task and first-order semantic representations in the reasoning task.

I further assessed RLPFC contributions to memory and reasoning in the second section of Chapter 2 by performing a transcranial direct current stimulation (tDCS) study using the same cognitive task and targeting left RLPFC with depolarizing anodal currents and hyperpolarizing cathodal currents (Rahman et al., 2013) to assess the causal effects of manipulating the excitability of left RLPFC. We discovered that excitatory anodal tDCS to left RLPFC improved episodic memory retrieval but not analogical reasoning performance. We propose that result is due to the fact that in RLPFC, the FPCN regions are solely adjacent to neighboring DMN regions (Power et al., 2011), which excited both FPCN and DMN networks simultaneously and potentially improved coupling between them. This appears to be supported by a recent study (Amadi et al., 2014) that analyzed the resting state functional connectivity of anodal stimulation to RLPFC, which showed increased functional connectivity for the DMN in addition to some nodes in the FPCN. Although RLPFC is certainly important for relational reasoning, it appears that stimulation of this region alone was insufficient to improve reasoning performance, as it seems that stimulating multiple behaviorally relevant nodes together was necessary for the improved performance in the memory task.

The importance of interactions between large-scale neural systems was further investigated in the third chapter in this dissertation. The first section in Chapter 3 in this dissertation investigated the same cognitive task as the previous two studies using fMRI data and graph theoretic analysis to simultaneously assess the functional connectivity of all nodes in the brain. I assessed whole-brain connectivity across the memory, reasoning, and perception tasks and discovered that episodic memory retrieval exhibits significantly more diffuse whole-brain connectivity, measured through the modularity network segregation measure (Newman, 2006), than the other tasks (Westphal et al., 2017). Although the FPCN and DMN are typically anti-correlated during rest (Fox et al., 2005), successful episodic memory retrieval should require the dynamic cognitive control FPCN system to have access to memory representations from the DMN. We found that connectivity between these two systems was much stronger in memory retrieval, compared to the other two tasks, and that the change in coupling from the other two tasks to memory was correlated with the change in modularity from the other two tasks to memory as well. These findings suggest the coupling between these two system is critical for maintaining internally-oriented trains of thought as the FPCN is able to focus conscious processing on internally-generated representations from the DMN (Dehaene et al., 1998; Smallwood et al., 2012; Westphal et al., 2017). We also found that the hippocampus interacted more strongly both networks during memory than the other tasks and with the DMN more than the FPCN for all tasks. These findings are consistent with other studies showing that the hippocampus likely acts as a memory hub that coordinates neocortical nodes/networks for generating memory retrieval (Geib et al., 2015; Schedlbauer et al., 2014; Teyler & Rudy, 2007). The results showing how memory can be enhanced by greater coupling between the FPCN and DMN in the third research study in this dissertation inspired me to study the executive control dysfunction in major depressive disorder that has been hypothesized to be exhibit an imbalance between the FPCN and DMN systems (Marchetti et al., 2012).

In the second section of Chapter 3 in this dissertation, I created a new cognitive task to investigate if the retrieval of negatively-valenced memories can induce executive control dysfunction in a subsequent fractal 2-back working memory task. This behavioral study showed that, as hypothesized, performance on the 2-back working memory task was impaired by when the task was preceded by negative memory retrieval but not neutral memory retrieval or undirected rest. This provides behavioral evidence suggesting that experiencing negative affect can disrupt the execution of an externally-directed cognitive task. This is hypothesized to result from a neural systems imbalance where the DMN is overly expressed (Hamilton et al., 2013), which makes it difficult for the FPCN to allocate attentional resources towards the task at hand.

Altogether, the studies in this dissertation investigated how the RLPFC and the collection of primarily prefrontal cortex brain regions it functionally couples with, the FPCN, are able to interact with the DMN to successfully retrieve memories and demonstrated how negative affect can potentially disrupt the relationship between the FPCN and DMN to temporarily create a memory state that can be difficult to disengage from. We also uncovered the RLPFC neural circuit that was associated with analogical reasoning and showed that RLPFC does not appear to contain functional subareas to produce the diverse cognition associated with it, but rather that it can contribute to abstract cognition through interacting with different neural systems that are domain specific.

REFERENCES

Al-Aidroos, N., Said, C. P., & Turk-Browne, N. B. (2012). Top-down attention switches coupling between low-level and high-level areas of human visual cortex. *Proc Natl Acad Sci U S A, 109*(36), 14675-14680. doi: 10.1073/pnas.1202095109

Alavash, M., Doebler, P., Holling, H., Thiel, C.M., & Gießing, C. (2015). Is functional integration of resting state brain networks an unspecific biomarker for working memory performance? *NeuroImage, 108*, 182-193.

Amadi, U., Ilie, A., Johansen-Berg, H., & Stagg, Charlotte J. (2014). Polarity-specific effects of motor transcranial direct current stimulation on fMRI resting state networks. *NeuroImage, 88*, 155-161.

Andrews-Hanna, J. R., Reidler, J. S., Sepulcre, J., Poulin, R., & Buckner, R. L. (2010). Functional-anatomic fractionation of the brain's default network. *Neuron, 65*(4), 550-562. doi: 10.1016/j.neuron.2010.02.005

Andrews-Hanna, J.R. (2012). The brain's default network and its adaptive role in internal mentation. *Neuroscientist, 18*(3), 251-270.

Anticevic, A., Barch, D.M., & Repovs, G. (2010). Resisting emotional interference: brain regions facilitating working memory performance during negative distraction. *Cogn. Affect. Behav. Ne., 10*(2), 159-173.

Anwander, A., Tittgemeyer, M., von Cramon, D.Y., Friederici, A.D., & Knösche, T.R. (2007). Connectivity-based parcellation of Broca's area. *Cereb. Cortex, 17*(4), 816-825.

Badre, D., & D'Esposito, M. (2007). Functional magnetic resonance imaging evidence for a hierarchical organization of the prefrontal cortex. *J. Cognitive Neurosci., 19*(12), 2082-2099.

Badre, D., & D'Esposito, M. (2009). Is the rostro-caudal axis of the frontal lobe hierarchical? *Nat. Rev. Neurosci., 10*(9), 659-669.

Barron, H.C., Vogels, T.P., Emir, U.E., Makin, T.R., O'Shea, J., Clare, S., . . . Behrens, T.E.J. (2016). Unmasking latent inhibitory connections in human cortex to reveal dormant cortical memories. *Neuron, 90*(1), 191-203.

Bassett, D.S., & Lynall, M.-E. (2014). Network Methods to Characterize Brain Structure and Function. In M. S. Gazzaniga & G. R. Mangun (Eds.), *The Cognitive Neurosciences* (Fourth ed., pp. 935-948): MIT Press.

Beck, S.M., Ruge, H., Walser, M., & Goschke, T. (2014). The functional neuroanatomy of spontaneous retrieval and strategic monitoring of delayed intentions. *Neuropsychologia, 52*, 37-50.

Bertolero, M. A., Yeo, B. T., & D'Esposito, M. (2015). The modular and integrative functional architecture of the human brain. *Proc Natl Acad Sci U S A, 112*(49), E6798-6807. doi: 10.1073/pnas.1510619112

Bikson, M., & Rahman, A. (2013). Origins of specificity during tDCS: anatomical, activity-selective, and input-bias mechanisms. *Front Hum Neurosci, 7*, 688.

Blondel, V.D., Guillaume, J., Lambiotte, R., & Lefebvre, E. (2008). Fast unfolding of communities in large networks. *J. Stat. Mech-Theory E., 2008*(10), P10008.

Braver, T.S., & Bongiolatti, S.R. (2002). The role of frontopolar cortex in subgoal processing during working memory. *NeuroImage, 15*(3), 523-536.

Braver, T.S., Reynolds, J.R., & Donaldson, D.I. (2003). Neural mechanisms of transient and sustained cognitive control during task switching. *Neuron, 39*(4), 713-726.

Bunge, S.A., Helskog, E.H., & Wendelken, C. (2009). Left, but not right, rostrolateral prefrontal cortex meets a stringent test of the relational integration hypothesis. *NeuroImage, 46*(1), 338-342.

Bunge, S.A., & Wendelken, C. (2009). Comparing the bird in the hand with the ones in the bush. *Neuron, 62*(5), 609-611.

Bunge, S.A., Wendelken, C., Badre, D., & Wagner, A.D. . (2005). Analogical reasoning and prefrontal cortex: evidence for separable retrieval and integration mechanisms. *Cereb. Cortex, 15*(3), 239-249.

Burgess, P.W., Dumontheil, I., & Gilbert, S.J. (2007). The gateway hypothesis of rostral prefrontal cortex (area 10) function. *Trends Cogn. Sci., 11*(7), 290-298.

Burgess, P.W., Gonen-Yaacovi, G., & Volle, E. (2011). Functional neuroimaging studies of prospective memory: What have we learnt so far? *Neuropsychologia, 49*(8), 2246-2257.

Cabeza, R., & Nyberg, L. (2000). Imaging cognition II: An empirical review of 275 PET and fMRI studies. *J Cogn Neurosci, 12*(1), 1-47.

Chan, M. Y., Park, D. C., Savalia, N. K., Petersen, S. E., & Wig, G. S. (2014). Decreased segregation of brain systems across the healthy adult lifespan. *Proc Natl Acad Sci U S A, 111*(46), E4997-5006. doi: 10.1073/pnas.1415122111

Charron, S., & Koechlin, E. (2010). Divided representation of concurrent goals in the human frontal lobes. *Science, 328*(5976), 360-363.

Cho, S., Moody, T.D., Fernandino, L., Mumford, J.A., Poldrack, R.A., Cannon, T.D., . . . Holyoak, K.J. (2010). Common and dissociable prefrontal loci associated with component mechanisms of analogical reasoning. *Cereb. Cortex, 20*(3), 524-533.

Christoff, K., & Gabrieli, J.D.E. (2000). The frontopolar cortex and human cognition: Evidence for a rostrocaudal hierarchical organization within the human prefrontal cortex. *Psychobiology, 28*(2), 168-186.

Christoff, K., Keramatian, K., Gordon, A.M., Smith, R., & Madler, B. . (2009). Prefrontal organization of cognitive control according to levels of abstraction. *Brain Res., 1286*, 94-105.

Christoff, K., Prabhakaran, V., Dorfman, J., Zhao, Z., Kroger, J.K., Holyoak, K.J., & Gabrieli, J.D.E. . (2001). Rostrolateral prefrontal cortex involvement in relational integration during reasoning. *NeuroImage, 14*(5), 1136-1149.

Christoff, K., Ream, J.M., Geddes, L.P.T., & Gabrieli, J.D.E. . (2003). Evaluating self-generated information: anterior prefrontal contributions to human cognition. *Behav. Neurosci., 117*(6), 1161-1168.

Chua, E.F., & Ahmed, R. (2016). Electrical stimulation of the dorsolateral prefrontal cortex improves memory monitoring. *Neuropsychologia, 85*, 74-79.

Ciaramelli, E., Grady, C. L., & Moscovitch, M. (2008). Top-down and bottom-up attention to memory: a hypothesis (AtoM) on the role of the posterior parietal cortex in memory retrieval. *Neuropsychologia, 46*(7), 1828-1851. doi: 10.1016/j.neuropsychologia.2008.03.022

Cocchi, L., Zalesky, A., Fornito, A., & Mattingley, J.B. (2013). Dynamic cooperation and competition between brain systems during cognitive control. *Trends Cogn. Sci., 17*(10), 493-501.

Cole, M.W., Reynolds, J.R., Power, J.D., Repovs, G., Anticevic, A., & Braver, T.S. (2013). Multi-task connectivity reveals flexible hubs for adaptive task control. *Nat. Neurosci., 16*(9), 1348-1355.

Comblain, C., D'Argembeau, A., & Van der Linden, M. (2005). Phenomenal characteristics of autobiographical memories for emotional and neutral events in older and younger adults. *Exp. Aging Res., 31*(2), 173-189.

Corbetta, M., & Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nat Rev Neurosci, 3*(3), 201-215. doi: 10.1038/nrn755

Cordova, N. I., Tompary, A., & Turk-Browne, N. B. (2016). Attentional modulation of background connectivity between ventral visual cortex and the medial temporal lobe. *Neurobiol Learn Mem, 134 Pt A*, 115-122. doi: 10.1016/j.nlm.2016.06.011

Davis, T., LaRocque, K.F., Mumford, J.A., Norman, K.A., Wagner, A.D., & Poldrack, R.A. (2014). What do differences between multi-voxel and univariate analysis mean? How subject-, voxel-, and trial-level variance impact fMRI analysis. *NeuroImage, 97*, 271-283.

De Berker, A.O., Bikson, M., & Bestmann, S. (2013). Predicting the behavioral impact of transcranial direct current stimulation: issues and limitations. *Front Hum Neurosci, 7*, 613.

Dehaene, S., Kerszberg, M., & Changeux, J. (1998). A neuronal model of a global workspace in effortful cognitive tasks. *P. Natl. Acad. Sci. USA, 95*(24), 14529-14534.

Denkova, E., Dolcos, S., & Dolcos, F. (2014). Neural correlates of 'distracting' from emotion during autobiographical recollection. *Soc. Cogn. Affect. Neurosci.*, nsu039.

Dobbins, I.G., & Han, S. (2006). Cue-versus probe-dependent prefrontal cortex activity during contextual remembering. *J. Cognitive Neurosci., 18*(9), 1439-1452.

Dobbins, I.G., & Wagner, A.D. (2005). Domain-general and domain-sensitive prefrontal mechanisms for recollecting events and detecting novelty. *Cereb. Cortex, 15*(11), 1768-1778.

Donaldson, D. I., Wheeler, M. E., & Petersen, S. E. (2010). Remember the source: dissociating frontal and parietal contributions to episodic memory. *J Cogn Neurosci, 22*(2), 377-391. doi: 10.1162/jocn.2009.21242

Donoso, M., Collins, A.G.E., & Koechlin, E. (2014). Foundations of human reasoning in the prefrontal cortex. *Science*, 1252254.

Dosenbach, N. U., Fair, D. A., Miezin, F. M., Cohen, A. L., Wenger, K. K., Dosenbach, R. A., . . . Petersen, S. E. (2007). Distinct brain networks for adaptive and stable task control in humans. *P. Natl. Acad. Sci. USA, 104*(26), 11073-11078. doi: 10.1073/pnas.0704320104

Dosenbach, N.U.F., Fair, D.A., Cohen, A.L., Schlaggar, B.L., & Petersen, S.E. (2008). A dual-networks architecture of top-down control. *Trends Cogn. Sci., 12*(3), 99-105.

Duncan, J., & Owen, A. M. (2000). Common regions of the human frontal lobe recruited by diverse cognitive demands. *Trends Neurosci., 23*(10), 475-483.

Ehring, T., Tuschen-Caffier, B., Schnülle, J., Fischer, S., & Gross, J.J. (2010). Emotion regulation and vulnerability to depression: spontaneous versus instructed use of emotion suppression and reappraisal. *Emotion, 10*(4), 563.

Erber, R., & Tesser, A. (1992). Task effort and the regulation of mood: The absorption hypothesis. *J. Exp. Soc. Psychol., 28*(4), 339-359.

Fedorenko, E., Duncan, J., & Kanwisher, N. (2013). Broad domain generality in focal regions of frontal and parietal cortex. *P. Natl. Acad. Sci. USA, 110*(41), 16616-16621.

Fornito, A., Harrison, B.J., Zalesky, A., & Simons, J.S. (2012). Competitive and cooperative dynamics of large-scale brain functional networks supporting recollection. *P. Natl. Acad. Sci. USA, 109*(31), 12788-12793.

Fortunato, S. (2010). Community detection in graphs. *Phys. Rep., 486*(3), 75-174.

Fox, M.D., Snyder, A.Z., Vincent, J.L., Corbetta, M., Van Essen, D.C., & Raichle, M.E. (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *P. Natl. Acad. Sci. USA, 102*(27), 9673-9678.

Fransson, P. (2005). Spontaneous low-frequency BOLD signal fluctuations: an fMRI investigation of the resting-state default mode of brain function hypothesis. *Hum Brain Mapp, 26*(1), 15-29. doi: 10.1002/hbm.20113

Friston, K.J., Buechel, C., Fink, G.R., Morris, J., Rolls, E., & Dolan, R.J. (1997). Psychophysiological and modulatory interactions in neuroimaging. *NeuroImage, 6*(3), 218-229.

Gaynor, A.M., & Chua, E.F. (2016). tDCS over the prefrontal cortex alters objective but not subjective encoding. *Cognitive Neuroscience*, 1-6.

Geib, B. R., Stanley, M. L., Wing, E. A., Laurienti, P. J., & Cabeza, R. (2015). Hippocampal Contributions to the Large-Scale Episodic Memory Network Predict Vivid Visual Memories. *Cereb Cortex*. doi: 10.1093/cercor/bhv272

Gerlach, K. D., Spreng, R. N., Madore, K. P., & Schacter, D. L. (2014). Future planning: default network activity couples with frontoparietal control network and reward-processing regions during process and outcome simulations. *Soc Cogn Affect Neurosci, 9*(12), 1942-1951. doi: 10.1093/scan/nsu001

Gilbert, S.J. (2011). Decoding the content of delayed intentions. *J. Neurosci., 31*(8), 2888-2894.

Gilbert, S.J., Frith, C.D., & Burgess, P.W. . (2005). Involvement of rostral prefrontal cortex in selection between stimulus-oriented and stimulus-independent thought. *Eur. J. Neurosci., 21*(5), 1423-1431.

Gilbert, S.J., Gonen-Yaacovi, G., Benoit, R.G., Volle, E., & Burgess, P.W. (2010). Distinct functional connectivity associated with lateral versus medial rostral prefrontal cortex: a meta-analysis. *NeuroImage, 53*(4), 1359-1367.

Gilbert, S.J., Spengler, S., Simons, J.S., Steele, J.D., Lawrie, S.M., Frith, C.D., & Burgess, P.W. (2006). Functional specialization within rostral prefrontal cortex (area 10): a meta-analysis. *J. Cognitive Neurosci., 18*(6), 932-948.

Goldberg, R.F., Perfetti, C.A., Fiez, J.A., & Schneider, W. (2007). Selective retrieval of abstract semantic knowledge in left prefrontal cortex. *J. Neurosci., 27*(14), 3790-3798.

Gray, S.J., Brookshire, G., Casasanto, D., & Gallo, D.A. (2015). Electrically stimulating prefrontal cortex at retrieval improves recollection accuracy. *cortex, 73*, 188-194.

Green, A.E., Fugelsang, J.A., Kraemer, D.J.M., Shamosh, N.A., & Dunbar, K.N. . (2006). Frontopolar cortex mediates abstract integration in analogy. *Brain Res., 1096*(1), 125-137.

Green, A.E., Kraemer, D.J.M, Fugelsang, J.A., Gray, J.R., & Dunbar, K.N. . (2010). Connecting long distance: semantic distance in analogical reasoning modulates frontopolar cortex activity. *Cereb. Cortex, 20*(1), 70-76.

Gross, J.J. (2002). Emotion regulation: Affective, cognitive, and social consequences. *Psychophysiology, 39*(3), 281-291.

Gross, J.J., & John, O.P. (2003). Individual differences in two emotion regulation processes: implications for affect, relationships, and well-being. *J. Pers. Soc. Psychol., 85*(2), 348.

Gusnard, D. A., Raichle, M. E., & Raichle, M. E. (2001). Searching for a baseline: functional imaging and the resting human brain. *Nat Rev Neurosci, 2*(10), 685-694. doi: 10.1038/35094500

Hamilton, J.P., Chen, M.C., & Gotlib, I.H. (2013). Neural systems approaches to understanding major depressive disorder: an intrinsic functional organization perspective. *Neurobiol. Dis., 52*, 4-11.

Hamilton, J.P., Furman, D.J., Chang, C., Thomason, M.E., Dennis, E., & Gotlib, I.H. (2011). Default-mode and task-positive network activity in major depressive disorder: implications for adaptive and maladaptive rumination. *Biol. Psychiat., 70*(4), 327-333.

Huijbers, W., Pennartz, C. M., Cabeza, R., & Daselaar, S. M. (2011). The hippocampus is coupled with the default network during memory retrieval but not during memory encoding. *PloS one, 6*(4), e17463. doi: 10.1371/journal.pone.0017463

Javadi, A.H., & Cheng, P. (2013). Transcranial direct current stimulation (tDCS) enhances reconsolidation of long-term memory. *Brain Stimul., 6*(4), 668-674.

Javadi, A.H., & Walsh, V. (2012). Transcranial direct current stimulation (tDCS) of the left dorsolateral prefrontal cortex modulates declarative memory. *Brain Stimul., 5*(3), 231-241.

Jeong, W., Chung, C. K., & Kim, J. S. (2015). Episodic memory in aspects of large-scale brain networks. *Front Hum Neurosci, 9*, 454. doi: 10.3389/fnhum.2015.00454

Jimura, K., & Poldrack, R.A. (2012). Analyses of regional-average activation and multivoxel pattern information tell complementary stories. *Neuropsychologia, 50*(4), 544-552.

Juvina, I., & Taatgen, N.A. (2007). *Modeling control strategies in the n-back task.* Paper presented at the Proceedings of the 8th international conference on cognitive modeling.

Kaiser, R.H., Andrews-Hanna, J.R., Metcalf, C.A., & Dimidjian, S. (2015). Dwell or Decenter? Rumination and Decentering Predict Working Memory Updating After Interpersonal Criticism. *Cognitive Ther. Res., 39*(6), 744-753.

Keeser, D., Meindl, T., Bor, J., Palm, U., Pogarell, O., Mulert, C., . . . Padberg, F. (2011). Prefrontal transcranial direct current stimulation changes connectivity of resting-state networks during fMRI. *J. Neurosci., 31*(43), 15284-15293.

Kennedy, D.N., Lange, N., Makris, N., Bates, J., Meyer, J., & Caviness, V.S. (1998). Gyri of the human neocortex: an MRI-based analysis of volume and variance. *Cereb. Cortex, 8*(4), 372-384.

King, D.R., de Chastelaine, M., Elward, R.L., Wang, T.H., & Rugg, M.D. (2015). Recollection-Related Increases in Functional Connectivity Predict Individual Differences in Memory Accuracy. *J. Neurosci., 35*(4), 1763-1772.

Knowlton, B.J., Morrison, R.G., Hummel, J.E., & Holyoak, K.J. (2012). A neurocomputational system for relational reasoning. *Trends Cogn Sci, 16*(7), 373-381.

Koechlin, E., Basso, G., Pietrini, P., Panzer, S., & Grafman, J. . (1999). The role of the anterior prefrontal cortex in human cognition. *Nature, 399*, 148-151.

Koechlin, E., & Hyafil, A. (2007). Anterior prefrontal function and the limits of human decision-making. *Science, 318*(5850), 594-598.

Koechlin, E., Ody, C., & Kouneiher, F. (2003a). The architecture of cognitive control in the human prefrontal cortex. *Science, 302*(5648), 1181-1185. doi: 10.1126/science.1088545

Koechlin, E., Ody, C., & Kouneiher, F. . (2003b). The architecture of cognitive control in the human prefrontal cortex. *Science, 203*(5648), 1181-1185.

Krawczyk, D. C. (2012). The cognition and neuroscience of relational reasoning. *Brain Res., 1428*, 13-23. doi: 10.1016/j.brainres.2010.11.080

Krawczyk, D. C., Michelle McClelland, M., & Donovan, C. M. (2011). A hierarchy for relational reasoning in the prefrontal cortex. *Cortex, 47*(5), 588-597. doi: 10.1016/j.cortex.2010.04.008

Krawczyk, D.C., McClelland, M.M., Donovan, C.M., Tillman, G.D., & Maguire, M.J. (2010). An fMRI investigation of cognitive stages in reasoning by analogy. *Brain Res., 1342*, 63-73.

Kriegeskorte, N., Goebel, R., & Bandettini, P. (2006). Information-based functional brain mapping. *P. Natl. Acad. Sci. USA, 103*(10), 3863-3868.

Kroger, J.K., Sabb, F.W., Fales, C.L., Bookheimer, S.Y., Cohen, M.S., & Holyoak, K.J. (2002). Recruitment of anterior dorsolateral prefrontal cortex in human reasoning: a parametric study of relational complexity. *Cereb. Cortex, 12*(5), 477-485.

Lapenta, O.M., Minati, L., Fregni, F., & Boggio, P.S. (2013). Je pense donc je fais: transcranial direct current stimulation modulates brain oscillations associated with motor imagery and movement observation. *Front Hum Neurosci, 7*(256).

Lepage, M., Ghaffar, O., Nyberg, L., & Tulving, E. . (2000). Prefrontal cortex and episodic memory retrieval mode. *P. Natl. Acad. Sci. USA, 97*(1), 506-511.

Levens, S.M., Muhtadie, L., & Gotlib, I.H. (2009). Rumination and impaired resource allocation in depression. *J. Abnorm. Psychol., 118*(4), 757.

Liang, X., Zou, Q., He, Y., & Yang, Y. (2016). Topologically Reorganized Connectivity Architecture of Default-Mode, Executive-Control, and Salience Networks across Working Memory Task Loads. *Cereb Cortex, 26*(4), 1501-1511. doi: 10.1093/cercor/bhu316

Malmivuo, J., & Plonsey, R. (1995). *Bioelectromagnetism: principles and applications of bioelectric and biomagnetic fields*: Oxford University Press, USA.

Manenti, R., Brambilla, M, Petesi, M, Ferrari, C, & Cotelli, M. (2013). Enhancing verbal episodic memory in older and young subjects after non-invasive brain stimulation. *Frontiers in aging neuroscience, 5*, 49.

Marchetti, I., Koster, E.H.W., Sonuga-Barke, E.J., & De Raedt, R. (2012). The default mode network and recurrent depression: a neurobiological model of cognitive risk factors. *Neuropsychol. Rev., 22*(3), 229-251.

Marquand, A.F., Mourão-Miranda, J., Brammer, M.J., Cleare, A.J., & Fu, C.H.Y. (2008). Neuroanatomy of verbal working memory as a diagnostic biomarker for depression. *Neuroreport, 19*(15), 1507-1511.

McKinley, R.A., McIntire, L., Bridges, N., Goodyear, C., Bangera, N.B., & Weisend, M.P. (2013). Acceleration of image analyst training with transcranial direct current stimulation. *Behav. Neurosci., 127*(6), 936.

McLaren, D.G., Ries, M.L., Xu, G., & Johnson, S.C. . (2012). A generalized form of context-dependent psychophysiological interactions (gPPI): a comparison to standard approaches. *NeuroImage, 61*(4), 1277-1286.

Menon, V., & Uddin, L.Q. (2010). Saliency, switching, attention and control: a network model of insula function. *Brain Struct. Funct., 214*(5-6), 655-667.

Merzagora, A.C., Foffani, G., Panyavin, I., Mordillo-Mateos, L., Aguilar, J., Onaral, B., & Oliviero, A. (2010). Prefrontal hemodynamic changes produced by anodal direct current stimulation. *NeuroImage, 49*(3), 2304-2310.

Meunier, D., Fonlupt, P., Saive, A. L., Plailly, J., Ravel, N., & Royet, J. P. (2014). Modular structure of functional networks in olfactory memory. *NeuroImage, 95*, 264-275. doi: 10.1016/j.neuroimage.2014.03.041

Meunier, D., Lambiotte, R., & Bullmore, E. T. (2010). Modular and hierarchically modular organization of brain networks. *Front Neurosci, 4*, 200. doi: 10.3389/fnins.2010.00200

Mitchell, K.J., & Johnson, M.K. (2009). Source monitoring 15 years later: What have we learned from fMRI about the neural mechanisms of source memory? *Psychol. Bull., 135*(4), 638-677.

Momennejad, I., & Haynes, J. (2012). Human anterior prefrontal cortex encodes the 'what'and 'when'of future intentions. *NeuroImage, 61*(1), 139-148.

Morrow, J., & Nolen-Hoeksema, S. (1990). Effects of responses to depression on the remediation of depressive affect. *Journal of personality and social psychology, 58*(3), 519.

Newman, M.E.J. (2006). Modularity and community structure in networks. *P. Natl. Acad. Sci. USA, 103*(23), 8577-8582.

Nitsche, M.A., Cohen, L.G., Wassermann, E.M., Priori, A., Lang, N., Antal, A., . . . Fregni, F. (2008). Transcranial direct current stimulation: state of the art 2008. *Brain Stimul., 1*(3), 206-223.

Nitsche, M.A., Liebetanz, D., Lang, N., Antal, A., Tergau, F., & Paulus, W. (2003). Safety criteria for transcranial direct current stimulation (tDCS) in humans. *Clin. Neurophysiol., 114*(11), 2220-2222.

Nolen-Hoeksema, S. (1991). Responses to depression and their effects on the duration of depressive episodes. *J. Abnorm. Psychol., 100*(4), 569-582.

Nyhus, E., & Badre, D. (2015). Memory Retrieval and the Functional Organization of Frontal Cortex. In D. R. Addis, M. Barense & A. Duarte (Eds.), *The Wiley Handbook on the Cognitive Neuroscience of Memory* (1st ed., pp. 131-149): John Wiley & Sons.

Park, C., Chang, W.H., Park, J., Shin, Y., Kim, S.T., & Kim, Y. (2013). Transcranial direct current stimulation increases resting state interhemispheric connectivity. *Neurosci. Lett., 539*, 7-10.

Peña-Gómez, C., Sala-Lonch, R., Junqué, C., Clemente, I.C., Vidal, D., Bargalló, N., . . . Bartrés-Faz, D. (2012). Modulation of large-scale brain networks by transcranial direct current stimulation evidenced by resting-state functional MRI. *Brain Stimul., 5*(3), 252-263.

Pereira, F., Mitchell, T., & Botvinick, M. (2009). Machine learning classifiers and fMRI: a tutorial overview. *NeuroImage, 45*(1 Suppl), S199-209. doi: 10.1016/j.neuroimage.2008.11.007

Petersen, S. E., & Dubis, J. W. (2012). The mixed block/event-related design. *NeuroImage, 62*(2), 1177-1184. doi: 10.1016/j.neuroimage.2011.09.084

Power, J.D., Cohen, A.L., Nelson, S.M., Wig, G.S., Barnes, K.A., Church, J.A., . . . Schlaggar, B.L. (2011). Functional network organization of the human brain. *Neuron, 72*(4), 665-678.

Ragland, J.D., Turetsky, B.I., Gur, R.C.., Gunning-Dixon, F., Turner, T., Schroeder, L., . . . Gur, R.E. (2002). Working memory for complex figures: an fMRI comparison of letter and fractal n-back tasks. *Neuropsychology, 16*(3), 370.

Rahman, A., Reato, D., Arlotti, M., Gasca, F., Datta, A., Parra, L.C., & Bikson, M. (2013). Cellular effects of acute direct current stimulation: somatic and synaptic terminal effects. *J. Physiol., 591*(10), 2563-2578.

Raichle, M. E. (2015). The brain's default mode network. *Annu Rev Neurosci, 38*, 433-447. doi: 10.1146/annurev-neuro-071013-014030

Raichle, M.E., MacLeod, A.M., Snyder, A.Z., Powers, W.J., Gusnard, D.A., & Shulman, G.L. (2001). A default mode of brain function. *P. Natl. Acad. Sci. USA, 98*(2), 676-682.

Ramnani, N., & Owen, A.M. (2004). Anterior prefrontal cortex: insights into function from anatomy and neuroimaging. *Nat. Rev. Neurosci., 5*(3), 184-194.

Ranganath, C., Johnson, M.K., & D'Esposito, M. (2000). Left anterior prefrontal activation increases with demands to recall specific perceptual information. *J. Neurosci., 20*(22), 19-57.

Reynolds, J.R., McDermott, K.B., & Braver, T.S. (2006). A direct comparison of anterior prefrontal cortex involvement in episodic retrieval and integration. *Cereb. Cortex, 16*(4), 519-528.

Rissman, J., Greely, H.T., & Wagner, A.D. (2010). Detecting individual memories through the neural decoding of memory states and past experience. *P. Natl. Acad. Sci. USA, 107*(21), 9849-9854.

Rissman, J., & Wagner, A.D. (2012a). Distributed representations in memory: insights from functional brain imaging. *Annual review of psychology, 63*, 101-128.

Rissman, J., & Wagner, A.D. (2012b). Distributed representations in memory: insights from functional brain imaging. *Annu. Rev. Psychol., 63*, 101-128.

Rive, M.M., van Rooijen, G., Veltman, D.J., Phillips, M.L., Schene, A.H., & Ruhé, H.G. (2013). Neural correlates of dysfunctional emotion regulation in major depressive disorder. A systematic review of neuroimaging studies. *Neurosci. Biobehav. R., 37*(10), 2529-2553.

Rubinov, M., & Sporns, O. (2010). Complex network measures of brain connectivity: uses and interpretations. *NeuroImage, 52*(3), 1059-1069.

Rugg, M. D., & Vilberg, K. L. (2013). Brain networks underlying episodic memory retrieval. *Curr Opin Neurobiol, 23*(2), 255-260. doi: 10.1016/j.conb.2012.11.005

Sakai, K., & Passingham, R.E. (2002). Prefrontal interactions reflect future task operations. *Nat. Neurosci., 6*(1), 75-81.

Sakai, K., & Passingham, R.E. (2006). Prefrontal set activity predicts rule-specific neural processing during subsequent cognitive performance. *J. Neurosci., 26*(4), 1211-1218.

Schedlbauer, A.M., Copara, M.S., Watrous, A.J., & Ekstrom, A.D. (2014). Multiple interacting brain areas underlie successful spatiotemporal memory retrieval in humans. *Scientific reports, 4*.

Scheibe, S., & Blanchard-Fields, F. (2009). Effects of regulating emotions on cognitive performance: what is costly for young adults is not so costly for older adults. *Psychol. Aging, 24*(1), 217.

Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., . . . Greicius, M. D. (2007). Dissociable intrinsic connectivity networks for salience processing and executive control. *J. Neurosci., 27*(9), 2349-2356. doi: 10.1523/JNEUROSCI.5587-06.2007

Sheline, Y.I., Barch, D.M., Price, J.L., Rundle, M.M., Vaishnavi, S.N., Snyder, A.Z., . . . Raichle, M.E. (2009). The default mode network and self-referential processes in depression. *P. Natl. Acad. Sci. USA, 106*(6), 1942-1947.

Shirer, W.R., Ryali, S., Rykhlevskaia, E., Menon, V., & Greicius, M.D. (2012). Decoding subject-driven cognitive states with whole-brain connectivity patterns. *Cereb. Cortex, 22*(1), 158-165.

Siegle, G.J., Ghinassi, F., & Thase, M.E. (2007). Neurobehavioral therapies in the 21st century: Summary of an emerging field and an extended example of cognitive control training for depression. *Cognitive Ther. Res., 31*(2), 235-262.

Siegle, G.J., Steinhauer, S.R., Thase, M.E., Stenger, V.A., & Carter, C.S. (2002). Can't shake that feeling: event-related fMRI assessment of sustained amygdala activity in response to emotional information in depressed individuals. *Biol. Psychiat., 51*(9), 693-707.

Simons, J.S., Gilbert, S.J., Owen, A.M., Fletcher, P.C., & Burgess, P.W. . (2005). Distinct roles for lateral and medial anterior prefrontal cortex in contextual recollection. *J. Neurophysiol., 94*(1), 813-820.

Simons, J.S., Henson, R.N.A., Gilbert, S.J., & Fletcher, P.C. . (2008). Separable forms of reality monitoring supported by the anterior prefrontal cortex. *J. Cognitive Neurosci., 20*(3), 447-457.

Smallwood, J.M., Brown, K., Baird, B., & Schooler, J.W. (2012). Cooperation between the default mode network and the frontal–parietal network in the production of an internal train of thought. *Brain Res., 1428*, 60-70.

Snodgrass, J.G., & Corwin, J. (1988). Pragmatics of measuring recognition memory: applications to dementia and amnesia. *J. Exp. Psychol. Gen., 117*(1), 34.

Sporns, O., & Betzel, R. F. (2016). Modular Brain Networks. *Annu Rev Psychol, 67,* 613-640. doi: 10.1146/annurev-psych-122414-033634

Spreng, R. N., Sepulcre, J., Turner, G.R., Stevens, W.D., & Schacter, D. L. (2013). Intrinsic architecture underlying the relations among the default, dorsal attention, and frontoparietal control networks of the human brain. *J Cogn Neurosci, 25*(1), 74-86.

Spreng, R.N., Stevens, W.D., Chamberlain, J.P., Gilmore, A.W., & Schacter, D.L. . (2010). Default network activity, coupled with the frontoparietal control network, supports goal-directed cognition. *NeuroImage, 53*(1), 303-317.

Stanley, M.L., Dagenbach, D., Lyday, R.G., Burdette, J.H., & Laurienti, P.J. (2014). Changes in global and regional modularity associated with increasing working memory load. *Frontiers in human neuroscience, 8*.

Stevens, A. A., Tappon, S. C., Garg, A., & Fair, D. A. (2012). Functional brain network modularity captures inter- and intra-individual variation in working memory capacity. *PloS one, 7*(1), e30468. doi: 10.1371/journal.pone.0030468

Teyler, T.J., & Rudy, J.W. (2007). The hippocampal indexing theory and episodic memory: updating the index. *Hippocampus, 17*(12), 1158-1169.

Todd, M.T., Nystrom, L.E., & Cohen, J.D. (2013). Confounds in multivariate pattern analysis: Theory and rule representation case study. *NeuroImage, 77*(15), 157-165.

Tomasi, D., Ernst, T., Caparelli, E.C., & Chang, L. (2006). Common deactivation patterns during working memory and visual attention tasks: An intra‐subject fMRI study at 4 Tesla. *Hum. Brain Mapp., 27*(8), 694-705.

Tong, F., & Pratte, M.S. (2012). Decoding patterns of human brain activity. *Annu. Rev. Psychol., 63*, 483-509.

Van Essen, D. C. (2005). A Population-Average, Landmark- and Surface-based (PALS) atlas of human cerebral cortex. *NeuroImage, 28*(3), 635-662. doi: 10.1016/j.neuroimage.2005.06.058

Vatansever, D., Menon, D.K., Manktelow, A.E., Sahakian, B.J., & Stamatakis, E.A. (2015). Default mode dynamics for global functional integration. *J. Neurosci., 35*(46), 15254-15262.

Velanova, K., Jacoby, L.L., Wheeler, M.E., McAvoy, M.P., Petersen, S.E., & Buckner, R.L. (2003). Functional–anatomic correlates of sustained and transient processing components engaged during controlled retrieval. *J. Neurosci., 23*(24), 8460-8470.

Vendetti, M.S., & Bunge, S.A. (2014). Evolutionary and Developmental Changes in the Lateral Frontoparietal Network: A Little Goes a Long Way for Higher-Level Cognition. *Neuron, 84*(5), 906-917.

Vincent, J.L., Kahn, I., Snyder, A.Z., Raichle, M.E., & Buckner, R.L. . (2008). Evidence for a frontoparietal control system revealed by intrinsic functional connectivity. *J. Neurophysiol., 100*(6), 3328-3342.

Vincent, J.L., Snyder, A.Z., Fox, M.D., Shannon, B.J., Andrews, J.R., Raichle, M.E., & Buckner, R.L. (2006). Coherent spontaneous activity identifies a hippocampal-parietal memory network. *J. Neurophysiol., 96*(6), 3517-3531.

Visscher, K.M., Miezin, F.M., Kelly, J.E., Buckner, R.L., Donaldson, D.I., McAvoy, M.P., . . . Petersen, S.E. (2003). Mixed blocked/event-related designs separate transient and sustained activity in fMRI. *NeuroImage, 19*(4), 1694-1708.

Vitali, P., Avanzini, G., Caposio, L., Fallica, E., Grigoletti, L., Maccagnano, E., . . . Villani, F. (2002). Cortical location of 10-20 system electrodes on normalized cortical MRI surfaces. *Int. J. Bioelectromagn., 4*, 147-148.

Volle, E., Gilbert, S.J., Benoit, R.G., & Burgess, P.W. (2010). Specialization of the rostral prefrontal cortex for distinct analogy processes. *Cereb. Cortex, 20*(11), 2647-2659.

Wagner, A.D., Paré-Blagoev, E.J., Clark, J., & Poldrack, R.A. (2001). Recovering meaning: left prefrontal cortex guides controlled semantic retrieval. *Neuron, 31*(2), 329-338.

Wagner, A.D., Shannon, B.J., Kahn, I., & Buckner, R.L. (2005). Parietal lobe contributions to episodic memory retrieval. *Trends Cogn. Sci., 9*(9), 445-453.

Watson, C.E., & Chatterjee, A. (2012). A bilateral frontoparietal network underlies visuospatial analogical reasoning. *NeuroImage, 59*(3), 2831-2838.

Weissman, D.H., Roberts, K.C., Visscher, K.M., & Woldorff, M.G. (2006). The neural bases of momentary lapses in attention. *Nat. Neurosci., 9*(7), 971-978.

Wendelken, C., & Bunge, S.A. . (2010). Transitive inference: distinct contributions of rostrolateral prefrontal cortex and the hippocampus. *J. Cognitive Neurosci., 22*(5), 837-847.

Wendelken, C., Bunge, S.A., & Carter, C.S. (2008). Maintaining structured information: an investigation into functions of parietal and lateral prefrontal cortices. *Neuropsychologia, 46*(2), 665-678.

Wendelken, C., Chung, D., & Bunge, S.A. (2012). Rostrolateral prefrontal cortex: Domain‐general or domain‐sensitive? *Hum. Brain Mapp., 33*(8), 1952-1963.

Wendelken, C., Nakhabenko, D., Donohue, S.E., Carter, C.S., & Bunge, S.A. (2008). "Brain Is to Thought as Stomach Is to??": Investigating the role of rostrolateral prefrontal cortex in relational reasoning. *J. Cognitive Neurosci., 20*(4), 682-693.

Westphal, A.J., Reggente, N., Ito, K., & Rissman, J. (2016). Shared and distinct contributions of rostrolateral prefrontal cortex to analogical reasoning and episodic memory retrieval. *Hum. Brain Mapp., 37*(3), 896-912. doi: 10.1002/hbm.23074

Westphal, A.J., Wang, S., & Rissman, J. (2017). Episodic memory retrieval benefits from a less modular brain network organization. *J. Neurosci., 37*(13), 3523-3531. doi: 10.1523/jneurosci.2509-16.2017

Worsley, K.J., Taylor, J.E., Tomaiuolo, F., & Lerch, J. (2004). Unified univariate and multivariate random field theory. *NeuroImage, 23*(1), 189.

Young, K.D., Erickson, K., & Drevets, W.C. (2012). Differential effects of emotionally versus neutrally cued autobiographical memories on performance of a subsequent cognitive task: effects of task difficulty. *Front. Psychol., 3*, 299.