2021

Combining MEG and FMRI to Examine Dynamic Task-Related Brain Activity with High Spatio-Temporal Resolution

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Recommended Citation

Nair, Sangeeta, "Combining MEG and FMRI to Examine Dynamic Task-Related Brain Activity with High Spatio-Temporal Resolution" (2021). *All ETDs from UAB*. 629.
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COMBINING MEG AND FMRI TO EXAMINE DYNAMIC TASK-RELATED BRAIN ACTIVITY WITH HIGH SPATIO-TEMPORAL RESOLUTION

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A DISSERATION

Submitted to the graduate faculty of The University of Alabama at Birmingham,
in partial fulfillment of the requirements for the degree of
Doctor of Philosophy

BIRMINGHAM, ALABAMA

2021

COMBINING MEG AND FMRI TO EXAMINE DYNAMIC TASK-RELATED BRAIN ACTIVITY WITH HIGH SPATIO-TEMPORAL RESOLUTION

SANGEETA NAIR

BEHAVIORAL NEUROSCIENCE

ABSTRACT

The characterization of brain networks contributing to healthy learning and memory can inform abnormalities and treatment approaches among clinical populations. A recent shift from lesion-based to network-based approaches of studying healthy and atypical brain development highlights the need for a more comprehensive understanding across spatiotemporal domains, particularly in the case of high-level cognitive processes. Both, associative learning and working memory involve distributed and interconnected networks of specialized brain regions. Dynamic communication within- and between- such systems are unable to be fully resolved by individual non-invasive imaging techniques such as fMRI or MEG. While fMRI serves as an ideal tool to investigate spatial contributions underlying sustained neural activity related to a task, MEG provides temporal resolution unparalleled by hemodynamic methods.

A framework aimed to integrate these complementary methods should be flexible enough to account for inconsistencies between the intrinsic sensitivities of fMRI and MEG and it should encourage a distributed solution that best captures the complex neural activity often spanning fronto-temporal areas.

This dissertation aims to develop a co-processing stream that integrates information from fMRI and MEG tasks in a data-driven manner to investigate the effects of a multimodal approach in evaluating high-level cognitive processes. The first aim was to characterize networks underlying associative learning and examine the effects of age, sex, and handedness on active and passive learning. We found broad fronto-parietal activity contributed to self-generation with that activity within specific task-related brain areas modulated by sex and age.

The second aim was to integrate fMRI and MEG data from the same paired-associate learning task within a Bayesian framework to improve temporal visualization of nodes within relevant networks. This work provided an implementable framework to merge such datasets, which was tested on an event-related Sternberg memory task within the third aim. Across studies, this work also shed light on what information may be gained by constraining MEG inverse solutions with fMRI spatial priors. Some benefits of incorporating fMRI spatial information to MEG source reconstruction include the ability to detect additional contributing brain areas during learning and memory, and to better characterize information flow between relevant brain areas.

Keywords: neuroimaging, fMRI, MEG, active generation, associative learning, verbal memory

DEDICATION

This work is dedicated to my parents, Nalini and Nikhilanand Nair, who wrote in a card at my undergraduate graduation: “Congratulations! Now go do more!” – Here it is. Your eternal encouragement and support have made me the person I am today. And to my dearest ammamma, Dr. Sati Nair, who paved the way with her deep value for education and own pursuit of doctorate studies. Whether or not warranted, she has believed in me since the day I was born, and it is a true honor to follow in her footsteps.

ACKNOWLEDGEMENTS

"Jump off the cliff and learn how to make wings on the way down."

– Ray Bradbury

It is an immense task to recite all who played a marked role in developing my wings these past five years. An unfortunate consequence of which being that this was always going to be an incomplete list of gratitude.

To my advisor Dr. Jerzy Szalfarski, who has been an incredible mentor to me across professional and personal domains. Thank you for your continuous support and guidance, especially through the most challenging hurdles of life and graduate school. I am forever grateful to have had the opportunity to work under someone as knowledgeable, passionate and prolific as yourself (with a sense of humor to boot!).

To my committee, who have offered immense patience and support throughout this process. I would especially like to thank Dr. Yingying Wang for taking the time to share valuable technical knowledge and feedback.

Thank you to past and present members of the Epilepsy Research Center. To Dr. Goodman for the much-needed coffee breaks and treasured advice. To Dr. Jane

Allendorfer for the years of spontaneous problem solving and constructive comments. And to Dr. Nenert for always willing to spend time teaching me something new.

To the UAB EPSCoR team, Drs. Mohammed, Gawne, Martin and Diana Pizarro, thank you for welcoming me into your project family with open arms. A special thank you to Jeffery Killen, who not only made data collection possible but deeply gratifying. I will forever cherish our long conversations in the MEG lab and am thankful for the life lessons, gained perspectives, and endless support your friendship has offered.

Thank you to Dr. Lawson, UAB EPSCoR, and the GRSP Scholars, whose financial and scientific contributions made this work possible. To the UAB Behavioral Neuroscience program director, Dr. Knight, for his academic guidance and direction. To Drs. Fishman, Müller, and Marinkovik of San Diego State University who sparked a fierce curiosity early in my graduate career by imparting their extensive knowledge and contagious enthusiasm.

To the lifelong friends made on this journey, Melissa, Lacy, Stephanie and Eliana, with whom I’ve shared laughs that hurt, tears that soothe, and conversations that have helped me grow. Thank you for coming through on the countless occasions I needed to be pulled up and dusted off to move forward.

To the Birmingham maker and small business communities, thank you for providing the healthiest, most rewarding creative outlet during my time here. These relationships and opportunities granted me a unique type of support that, at many times, my graduate studies were unable to offer.

Thank you to my parents, my friends and family who have encouraged me along the way. A special thank you to my dear husband Greg, for being my pillar of strength throughout these years. I truly could not have done this without your unyielding support and the quintessential calm, grounding stability you provide. To our sweet animals for bringing endless levity, love, and joy to my life, especially when I didn’t feel like smiling.

I consider myself so lucky to have such a rich network of thoughtful, intelligent, kind people behind everything I do.

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LIST OF ABBREVIATIONS

AFNI	Analysis of Functional NeuroImages software
ACC	anterior cingulate cortex
BOLD	blood oxygen level dependent
CRUNCH	Compensation-Related Utilization of Neural Circuits Hypothesis
DMN	default mode network
dlPFC	dorsolateral prefrontal cortex
EEG	electroencephalography
ERP	event-related potentials
FSL	FMRI software library
FA	fractional anisotropy
FWHM	full width half maximum
fMRI	functional magnetic resononance imaging
GIFT	Group ICA fMRI Toolbox
HAROLD	Hemispheric Asymmetry Reduction in OLder ADults
HERA	Hemispheric Encoding/Retrieval Asymmetry
HRF	hemodynamic response function
HUSH	Hemodynamics Unrelated to Sounds from Hardware
IC	independent component
ICA	independent component analysis

IFG	inferior frontal gyrus
IPL	inferior parietal lobe
MEG	magnetoencephalography
MFG	middle frontal gyrus
MTG	middle temporal gyrus
MNI	Montreal Neurological Institute
MSP	Multiple Sparse Priors
OFC	orbitofrontal cortex
PET	positron emission tomography
PCC	posterior cingulate cortex
PFC	prefrontal cortex
PCA	principle component analysis
SM	spatial map
SLF	superior longitudinal fasciculus
SPL	superior parietal lobe
STG	superior temporal gyrus
SMA	supplementary motor area
SMG	supramarginal gyrus
WM	working memory

INTRODUCTION

"See that the imagination of nature is far, far greater than the imagination of man."

– Richard P. Feynman

Dynamics of Memory

The process of memory formation has been well investigated and informed by various types of lesion, animal, behavioral, and neuroimaging studies. Human memory is divided into three major stages: sensory memory, short-term (or working) memory, and long-term memory (Squire and Zola 1996). Recent efforts have focused on evaluating the neuroanatomical and functional underpinnings of verbal learning and memory. In general, the learning and memory processes are complicated as they involve concurrent and sequential events with several brain structures and their connections all of which are important for successful encoding and/or learning. The nodes of this network include bilateral pre/frontal cortices, cingulate, and medial and lateral temporal regions (Krause et al. 1999; Mottaghy et al. 1999). In healthy controls, the process of word-pair learning studied with PET revealed strong linkages within the left hemisphere (Krause et al. 1999) and this was confirmed with fMRI (Mottaghy et al. 1999). FMRI relies on an endogenous contrast agent related to regional blood flow and can identify active brain regions that contribute to different cognitive and behavioral tasks with high spatial resolution. To date, the memory processes of encoding, retrieval, and familiarity have been evaluated with various fMRI tasks. Active learning via self-generation of information engages a wide range of cognitive functions, suggesting the recruitment of distributed, highly connected networks. A meta-analysis of successful memory effects across fMRI studies indicated substantial involvement of a broad fronto-temporal network including left inferior frontal cortex, insula, bilateral fusiform gyrus, and left medial temporal cortex (Kim 2011). More specifically, areas implicated in encoding and retrieval include inferior frontal gyrus (IFG) in long term memory (Poldrack et al. 1999; Baker et al. 2001) and lexical-semantic response selection (S L Thompson-Schill et al. 1997; Sharon L. Thompson-Schill, D'Esposito, and Kan 1999), dorsolateral prefrontal cortex in manipulating visuospatial information and memory formation (Paller and Wagner 2002), anterior cingulate cortex in conflict monitoring and attention (van Veen et al. 2001; Botvinick, Cohen, and Carter 2004; Moss et al. 2011), middle temporal gyrus in item analysis (Binder et al. 2009; R Cabeza and Nyberg 2000), and parahippocampal areas in encoding novel stimuli (Otten, Henson, and Rugg 2001).

In terms of lateralization, studies of healthy participants have clearly documented left fronto-temporo-occipital network involvement in immediate and delayed retrieval of verbal information (Dupont et al. 2002; Konishi et al. 2000). While various brain areas are involved in the learning process, hippocampi, parahippocampal gyri, dorso-lateral-prefrontal and lateral temporo-parietal cortex are most frequently identified in these studies. Other studies in healthy controls, including studies by our group, evaluated the process of verbal memory retrieval (Dupont et al. 2001; Eliassen, Holland, and Szaflarski

2008; Vannest et al. 2012) and also documented similar left-hemispheric network involvement.

While studying healthy brains provides tremendous insight into the processes required for efficient and effortless conduction of memory processes, the effects of disease states on these processes provide additional and invaluable information that can be later converted into developing specific interventions designed to alleviate such problems. For example, studies of retrieval and/or familiarity have documented differential effect of epilepsy on these processes. Due to the brain areas underlying memory processes being also involved in seizure generation, impairments in episodic memory is expected in patients with temporal lobe epilepsy (TLE) (Squire et al. 2015). The presence of such deficits in memory among patients with frontal lobe epilepsy (FLE) suggests that additional mechanisms associated with seizure propagation may be at play (Nair and Szaflarski 2020). The temporal resolution of fMRI alone does not allow for the direct assessment of the dynamics underlying relevant brain networks, raising questions around differential within-network communication among patients with focal epilepsies. An applicable framework aimed to fill this knowledge gap is crucial for understanding the distributed processes of verbal memory and developing interventions that may alleviate abnormalities within those networks.

Multimodal Neuroimaging

As an indirect measure of brain activity, fMRI primarily reflects oxygen consumption and metabolic neural activity, and is often used to identify regions of sustained neural activity with high spatial resolution (within millimeters) (Brown et al.

2007; Buxton et al. 2004; Logothetis et al. 2001). In recent years, fMRI has gained attention as a tool to investigate healthy brain development (Fair et al. 2009; Bressler and Menon 2010), functional connectivity underlying sensory and high-level cognitive functions (Bassett and Bullmore 2006; Sporns 2011; Kim 2011), network abnormalities across various clinical populations (Griffis et al. 2017; Allendorfer et al. 2013; S Nair 2016), and evaluating intervention and treatment effects over time (Gaston et al. 2020; Martin et al. 2019a; Murdaugh, Maximo, and Kana 2015).

Potential reasons for an increase in fMRI studies are multifold: as many clinical and research institutions have access to a 1.5T or 3T MRI scanner, fMRI is a widely available and implementable technique (Brown et al. 2007). Unlike positron emission tomography (PET), which is also grounded in principles of cerebral blood flow and metabolism, fMRI does not use radioactive isotopes due to its reliance on intrinsic contrast agents and, thus, it allows for the safe investigation of functional connectivity across time. Additionally, the rising popularity of resting-state fMRI (rs-fMRI) addresses a common practical concern among clinical research groups assessing differences in functional brain networks. Resting-state approaches allow for the elucidation of brain networks without placing complicated task demands on individuals who may otherwise be not be able to perform such task, greatly expanding the applicability of fMRI within various clinical populations (Lottman et al., 2019; Nair et al., 2018). As fMRI is broadly identified as a hemodynamic imaging technique, information gained about neural processing is largely dependent on a complex relationship between cerebral blood flow and oxidative metabolism (Buxton 2013; Buxton et al. 2004) and therefore limited in the information it can provide within the temporal domain. Neuronal activity takes place on the order of milliseconds, which is considerably faster than the 5-7 second hemodynamic response function (HRF) on which fMRI relies. Thus, hemodynamic approaches to brain function are unable to capture rapidly shifting or dynamic brain activity often underlying high-level cognitive processes. Previously described fMRI studies of healthy controls illustrate brain networks that contribute to various associative learning and working memory processes, but less is known of the dynamic communication between nodes in these networks and the effects of disease states on them.

Magnetoencephalography (MEG) and/or electroencephalography (EEG) are particularly well suited to answer questions regarding the timing of brain activity and information transfer. Both techniques measure neuronal activity and thus can preserve the timescale of such activity. EEG measures electric fields at the scalp surface, but different layers of tissue between the brain and scalp may distort the signal and make it difficult to localize the source of the measured activity (also called the “inverse problem”). MEG, often considered the magnetic equivalent of EEG, does not suffer from the same distortions and difficulties with solving the inverse problem (Hämäläinen 1992a). Foundations of MEG are based on the right-hand rule principle where electrical currents generated by postsynaptic neural activity produce a perpendicular magnetic field and small, but measurable magnetic signals at the scalp surface. Unlike electrical currents, these magnetic fields are not distorted by inhomogeneous layers of tissue, skull, and scalp between the brain and measuring device, rendering the determination of sources from MEG data much simpler and more reliable than with EEG. Though MEG has spatiotemporal strengths compared to EEG, the spatial resolution of MEG is still limited when compared to fMRI.

FMRI and MEG can be viewed as complementary methods due to their relative strengths, though they represent and measure different aspects of brain function (R. N. Henson et al. 2011; Hämäläinen 1992b; Brown et al. 2007; Dale et al. 2000). Studies that have directly compared the localizing ability of MEG and fMRI suggest the inclusion of fMRI constraints in inverse models of MEG source reconstruction may be beneficial (Wang, Holland, and Vannest 2012; Sharon and Hamalainen 2007). Sharon and Hamalainen, in a study directly comparing EEG, MEG, and EEG+MEG solutions to fMRI found the combination of EEG and MEG improved localization greater than either technique alone (Sharon and Hamalainen 2007). They demonstrated that superior localization, afforded by the combined approach, was not driven by an increased total number of sensors. This suggests that complementary physical properties of EEG and MEG enhance localization accuracy. Further, the correspondence between approaches supports the potential use for fMRI constraints within MEG and/or EEG data. Wang and colleagues (2012) evaluated spatial concordance between sources identified with fMRI and MEG during a verb generation task (Wang, Holland, and Vannest 2012) and found convergence across several well-established language areas. Although there was a considerable spatial overlap between modalities, areas of disagreement between the techniques highlighted the difference in sensitives of each method to brain activity.

The induced activity underlying high-order cognitive processes involves complex, integrated responses between distal brain areas. As such, it can be difficult to resolve source localization with existing inverse solutions that isolate a small number of focal sources (Wang, Holland, and Vannest 2012). Successful studies utilizing the strengths of both MEG and fMRI have largely focused on sensory or motor processing (Ahlfors et al.

1999; Auranen et al. 2009; Schulz et al. 2004; Tuunanen et al. 2003; Stippich et al. 1998), and resting state (Lottman et al. 2019). To date, only few studies have examined higher cognitive functions e.g., memory or language (Wang, Holland, and Vannest 2012; Dale et al. 2000; Stefan and da Silva 2013).

As both associative learning and working memory involve specialized networks comprised of distal brain regions, it is critical that approaches integrating fMRI and MEG allow for distributed source solutions and address areas of inconsistencies between modalities. Bayesian integration schemes like the parametric empirical Bayesian (PEB) framework for MEG source inversion use a probabilistic model that incorporates constraints (e.g. fMRI spatial priors) to determine an optimal source solution (R. N. Henson et al. 2011; R.N. Henson et al. 2009). In particular, the Multiple Sparse Priors (MSP) approach addresses concerns of widespread, whole-brain activity during high-order cognitive tasks: The data-driven nature of MSP automatically selects a sparse or distributed model that best characterizes complex neural activity. MSP also handles disagreement between modalities flexibly: The source solution must give high data likelihood (in terms of MEG) and be probable under the constraints of the priors (in terms of fMRI). MSP also allows for differential weighting of prior spatial information as "soft" constraints, which does not require a direct correspondence between MEG and fMRI sources (Baillet and Garnero 1997; R. N. Henson et al. 2011).

Possible Future Applications

Focal epilepsies account for 60-70% of all epilepsies (Jokeit, Bosshardt, and Reed 2011), and patients with temporal or frontal lobe epilepsies suffer from cognitive deficits across one or more domains including attention, memory and learning, mental processing, and executive functioning (Black et al. 2010; Dodrill 1986; Helmstaedter, Elger, and Lendt 1994; Kent et al. 2006a; Mitchell et al. 1992; Seidenberg et al. 1986). Traditional approaches to identifying epileptic tissue for resection primarily involved establishing the ictal onset zone, but there has been a steady shift over time from a "zone" to a "network" approach that better characterizes the complex, interregional interactions across the brain.

A network perspective is especially appropriate in understanding focal epilepsies: Atypical neural synchronization within focal areas affects whole brain, system-level dynamics (Spencer 2004; Burman and Parrish 2018; Fahoum et al. 2012), and functional regions that exhibit certain deficits can produce permanent neurological and psychological effects during interictal periods that may extend beyond the ictal onset zone (Laufs 2012). Difficulties with memory are the most frequent complaints in patients with epilepsy and can often serve as barriers to completing education and gainful employment and the negatively impact quality of life (Zhao et al. 2014; Black et al. 2010; Kent et al. 2006b). A network perspective to focal epilepsies, coupled with a data processing stream to identify spatiotemporal characteristics underling whole-brain networks expands upon traditional lesion-based approaches and may allow for a better understanding of widespread neurological effects, behavioral deficits, and inform intervention approaches (Diessen, Zweiphenning, and Jansen 2014; Kramer and Cash 2013).

Research Aims

Current work in the UAB Epilepsy Research Center focuses on evaluating the temporal and spatial characteristics of cognitive processes in persons with epilepsy to understand the effects of epilepsy and intervention on these processes. While the current focus is on evaluating network contributions in epilepsy, questions regarding ideal multimodal approaches remain unaddressed. We aimed to develop a data processing stream using cognitive data from healthy controls that could be applied to future studies of network abnormalities and behavioral deficits in persons with epilepsy. The questions informing this work include:

(1) What is the optimal data-driven method to derive regions of interest underlying a sparse-acquisition, verbal working memory fMRI task,

(2) How to optimally combine two imaging modalities (fMRI and MEG) in one robust analysis stream to provide better understanding of associative learning processes, and

(3) Can this pipeline be applied to data with a classic event-related design to better characterize the spatiotemporal correlates of working memory in healthy individuals?

Our overarching hypothesis is that a multimodal approach to associative learning and working memory within the MSP framework will yield improved spatiotemporal estimates than either method alone.

Manuscript 1 – The purpose of this study was to develop and employ a data-driven method to identify robust task-related networks underlying associative learning in a large sample of healthy individuals (n=174). We also examined the effects of sex, age, and handedness of the neural correlates of active and passive learning.

Manuscript 2 – The primary goal of this study was to develop a data processing stream that combined fMRI and MEG associative learning data to maximize the strengths of each modality within a Bayesian framework by applying MSP to constrain MEG source reconstructions with fMRI spatial priors. Using this technique, we expected that spatially constrained analyses of MEG data using whole-brain network analyses from fMRI would provide information about the temporal dynamics within active learning networks that was not available from fMRI or MEG data alone.

Manuscript 3 – The focus of this study was to test the established co-processing pipeline using data from a modified Sternberg task. We examined spatiotemporal characteristics of networks underlying working memory and aimed to highlight improvements seen using this constrained approach.

SEX, AGE, AND HANDEDNESS MODULATE THE NEURAL CORRELATES OF ACTIVE LEARNING

by

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Frontiers in Neuroscience 13:961

Format adapted for dissertation

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CHAPTER 1

SEX, AGE, AND HANDEDNESS MODULATE THE NEURAL CORRELATES OF ACTIVE LEARNING

Abstract

Self-generation of material compared to passive learning results improved memory performance; this may be related to recruitment of a fronto-temporal encoding network. Using a verbal paired-associate learning fMRI task, we examined the effects of sex, age, and handedness on the neural correlates of self-generation.

Data from 174 healthy English-speaking participants (78M, 56 atypically handed; ages 19–76) were preprocessed using AFNI and FSL. Independent component analysis was conducted using GIFT (Group ICA fMRI Toolbox). Forty-one independent components were temporally sorted by task time series. Retaining correlations ($r > 0.25$) resulted in three task-positive ("generate") and three task-negative ("read") components. Using participants' back-projected components, we evaluated the effects of sex, handedness, and aging on activation lateralization and localization in task-relevant networks with two-sample t -tests. Further, we examined the linear relationship between sex and neuroimaging data with multiple regression, covarying for scanner, age, and handedness.

Task-positive components identified using ICA revealed a fronto-parietal network involved with self-generation, while task-negative components reflecting passive reading

showed temporo-occipital involvement. Compared to older adults, younger adults exhibited greater task-positive involvement of the left inferior frontal gyrus and insula, whereas older adults exhibited reduced prefrontal lateralization. Greater involvement of the left angular gyrus in task-positive encoding networks among right-handed individuals suggests the reliance on left dominant semantic processing areas may be modulated by handedness. Sex effects on task-related encoding networks while controlling for age and handedness suggest increased right hemisphere recruitment among males compared to females, specifically in the paracentral lobe during self-generation and the suparmarginal gyrus during passive reading.

Identified neuroimaging differences suggest that sex, age, and handedness are factors in the differential recruitment of encoding network regions for both passive and active learning.

INTRODUCTION

Active and passive learning are the mainstays of acquiring new knowledge. Active learning involves thoughtful analysis of and engagement with new content while reading complete information is a form of passive learning that does not require engaging with the material. The benefits of active learning have been well studied, and active engagement in the classroom has been widely shown to improve retention of information, academic achievement, and self-esteem (Prince, 2004; Schefft and Biederman, 1990; Springer et al., 1999).

Active Learning

Actively learning and memorizing new, language-related information has been shown to improve retention of information over passive reading (McDaniel et al., 1988, Olofsson and Nilsson, 1992). Self-generation is a type of active learning strategy that involves the discovery and production of an item based on incomplete information. During self-generation, the individual takes a role in the process of generating the target item based on a cue, or a piece of information that aids in retrieval of the target item (Jacoby, 1978). For example, the use of mnemonic devices can aid in retrieval and bolster memory of target items among aging adults (Hill, Allen, and Gregory, 1990; Derwinger, Neely, Bäckman, 2005). There is a consensus that such active participation leads to improved outcomes compared to passive participation among healthy individuals across a range of domains including memory, coordination of selective attention, mood state, self-esteem, and with generalization of new knowledge (Markant et al., 2016; Schefft and Biederman, 1990; Walsh et al., 1995). Self-generation techniques have been shown to also improve memory across numerous clinical groups, including Alzheimer's disease and dementia (Lipinska et al., 1994; Souliez et al., 1996, Barrett et al., 2000), Parkinson's disease (Barrett et al., 2000), traumatic brain-injury (Schefft et al., 2008a), epilepsy (Schefft et al., 2008b), and aphasia (Marshall et al., 1994).

The benefit of active over passive learning is due to the nature of the process itself: generation is a problem-solving task where one obtains the solution by engaging in some series of operations (e.g. finding relations among cues). Several cognitive mechanisms by which generation improves retention have been proposed (Nyberg, 2002; Otten et al., 2001; Craik, 2002). For example, the process of active self-generation increases distinctiveness or relevance of target words compared to read words and thus increases retention of the target words (McDaniel et al., 1988; Walsh et al., 1995). Or, enhanced memory may be the result of improved self-esteem by having successfully solved a problem (Olofsson and Nilsson, 1992). Another postulated mechanism states that enhanced retention and memory from self-generation may be due to a deeper level of cognitive processing required for active compared to passive reading (Craik & Lockhart., 1972, Craik, 2002, Lespinet-Najib et al., 2004).

Neural correlates of active learning and deep semantic processing

Neuroimaging studies have reported recruitment of a frontal and medial temporal encoding network during tasks requiring a deeper level of processing (Otten et al., 2001;

Nyberg 2002). Across a range of tasks that demand deep semantic processing and attention, greater activity in the left prefrontal cortex has been associated with better memory performance (Kapur et al., 1994; Demb et al., 1995; Shallice et al., 1994; Buckner et al., 1999; McDermott et al., 1999). Additional cortical and subcortical regions implicated in successful encoding of new information include bilateral lingual, fusiform, inferior frontal, and parahippocampal gyri, premotor and medial parietal cortices, anterior cingulate cortex, thalami, and left insula (Kapur et al., 1995; Fletcher & Henson, 2001; Szaflarski et al., 2004; Kim 2011). One neuroimaging study examined brain areas involved in shallow vs. deep semantic processing to suggest the bilateral inferior prefrontal cortex and left anterior and posterior hippocampus to be differentially activated depending on the depth of processing, particularly in verbal memory encoding (Otten et al., 2001). Successful non-semantic encoding (alphabetical task) was shown to recruit a specific subset of brain regions (Otten et al., 2001). Similar studies employing tasks isolating semantic vs. shallow processing have found that deeper semantic processing was associated with increased activity in the left prefrontal regions (Kapur et al., 1994; Grady et al., 1998; Buckner et al., 2000; Cabeza and Nyberg, 2000). It has been suggested that encoding of verbal/semantic information may be left lateralized, while nonverbal encoding (e.g. scenes) may involve bilateral recruitment (Nyberg et al., 1996).

Lateralization effects have also been seen with episodic memory encoding and retrieval, described via the HERA model (Hemispheric Encoding/Retrieval Asymmetry; Tulving et al., 1994; Nyberg et al., 1996). Originally described in young participants, the HERA model purports hemispheric asymmetry of the prefrontal cortex (PFC), finding more involvement of the left PFC during encoding of episodic long-term memory and recruitment of right PFC during retrieval of episodic long-term memory (Tulving et al., 1994). However, the HERA model did not generalize to older populations, where bilateral PFC involvement was seen during both encoding and retrieval stages of an episodic memory task (Cabeza et al., 1997a, b). Lateralization may also be related to age (Allendorfer et al., 2012a; Szaflarski et al., 2006, 2012) with this concept resulting in the development of the HAROLD (Hemispheric Asymmetry Reduction in OLder ADults) model of functional lateralization (Cabeza, 2002; Nenert et al., 2017; See Section 1.4).

Active learning is a top-down approach to problem solving that, depending on the task, can involve a range of cognitive functions including attention, cognitive effort, item distinctiveness, working memory, and semantic and conceptual processing (Rosner et al., 2013). It engages a wide range of cognitive functions, suggesting distributed and highly connected networks. Theories of executive control and working memory suggest prefrontal regulation of posterior brain activity (Miller and Cohen, 2001; Shimamura, 2008), and a broad fronto-temporal network has been supported by neuroimaging findings from other groups (Nyberg, 2002; Kirchoff & Buckner, 2006; Qin et al., 2007; Otten et al., 2001). Specifically, studies of encoding and retrieval have reported recruitment of inferior frontal gyrus (IFG; long-term memory; Bookheimer, 2002; Baker et al., 2001; Poldrack et al., 1999), dorsolateral prefrontal cortex (manipulation of visuospatial information and long-term memory formation; Frith et al., 1991; Paller and Wagner, 2003), cingulate gyrus (conflict monitoring, attention; van Veen et al., 2001; Botvinick et al., 2004), middle temporal gyrus (verbal or item analysis; Binder et al., 2009; Cabeza and Nyberg, 2000), and parahippocampal areas (memory; Otten et al., 2001). Further, a meta-analysis of successful memory effects indicated broad involvement of the fronto-temporal network including the left inferior frontal cortex/insula, bilateral fusiform cortex, and left medial temporal cortex (Kim, 2011).

Finally, one study examined active learning processes via paired-associates encoding and verbal self-generated responses fMRI task (Vannest et al., 2012) to show results consistent with the depth of processing literature (Tulving et al., 1994). The nature of the self-generation condition forces participants to access knowledge of various semantic elements of both, the cue and target words, leading to deeper cognitive processing than the reading condition. Their results supported previous behavioral findings of improved memory performance in self-generation, as well as participation of left lateralized fronto-parietal areas during active encoding (Vannest et al., 2012, 2015).

Sex differences of memory and language: Lateralization and depth of processing

Sex differences in the lateralization of memory and language domains have been previously identified (Shaywitz et al., 1995). One study investigating phonological processing found that males showed strong left lateralized activation in the IFG while females had more diffuse, bilateral involvement (Shaywitz et al., 1995). In general, other studies have also supported lateralization effects across brain areas: females typically show widespread, right hemispheric involvement during semantic tasks where males show a strong left lateralized effect (Kimura, 1983; Pugh et al., 1996; Jaeger et al., 1998; Phillips et al., 2000). While cognitive strategies may differ between sexes, both often perform similarly on behavioral measures (Shaywitz et al., 1995; Berenbaum et al., 1997; Weiss et al., 2006). However, females do show some advantages in verbal memory, verbal fluency and production, and tasks with meaningful, semantic content (Andreano and Cahill, 2009; Kimura and Clarke, 2002; Kimura and Seal, 2003). As verbal fluency and lexical access depend on a number of cognitive functions and brain systems, one study examined the effect of sex when controlling for memory performance of a verb generation task (Allendorfer et al., 2012b). Their results suggest that both sexes actually display similar activation patterns when controlling for in-scanner performance, though minor differences were observed (Allendorfer et al., 2012b).

A study of event-related potentials (ERP) examining dynamics of passive language processing found that the temporal characteristics of the early stages of lexical-semantic encoding are similar among both sexes (Wirth et al., 2006). However, differences in higher-order, controlled semantic processing suggest females engage in a deeper level of processing compared to males, demonstrating faster processing of related words (as measured by the N400). There is also support for differential organization of information across sexes during verbal learning tasks (Sunderaraman et al., 2013; Kramer et al., 1988) suggesting different processing strategies during encoding (Mulligan and Lozito, 2004).

Age-related changes in self-generation

Aging has been suggested to impact the lateralization of language networks underlying semantic processing (Allendorfer et al., 2012a; Szaflarski et al., 2006, 2012). The HAROLD model proposes that language functions in the brain become less lateralized with age, which may be due to a compensatory mechanisms during aging (compensation view), or increased difficulty recruiting domain-specific neural networks (dedifferentiation view; Cabeza, 2002). Initially developed in respect to pre-frontal activity, the HAROLD model may also be generalized to temporal and parietal brain areas (Grady et al., 2002, 2000; Bellis et al., 2000).

An investigation into age-related changes in the neural bases of encoding found that although overall memory performance of self-generated words decreased among older individuals, self-generated words were better remembered compared to read words across all age groups (Vannest et al., 2015). In this study, age-related decreases in connectivity of networks associated with self-generation did not correspond to a decrease in memory performance suggesting that these networks may be less affected by age-related "dedifferentiation" (less specialization of a network; Cabeza, 2002). A potential effect of dedifferentiation may be reduced lateralization seen in older adults during implicit memory tests (Bergerbest et al., 2009), where they tend to show bilateral brain activation in domains that younger adults show strong unilateral activation (Szaflarski et al., 2006; Logan et al., 2002; Morcom et al., 2003; Rosen at al., 2002).

Impact of handedness on semantic encoding and retrieval

Handedness and language lateralization are linked genetically (Szaflarski et al., 2002; Szaflarski et al., 2012). One study theorized that atypical-handers (left- or mixed-handers) may have a retrieval advantage over right handers due to higher dependence of these processes on interhemispheric communication (Christman & Propper, 2001; Prichard, Propper, & Christman, 2013). Increased right hemispheric access among atypical-handers is supported by studies showing a relationship between handedness and corpus callosum volume where larger volume is associated with atypical-handedness (Habib et al., 1991; Luders et al., 2010; Witelson & Goldsmith, 1991). While encoding of verbal information involves left prefrontal areas, retrieval of that information recruits right prefrontal areas (Tulving et al, 1994). This suggests that increased access to the right hemisphere may aid in retrieval, consistent with the HERA model of hemispheric asymmetry during episodic memory encoding and retrieval (Chu, Abeare, & Bondy, 2012; Propper, Christman, & Phaneuf, 2005; Propper & Christman, 2004; Tulving et al., 1994). However, a recent study did not find any behavioral differences due to handedness in working memory tasks, though their findings of an advantage among atypical handers during episodic retrieval were consistent with previous literature (Sahu et al., 2016).

In view of the available studies, our main objective was to examine the neural correlates of semantic learning during self-generation and investigate the role sex may play in brain participation during this process. We investigate these questions within a two-level analysis framework: The first level of analysis identifies task-related networks using a hypothesis-independent source separation technique, independent component analysis (ICA), and by temporally sorting components based on the task time series. We then compare subject component maps for the identified task-related networks in a series of subsequent hypothesis-driven analyses regarding the role sex, age, and handedness may play in the recruitment of these task-related networks (Bartels and Zeki, 2005). We hypothesized sex differences in support of a left lateralized language network among males and more widespread, bilateral processing among females to be associated with similar behavioral outcomes between sexes. The present study also investigated the role age and personal handedness may play in active encoding, and if any differences remain among sexes when taking these variables into account. We hypothesized that the self-generation process would be affected by these factors in such a way that age would affect the robustness or degree of connectivity in fronto-parietal, task-related networks. In addition, potential compensatory mechanisms may play a role in performance if these factors impact self-generation and active encoding.

METHODS

Participants

Participants were 174 native English-speaking adults (96 female; 56 atypically-handed; ages 19-76) with no history of neurological or psychiatric disorders (Table 1). Handedness was determined using the derived laterality quotient from the Edinburgh Handedness Inventory (Oldfield, 1971). Participants were coded categorically as follows: atypically-handed from -100 to +49 and right-handed from +50 to +100. The Institutional Review Boards at the University of Cincinnati, the Cincinnati Children's Hospital Medical Center, and the University of Alabama at Birmingham approved this project (NIH R01-NS04828), and all participants provided written informed consent.

Table 1

Participant Demographics

	Male participants (N = 78)	Female participants (N = 96)	All participants (N = 174)
Age			
Mean (SD)	40.71 (14.1)	41.66 (15.0)	41.23 (14.6)
Min - Max	19 - 74	19 - 76	19 - 76
Handedness (#)			
Right	54	64	118
Atypical	24	32	56
In-scanner Performance (%)			
Read			
Correct	71.3%	87.9%	80.6%
Incorrect	24.0%	11.8%	17.1%
No response	4.8%	0.25%	2.3%
Generate			
Correct	58.2%	71.0%	65.3%
Incorrect	31.2%	20.0%	24.9%
No response	10.7%	9.0%	9.7%
Post-test Accuracy (%)			
Read	70.7%	74.0%	72.5%
Generate	73.7%	76.5%	75.2%

Materials

Related word pairs were chosen from previous studies, with all included words under 6 letters long (Basso et al., 1994; Schefft et al., 2008a, Schefft et al., 2008b; Siegel et al., 2012). The 60 selected word pairs were evenly distributed across 5 relationship classes: associates (e.g., *lock – key*), category members (e.g., *saucer – bowl*), synonyms (e.g., *street – road*), antonyms (e.g., *hot – cold*), and rhymes (e.g., *care – dare*) (Siegel et al., 2012).

Paired-associate learning task and recognition

This fMRI task was previously utilized by our group (Basso et al., 1994; Schefft et al., 2008b; Vannest et al., 2012, 2015; Siegel et al., 2012). Also data from some of the participants were included in previous studies (Vannest et al., 2012, 2015; Siegel et al., 2012). Briefly, the verbal paired-associate learning task was presented during the fMRI scanning session, and a recognition post-test was administered in a testing room thereafter (see section 2.5). During the in-scanner task, 60 word pairs were presented either in full (e.g., *spider – web*) or with the second word partially missing (e.g., *bed – p******), and participants were instructed to say the second word aloud (Figure 1a). In the "read" condition (e.g., *spider – web*), participants simply read the second word in the pair aloud. In the "generate" condition (e.g., *bed – p******), participants had to first self-generate the target word and then say it aloud. In-scanner responses were monitored and transcribed.

After the scanning session, participants performed a recognition test evaluating their memory of the second word in each word pair that was presented during the fMRI task. All 60 words presented during the fMRI task across both "read" and "generate" conditions (30 words per condition) were included in the post-test in a three-item forced-choice format. The target word and two foils were presented on a computer screen, and participants indicated which of the three words they recognized from the in-scanner task with a key press on the computer (Figure 1b). The post-test was self-paced; the test would advance to the next set of three items once the subject had responded. Post-test performance scores were analyzed for any statistical differences using Wilcoxon signed-rank tests for "read" vs. "generated" words across all participants, and among males vs.

females, atypically-handed vs. right handed participants, and older adults vs. younger (see Section 3.1).

MRI Acquisition

Anatomical and functional MRI data were acquired for the 174 participants included in analysis across two scanners: a 3T Philips Achieva MRI scanner at the University of Cincinnati provided by the Imaging Research Center (151 participants) and a 3T head-only Siemens Magnetom Allegra MRI scanner at the University of Alabama at Birmingham provided by the Civitan Functional Neuroimaging Laboratory (23 participants). Across both scanners, data were acquired using a clustered-sparse temporal image acquisition, HUSH: Hemodynamics Unrelated to Sounds from Hardware (Schmithorst & Holland, 2004; see Figure 2). Aside from the ability to record overt responses inside the scanner, the HUSH partially silent event-related design takes advantage of the delayed response of canonical hemodynamic response function (HRF). The positive peak of the HRF occurs approximately 4 to 6 seconds post-stimulus presentation and response (Buxton et al., 2004), allowing us to capture activity taking place seconds preceding data collection. Scanner type was used as covariate in all analyses.

3T Philips Achieva MRI scanner (Cincinnati Children's Hospital Medical Center). 151 participants. High-resolution T1-weighted anatomical images were acquired (TR: 8.1s, TE: 2.17ms, FOV: 25.0 cm x 21.1 cm x 18.0 cm, matrix: 252 x 211, flip angle: 8 degrees, slice thickness: 1mm). Functional T2*-weighted images were obtained using the HUSH silent clustered-sparse temporal image acquisition (TR: 2000ms, TE: 38ms, FOV: 24.0

cm x 24.0 cm x 12.8 cm, flip angle: 90 degrees, matrix: 64x64, slice thickness: 4mm, 32 axial slices with 0% distance factor; voxel size: 3.75mm x 3.75mm x 4mm).

3T Siemens Magnetom Allegra MRI scanner (University of Alabama at Birmingham). 23 participants. High-resolution T1-weighted anatomical images were acquired (TR: 2.3s, TE: 2.17ms, FOV: 25.6 cm x 25.6 cm x 19.2 cm, matrix: 256 x 256, flip angle: 9 degrees, slice thickness: 1mm). Functional T2*-weighted images were obtained with the HUSH silent clustered-sparse temporal image acquisition (TR: 2000ms, TE: 35ms, FOV: 24.0 cm x 24.0 cm x 12.8 cm, flip angle: 70 degrees, matrix: 64x64, slice thickness: 4mm, 30 axial slices with 7% distance factor; voxel size: 3.8mm x 3.8mm x 4mm).

FMRI stimuli were presented using a silent event-related design as described in detail previously (Allendorfer et al., 2012b; Vannest et al., 2012; 2015). Briefly, for each stimulus, a word pair was presented for 6 seconds and participants were instructed to read the second word out loud; audio responses were recorded. This was followed by 6 seconds of data collection (3 image volumes) with the word “STOP,” instructing participants to stop talking during acquisition. A total of 180 whole-brain volumes were collected across the full 12 minutes of the task. The task was not dependent on a verbal response: if there was no response after a word pair was presented, the task would continue uninterrupted (Vannest et al., 2012; 2015).

FMRI data preprocessing

Data were processed using Analysis of Functional NeuroImages software (AFNI; Cox 1996) and FMRI software library (FSL; Smith et al., 2004). Functional images were first split into three separate parts: the first, second, and third volumes for each stimulus presentation were separated into three separate functional images in order to account for signal intensity changes in the HRF over time (Schmithorst & Holland, 2004). See Figure 3 for a schematic of the analysis pipeline. Functional images were then motion corrected using AFNI's *align_epi_anat.py* and *3dvolreg*. Functional images were registered to the anatomical images using FSL's FLIRT (Jenkinson et al., 2002), images were resampled to 3mm isotropic voxels, and standardized to the MNI152 template atlas using FSL's nonlinear registration tool (FNIRT). We smoothed all participants' datasets to an effective smoothness of a Gaussian FWHM of 6mm using AFNI's *3dBlurToFWHM*. Functional volumes did not undergo any additional filtering or artifact regression prior to Group ICA (Calhoun et al., 2001). Trials were not excluded based on participant responses. Participants undergo the process of encoding word pair associates whether or not they produce the correct word in the scanner; therefore all trials were used for each subject in the second level analyses.

Group ICA

Group spatial ICA was carried out using GIFT in Matlab software (Group ICA fMRI Toolbox, v4.0b) for each of the three image volume sets by first conducting two principle component analyses (PCAs) for data reduction. Subject-specific PCA was conducted as the first round of PCA to reduce each subject's functional data, yielding 51 components. Subjects data are then temporally concatenated and data underwent a second round of PCA, yielding 41 components (Erhardt et al., 2011; Calhoun et al., 2001). Group level independent components were derived using the Infomax ICA algorithm, yielding

41 group level components (for each of the three HUSH image volumes). The number of independent components was chosen in accordance to a similar previous study from our group (Vannest et al., 2015). Subject-specific spatial maps (SMs) were derived with GIFT's GICA3 back-reconstruction method (Calhoun et al., 2001, 2002; Erhardt et al., 2010). GICA3 estimates subject-specific time-courses and SMs from mixing matrices derived in PCA data reduction steps, and has been shown to provide more robust results with more intuitive interpretation (Erhardt et al., 2010).

GIFT's temporal sorting tool allows for the classification of components by temporal characteristics, comparing the model's timecourse to the time courses of independent components (Rachakonda et al., 2007). Using the correlation function in the temporal sorting tool, group-level components were sorted by binary task time series (model timecourse) and components with a correlation coefficient $|r| > 0.25$ were identified as task-related components. The binary task time series used designated "1" for the "generate" condition (active generation, task-positive) and "0" for the "read" condition (passive reading, task-negative). See Figure 3 for an example of the binary task time series used.

Components with a correlation coefficient of $r > 0.25$ were identified as task-positive (correlating with the "generate" condition), and components with a correlation coefficient of $r < -0.25$ were identified as task-negative (correlating with the "read" condition) and were retained. Components with a correlation coefficient between $-0.25 > r > 0.25$ were excluded from all further analyses. Components were visually inspected and regionally similar/matching components were identified across all three image volumes. If a component met threshold for task-relatedness ($|r| > 0.25$) across more than one of the three image volumes, then the most highly correlated volume was selected for further analysis. These six derived task-related components represent statistically independent sources contributing to task-positive and task-negative networks and do not reflect a specific contrast within the task (generate vs. read).

Relationships between task-related components and sex, handedness, and age

To compare differences in network extent among our participants, we utilize an approach available within the group ICA toolbox (GIFT). GIFT produces subject specific SMs for each independent component by implementing a series of back-reconstruction steps from each component at the group level (Calhoun et al., 2001; Meier et al., 2012). To investigate the effects sex, handedness, and age may have on task-positive and task-negative networks, we conducted a second level analysis by extracting SMs from each subjects' individual dataset for each corresponding task-related component (components that met a correlation threshold of $|r| > 0.25$).

A total of six components met threshold for task-relatedness, and participants corresponding SMs were used in a series of two-sample t-tests using AFNI's *3dttest++*. We used two-sample t-tests to examine any spatial differences in network extent of task-related components between sexes (male vs. female), handedness (atypical vs. right), and age (<50 vs. ≥50 years old) groups, (including scanner type as a covariate). We were also interested in if any differences between males and females could be attributed to handedness, and ran separate two-sample t-tests comparing males and females (one for right-handed individuals, one comparing atypically-handed individuals).

To examine age as a continuous variable as well as the effect of sex differences while controlling for scanner and handedness, we conducted multiple regression analyses using AFNI's *3dRegAna*. All analyses were corrected for multiple comparisons using Monte Carlo simulations and results were considered significant if clusters met the threshold of $p<0.05$ when corrected for multiple comparisons (AFNI's *3dClustSim* yielded: cluster size at least 171 voxels when corrected at $p<0.05$ and 80 voxels when corrected at $p<0.01$). Additionally, we investigated if sex differences change with age across all task-related components using a linear mixed-effects modeling approach with AFNI's *3dLME*, with our model specification testing for an interaction effect between sex and age, while controlling for scanner and handedness.

RESULTS

Performance data

A Wilcoxon signed-rank test conducted in SPSS Statistics 25 showed that post-test accuracy for the "generated" words (M(SD), %: 22.57(3.7), 75.2%) and the "read" words (21.75(3.9), 72.5%) was significantly different after encoding ($Z=-2.643$, $p=0.008$). Independent-samples t-tests revealed no significant differences between sexes or handedness groups for memory of read words ($p=0.099$ and $p=0.863$, respectively) or generated words ($p=0.135$ and $p=0.219$, respectively). For memory of "read" words, differences were found between older (M(SD), %: 20.67(4.0), 68.9%) and younger (22.23(3.8), 74.1) adults ($p=0.014$), as well as memory of "generated" words between older (21.46(3.9), 70.2%) and younger (23.07(3.5), 75.5%) adults ($p=0.008$). Multiple linear regressions revealed no sex differences in post-test accuracy after controlling for age. Sex was not a predictor of memory performance on generated words while controlling for age and handedness F(3, 169) =1.387, *p*=0.303, R^2=0.024. Sex was also not a significant predictor of memory performance on read words while controlling for age and handedness F(3, 169)=1.758, *p*=0.058, R^2=0.030. Additionally, there were no interaction effects of age and sex on performance of generated words F(4,168)=1.109, *p*=0.590, R^2=0.026, or on read words F(4, 168)=1.377, *p*=0.613, R^2=0.032.

Group ICA: Task-positive components

Of the 41 components, three components were identified as task-positive, meeting a threshold of $r > 0.25$ for the generate condition (Table 2 and Figure 4a-c). The component with the highest correlation with the task (r=0.4244) included bilateral fusiform gyri, bilateral declive, and right inferior temporal gyrus, middle occipital gyrus, middle temporal gyrus (MTG), precuneus, and superior parietal lobule. The second highest correlated task-positive component (r=0.3784) included left middle frontal gyrus, bilateral IFG, left ventral anterior insula, left precentral gyrus, and left inferior parietal lobule (IPL). The third component (r=0.3573) included bilateral IFG, bilateral superior temporal gyri (STG), cingulate gyrus, anterior cingulate cortex, and bilateral ventral anterior insula.

Table 2:

MNI coordinates for task-positive and task-negative components

IC	r	Hush volume	Location	X	Y	Z
		Task-positive components *(Figure 4)*				
4a	0.4244	2	L fusiform gyrus	-46	-58	-16
			R fusiform gyrus	40	-66	-20
			R interior temporal gyrus	50	-56	-16
			L declive	-32	-58	-20
			R declive	38	-58	-22
			L middle occipital gyrus	-32	-84	6
			R middle occipital gyrus	42	-71	-16
			R MTG	54	-58	-14
			L precuneus	-24	-70	36
			R precuneus	32	-72	34
			L superior parietal lobule	-22	-66	48
			R superior parietal lobule	24	-64	44
			R IPL	36	-54	50
			L cuneus	-26	-78	28
			L culmen	-30	-50	-22
			R culmen	36	-52	-24
4b	0.3784	2	L middle frontal gyrus	-44	40	-2
			L IFG	-46	26	18
			R IFG	46	30	14
			L ventral anterior insula	-46	10	12
			L precentral gyrus	-50	12	8
			L IPL	-34	-56	42

			R IPL	36	-58	46
			L STG	-46	16	-8
			L medial frontal gyrus	-2	28	38
			L cingulate gyrus	-2	24	40
4c	0.3573	2	L IFG	-40	18	-12
			R IFG	44	16	-8
			L STG	-44	16	-12
			R STG	44	16	-12
			L cingulate gyrus	0	22	36
			R cingulate gyrus	2	24	32
			L ACC	0	32	22
			R ACC	2	36	22
			L insula	-40	14	-4
			R insula	36	18	0
Task-negative components *(Figure 4)*						
4e	-0.3019	2	L posterior insula	-44	-4	-6
			R posterior insula	44	-12	4
			L STG	-56	4	-4
			R STG	48	-2	-4
			L transverse temporal gyrus	-40	-24	10
			R transverse temporal gyrus	48	-24	10
			R precentral gyrus	48	-14	6
			R postcentral gyrus	56	-26	14
4f	-0.2740	2	L precuneus	0	-72	36
			R precuneus	2	-72	40
			L cuneus	0	-72	32
			R cuneus	4	-72	32
			L cingulate gyrus	0	-26	28
			R cingulate gyrus	2	-44	32

			L PCC	-4	-38	22
			R PCC	4	-36	22
			L IPL	-34	-58	40
			R IPL	40	-58	44
			L angular gyrus	-34	-58	36
			R angular gyrus	44	-60	34
			L supramarginal gyrus	-44	-56	26
4g	-0.2607	3	L PCC	-8	-56	4
			R PCC	10	-54	4
			L culmen	-6	-46	0
			R culmen	6	-46	-2
			L parahippocampal gyrus	-10	-50	0
			L lingual gyrus	-12	-54	2
			L precuneus	-4	-62	16
			R precuneus	4	-64	20
			L fusiform gyrus	-26	-40	-16
			L superior frontal gyrus	-18	34	36
			L middle frontal gyrus	-22	22	42
			R middle frontal gyrus	26	20	44

Note: L: left; R: right. MTG: middle temporal gyrus; IFG: inferior frontal gyrus; IPL: inferior parietal lobe; STG: superior temporal gyrus; ACC: anterior cingulate cortex; PCC: posterior cingulate cortex.

Group ICA: Task-negative components

Three components were identified as task-negative, meeting a threshold of $r < -0.25$ for the read condition (Table 2 and Figure 4d-f). Components are listed from highest correlation: the first component (r=-0.3019) included bilateral posterior insula, STG, transverse temporal gyri, and right pre- and post-central gyri. The second component (r=-0.2740) included bilateral cuneus and precuneus, cingulate gyri, posterior cingulate cortex, and right IPL. The third component (r=-0.2607) included posterior cingulate cortex and left culmen.

Relationships between task-related components, sex, handedness, and age

Two-sample t-tests revealed differences in spatial extent in task-related brain activity recruited between sexes during self-generation and passive reading. All results presented meet a threshold of $p<0.05$ corrected. For males compared to females during self-generation, network extent was greater in right postcentral gyrus (Figure 5a) and left dorsal anterior insula (Figure 5b), and in left supramarginal gyrus (Figure 5c) and right STG (Figure 5d) during reading. For right-handers compared to atypical-handers, extent was larger in left insula (Figure 6d) and angular gyrus (Figure 6c) during reading and self-generation respectively, and smaller in left cuneus (Figure 6a) and posterior cingulate cortex (PCC; Figure 6b) during generation.

Separate analyses of right- and atypically-handed individuals between-group sex differences showed somewhat different effects across groups. Right-handed males showed increased recruitment in right middle occipital gyrus compared to right-handed females during self-generation, while atypically-handed individuals did not show this sex effect. Right-handed females also showed increased recruitment in right superior temporal gyrus compared to males during self-generation that was not seen among atypically-handed individuals. During reading, right-handed females showed increased recruitment of right middle frontal gyrus and right cuneus compared to right-handed males, but this difference was not seen among atypically-handed individuals.

Younger adults (<50 years old) displayed more widespread involvement during both self-generation and passive reading compared to older adults (≥50 years old) across a range of areas (Figure 7a, 7c-h) except for left middle frontal gyrus (Figure 7b), which showed greater recruitment during self-generation among older compared to younger adults (corrected $p<0.05$). During self-generation, younger adults showed greater recruitment across bilateral insula, anterior and middle cingulate cortices (Figure 7a), and left IFG (Figure 7a,d), and bilateral middle occipital gyri (Figure 7c). During passive reading, younger adults showed greater involvement across right precuneus (Figure 7e), bilateral precuneus (Figure 7f), posterior cingulate cortices (Figure 7f,h), and right inferior parietal lobe (Figure 7g).

Regression and mixed-effects modeling results

Multiple linear regression analyses allowed us to examine 1) age as a continuous variable while controlling for scanner type, and 2) the effect of sex on task-related components while controlling for age, handedness, and scanner type. All results presented meet a threshold of $p<0.01$ corrected. Subjects extracted z-scores represent deviation from the group level within that component. Self-generation areas showed decreased recruitment (via subject specific extracted z-scores) with increasing age across frontal and temporo-parietal areas. Passive encoding areas including STG, PCC, and IPL also showed decreased recruitment as age increases. We also found that during self-generation, males recruit right paracentral areas (Figure 8a) and left dorsal anterior insula (Figure 8c) more than females, while females recruit right middle temporal gyrus (Figure 8b) compared to males. During passive reading, men recruit right supramarginal gyrus/ superior temporal gyrus areas (Figure 8d) compared to women while controlling for age, handedness, and scanner.

A linear mixed-effects model examining task-related components revealed a significant interaction between sex and age while controlling for scanner and handedness in task-positive networks (Figure 9a). In the active generation condition, as age increases, males show increased recruitment of the left supramarginal gyrus while this pattern does not exist in females, though the slope of the trend line shows an opposite pattern of decreased recruitment as age increases. Results presented meet a corrected threshold of $p<0.01$ and the relationship between individual subjects extracted average z-score from the left supramarginal gyrus (SMG) and age are shown for males and females separately, with the regression line displayed controlling for handedness and scanner to show direction of the effect (Figure 9b).

DISCUSSION

We examined network differences underlying active and passive memory encoding using a verbal paired-associate learning task. Overall, the results of the analyses are consistent with previous behavioral studies and indicate that generated words during the encoding task were remembered more accurately in post-testing than read words (Olofsson and Nilsson, 1992; Schefft and Biederman, 1990; Vannest et al., 2012, 2015), though the inclusion of both semantically and phonologically related words might have impacted the recognition of read and generated words to some degree (Siegel et al., 2012). However, this effect is likely small and, thus, not investigated here. ICA revealed a broad fronto-parietal network underlying self-generation, while passive reading showed strong temporal-occipital contributions. Further investigation of self-generation and passive reading showed sex, age, and handedness differences in regional patterns of network involvement.

Sex, age, and handedness differences in active vs. passive learning

Sex effects. There is a wide body of work suggesting that networks supporting semantic and phonological processing may be more left lateralized in healthy, right-handed males compared to females, who tend to show more bilateral and widespread pattern of network involvement (Binder et al., 2009). In previous studies, this differential sex effect was seen in superior and middle temporal areas during a story-listening task (Kansaku et al., 2000). However, we did not observe this effect during passive reading, where a greater spatial extent of task-negative related activation in the right superior temporal gyrus was observed in males compared to females. Considering the role personal handedness plays in the neural organization of language (Kansaku and Kitazawa, 2001; Szaflarski et al., 2002; 2006; Tzourio-Mazoyer et al., 2010a), and the inclusion of only (or predominantly) right-handed participants in studies of sex differences in language distribution, our findings in a large sample of right- and atypical-handers may reflect differential recruitment during semantic or phonological processing than previously observed (Andreano and Cahill, 2009).

Further investigation of sex differences between right- and atypically-handed individuals revealed that during self-generation, right-handed females show increased recruitment in right superior temporal gyrus compared to right-handed males that was not seen in the atypically-handed group. Right-handed females also showed right-lateralized activity compared to right-handed males during reading in the middle frontal gyrus, which was not seen among atypically-handed individuals. While females have demonstrated more bilateral involvement in posterior temporal areas during linguistic processing compared to males, females have shown a similar left-lateralized pattern to men in the angular and supramarginal gyri (Kansaku et al., 2000). Our findings reveal greater recruitment among males in left supramarginal gyrus while reading compared to females, and also an interaction effect with sex and age during generation where males show greater recruitment of the left SMG as age increases while females do not show this effect, suggesting differential recruitment of resources in processing phonological inputs and outputs based on sex and age during both passive and active encoding (Oberhuber et al., 2016; Stoeckel et al., 2009).

Age effects. During self-generation, older adults showed lesser network recruitment than younger adults in frontal areas including left inferior frontal gyrus and bilateral insula, as well as bilateral middle occipital gyrus. Our findings of left IFG engagement during active encoding among younger but not older adults is consistent with previous reports of greater prefrontal lateralization among younger adults (Cabeza, 2002; Morcom et al., 2003). This age-related reduced lateralization of this task-related activity may reflect a decreased specialization of brain areas relevant for task demands (Cabeza, 2002). One region implicated among older compared to younger adults was the left middle frontal gyrus. This increased recruitment among older adults may be related to a compensatory mechanism (Morcom et al., 2003) during semantic processing necessary for similar performance.

During passive reading, older adults exhibited reduced recruitment compared to younger adults across posterior and parietal brain regions including bilateral precuneus, posterior cingulate cortex, and right inferior parietal lobe. This is in contrast to previous studies indicating older adults involve posterior brain regions more compared to younger adults (Morcom et al., 2003). Our findings of greater PCC recruitment in younger compared to older adults suggests passive reading aloud may be a more effortful for older adults, or even simply that passive reading engages different networks among younger vs. older adults reflecting differential strategies between the groups (Berlingeri et al., 2013). This compensation view is contrasted with a dedifferentiation perspective of the age-related differences in brain activity. The CRUNCH (Compensation-Related Utilization of Neural Circuits Hypothesis) model provides a framework for age-related increases in activation in different brain areas, not specific to hemispheric side (Reuter-Lorenz and Cappell, 2008; Berlingeri et al., 2013). Considering the level of task demand is relevant in interpreting our findings of greater recruitment in younger adults compared to older adults during both passive reading and active generation within the CRUNCH model (Berlingeri et al., 2013). When engaging in tasks with overall lower cognitive load, neural effects supporting the CRUNCH model may not be elucidated (Jamadar, 2018).

An examination of age as a continuous variable yielded several components showing age-related decreases across both self-generation and passive reading: two out of three task-positive components showed age-related decreases with subject component relatedness (Figure 4a,c), whereas age increases, our relatedness measure decreases across inferior frontal, superior temporal, and superior parietal brain areas. Other studies have supported age-related decreases in parietal areas across various cognitive tasks (Grady et al., 2010), and during self-generation (Vannest et al., 2015). Two out of three task-negative components also showed age-related decreases (Figure 4f,g) across temporal and posterior cingulate areas during reading, consistent with evidence of decreased default mode related activity among older individuals (Grady et al., 2010; Mevel et al., 2013; Vannest et al., 2015).

Handedness effects. Handedness plays an important role in hemispheric language dominance (Geschwind and Galaburda, 1985; Szaflarski et al., 2002, 2012). Neuroanatomical differences exist between right-handed and atypically-handed individuals, particularly in terms of the planum temporale (Foundas et al., 1995, 2003; Shapleske et al., 1999). Studies also show a negative relationship between corpus callosum volume and degree of handedness, where increasing atypical handedness is associated with larger corpus callosum volumes (Habib et al., 1991; Witelson & Goldsmith, 1991), which may be influenced by increased interhemispheric information transfer among atypical- compared to right-handers (Sahu et al., 2016; Gao et al., 2015; Tzourio-Mazoyer et al., 2010). Interhemispheric communication time has been linked to brain volume, and larger brains have been shown to group quick cognitive functions in one hemisphere (Ringo et al., 1994). Our findings of right-handers compared with atypical-handers showing left angular gyrus involvement during self-generation and left insular involvement during passive reading may be due to the left-dominant language processing seen among right-handers, while atypical-handers may have substantial interhemispheric communication to lighten processing load.

While left angular gyrus activation has been associated with language ability (Van Ettinger-Veenstra et al., 2016) and semantic processing (Hartwigsen et al., 2016; Seghier and Price, 2013), an examination of functional properties and subdivisions of the angular gyrus reveal an integrative role across multisensory domains, including reorienting attention and familiar problem solving (Seghier and Price, 2013). Activation of left angular gyrus may also be modulated by several factors, including reading level and age (Meyler et al., 2007; Meyler et al., 2008), while sex and handedness as potential modulatory factors of the angular gyrus have not been studied in depth (Seghier and Price, 2013). Recruitment of the left angular gyrus among right-handers during self-generation in the present study may be related to increased reliance on left dominant semantic processing areas compared to atypical handers. Gray matter asymmetry between left- and right- handed individuals suggests less specialization for speech in the left hemisphere among left-handed individuals (Hervé et al., 2006), and right-handed individuals have shown more left lateralized patterns of activity compared to left-handed individuals (Gao et al., 2015), suggesting organizational differences in semantic processing between left- and atypically- handed individuals.

Sex effects, controlling for age and handedness. Our analyses of sex effects on task-related components while controlling for age, handedness, and scanner reveal a similar pattern in terms of the involvement of the left dorsal anterior insula during self-generation among males and right middle temporal gyrus among females, but also reveals right hemisphere differences among sexes (males > females) in the paracentral lobe during self-generation and in the supramarginal gyrus during passive reading. The role of the anterior insula in affective and cognitive functions suggest that our findings of increased involvement of left dorsal anterior insula among males compared to females may be related to a lateralization effect of performance monitoring (Dosenbach et al., 2006), attention orienting (Corbetta and Shulman, 2002), or salience (Seeley et al., 2007; Menon & Uddin, 2010). Our previous study examining verb generation suggested sex lateralization effects may be dependent on performance and language ability, and found a similar right lateralized pattern for males in caudate/anterior cingulate gyrus when controlling for performance (Allendorfer et al., 2012b). Another study investigated any relationship between white matter integrity of the superior longitudinal fasciculus (SLF) and language functioning across healthy, right-handed participants ranging from 19-76 years old (Madhavan et al., 2014). An examination of sex differences across adulthood in mean fractional anisotropy (FA) values of the SLF found a differential pattern of decline in FA of the SLF across aging males and females, as well as with language functioning as measured by performance on the Controlled Oral Word Association Test.

Attention and salience during encoding implicates a fronto-parietal network

A “network” approach to functional organization in the brain suggests the brain responds to environmental demands (sensory or cognitive) by recruiting brain areas that aid in signal processing. This large-scale distribution of resources results in sets of regions showing statistical dependence in relation to the specific demand or task. More recent approaches to cognitive neuroscience involve a framework with several differentiated and interacting networks underlying human brain function (Menon and Uddin, 2010) with these networks having specific profiles of activation and deactivation.

A fronto-parietal network, including the posterior parietal cortex (PPC) and areas of the prefrontal cortex (Buckner et al., 1999; Otten et al., 2001), has been shown to underlie visual attention (Corbetta et al., 2002; Corbetta et al., 2008). Involvement of the inferior parietal lobe (IPL) in this network may be related to maintaining attention on task goals and encoding events in the environment (Singh-Curry & Husain, 2009; Rueckart & Grafman, 1998; Adler et al., 2001; Vandenberghe et al., 2001) or performance (Donnelly et al., 2011). In this study, task-positive components underlying self-generation showed broad fronto-parietal involvement, including left IPL (Figure 4b), suggesting an increase in attentional demands when self-generating compared to reading. One study examined how differential attention during verbal encoding modulates fronto-parietal brain activity, finding significant contributions from the middle frontal gyri (MFG) during high-attention stimuli (Christiensen et al., 2012). The MFG has been hypothesized to be an area of integration between dorsal and ventral attention streams, serving as a gateway between top-down and bottom-up attention and playing a major role in controlling and reorienting attention (Japee et al., 2015). In this study, generating the second word in the pair involves using the presented cue and a top-down search of known words semantically or phonologically related to the first word. Our findings of left MFG recruitment during self-generation suggests increased allocation of resources to this brain region during active encoding.

The “salience network” refers to a group of brain regions involved in cognitive or emotional arousal; it includes the anterior insula, dorsal anterior cingulate cortex (dACC), and several subcortical and limbic structures (Seeley et al., 2007; Kay et al., 2012; Morgan et al., 2008; Menon, 2015). Implication of the insular cortex in neuroimaging studies suggests its role in salience and stimuli detection, facilitating attention and working memory during task switching (Menon and Uddin, 2010; Sridharan et al., 2008). In this study, the insula and anterior cingulate cortex were identified in task-positive components, likely contributing to sustained attention during self-generating word pairs. Our examination of sex differences suggests males may recruit brain areas involved with sustained attention and task switching attention compared to females during self-generation. The two clusters in left insula and right postcentral gyrus that were involved with self-generation among males compared to females may be, perhaps, serving as an attention modulating mechanism when task demands increase during active encoding (Steinmetz et al., 2000); similar sex-differences were observed in developmental but not adult studies of language lateralization (Szaflarski et al., 2002, 2012). The insula was also implicated in our examination of handedness and brain regions underlying reading aloud in that right-handers showed greater extent in the left insula involvement compared to atypical-handers. A study of effective connectivity during a Chinese semantic task found that left-handers showed differential effective connectivity between the insula and prefrontal / occipital areas compared to right-handers, suggesting differential information processing among atypical-handed individuals during visual and semantic word retrieval of Chinese characters (Gao et al., 2015). Due to the integrative role of the insula in bottom-up and top-down processing, these authors hypothesized that handedness may impact information transfer at a causal, system level during semantic word retrieval.

A dynamic network underlies the encoding process

A meta-analysis of 74 fMRI encoding and memory studies revealed five main brain areas consistently associated with subsequent memory. The study also examines how patterns of activity are modulated by task-related conditions (nature of material: verbal or pictorial; type of encoding: item or associative) (Kim 2011). Findings support the "task-dependency" principle that the encoding process cannot be reduced to a fixed set of brain areas, but rather the neural correlates of encoding should be viewed as a dynamic network that responds to task-specific requirements (Kim, 2011; Otten and Rugg, 2001; Rugg et al., 2002). Therefore, it is the type of encoding task that determines which regions are functionally relevant and will be recruited for successful processing and will show subsequent memory effects.

There is also evidence suggesting certain aspects of network organization and recruitment during encoding may be dependent on specific demographic variables such as age (Allendorfer et al., 2012a; Szaflarski et al., 2006, 2012; Maillet & Rajah, 2014; de Chastelaine et al., 2016), sex (Hill et al., 2014; Mulligan and Lozito, 2004), or handedness (Seghier and Price, 2013). Our findings support differential recruitment of these dynamic networks underlying encoding during self-generation based on a number of variables. In task-positive networks, older adults showed reduced prefrontal lateralization compared to younger adults as left IFG showed greater spatial extent of activation among younger adults than older adults. Right-handed individuals also displayed greater recruitment on left semantic processing areas compared to left-handed individuals in these same task-positive networks. The influence of sex on task-related networks suggests increased right hemisphere recruitment among males compared to females during both self-generation and passive reading. These findings provide some insight into networks underlying active and passive encoding, and how the recruitment of these dynamic networks may be influenced by demographic factors like age, sex, and preferred handedness.

Conclusions

In summary, independent component analysis of a verbal paired-associate learning fMRI task revealed fronto-parietal network contributions during self-generation of word pairs, and recruitment of temporo-occipital areas during reading words aloud. Sex, handedness, and age groups showed similar memory performance, but significant differences in task-positive and task-negative brain areas across groups suggest differential recruitment of encoding network areas to achieve similar performance levels.

ACKNOWLEDGEMENTS

The authors thank Christi Banks and Amber N. Martin for help with data collection, and Miriam Siegel and Kathleen A. Hernando for transcribing the fMRI task audio responses and scoring the recognition post-tests. This study was supported by NIH R01 NS048281 (JPS); Ms. Nair is supported by the Graduate Research Scholars Program

(GRSP) under the Alabama Established Program to Stimulate Competitive Research (AL EPSCoR) from the National Science Foundation (parent grant OIA-1632891 (JPS)).

Disclosure of Interest

The authors have no competing interests and no disclosures.

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FIGURES

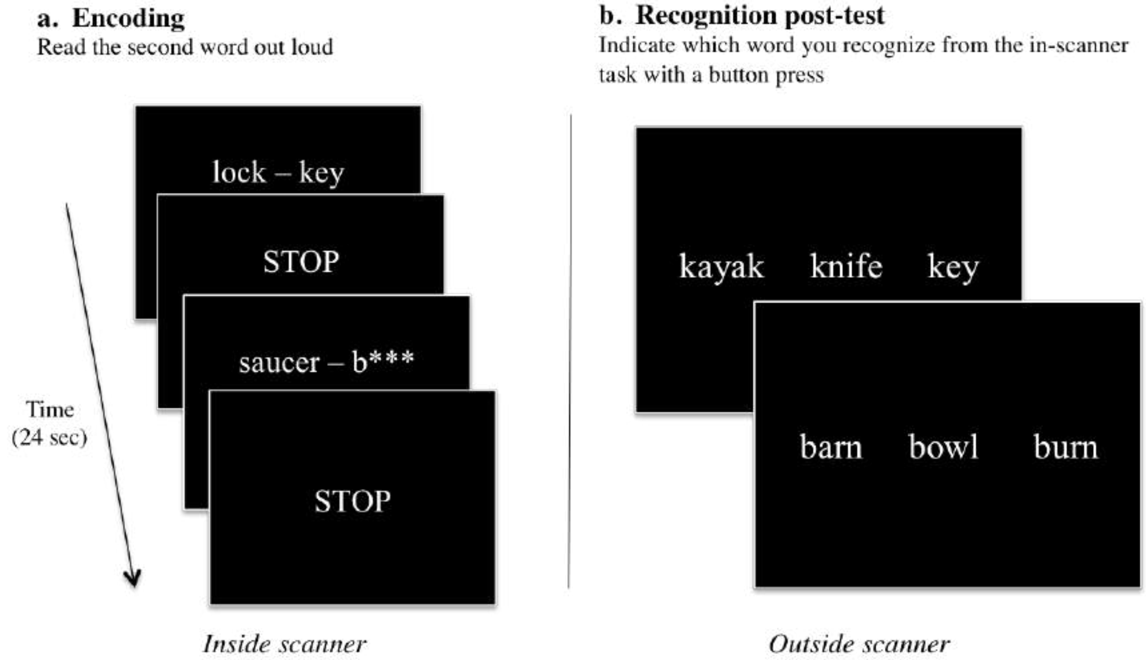


Figure 1. A schematic of the two parts of the verbal paired-associate learning fMRI task consisting of *a)* an in-scanner encoding task, and a *b)* post-fMRI recognition test. During the fMRI encoding task, word pairs are presented on the screen for 6 seconds, and participants are instructed to read (or generate) the second word of the word pair aloud. The STOP screen instructs participants to stop talking while three image volumes are acquired for a total of 6 seconds. This continues for all 60 word-pair stimuli, for a total of 12 minutes. After scanning, participants conduct a recognition post-test in a nearby facility testing room. Participants are presented with three words: one target word they had been exposed to during the in-scanner encoding task, and two foils, and participants are instructed to indicate which of the three words they recognize from the task.

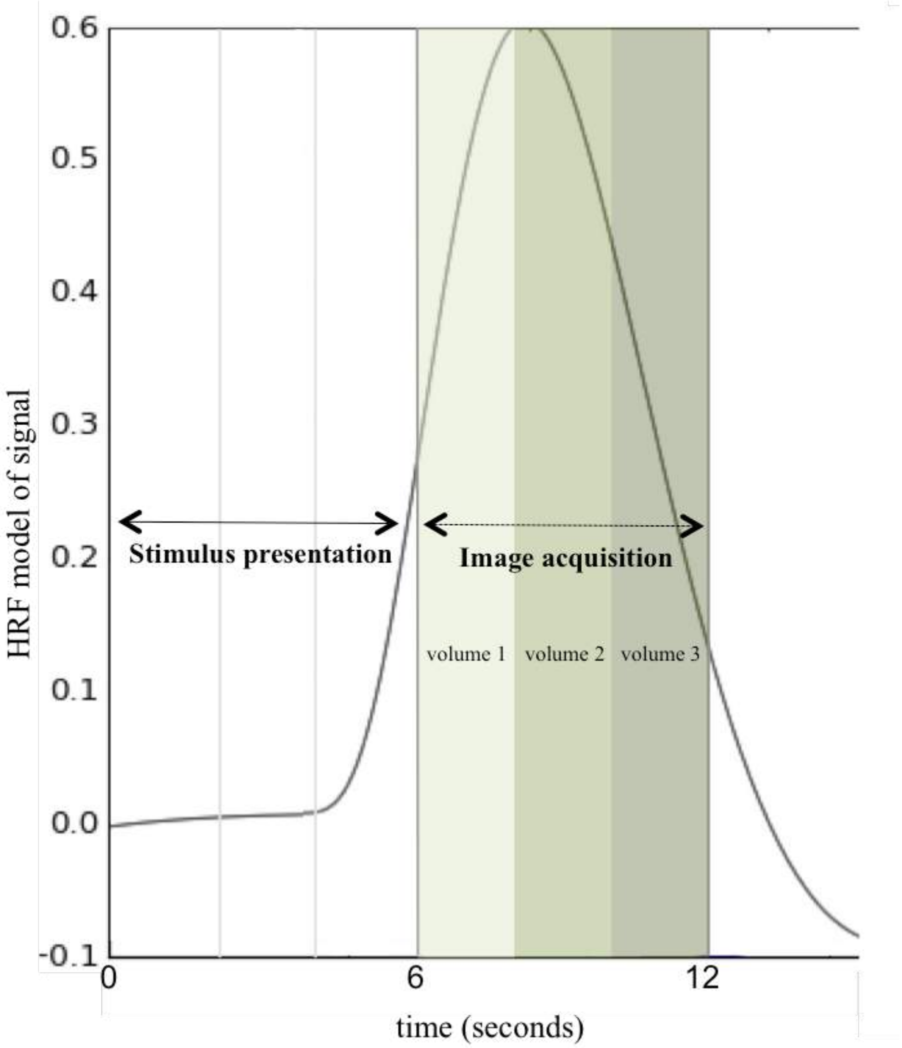


Figure 2. HUSH Image Acquisition. A schematic of one stimulus presentation and image acquisition period (total of 12 seconds) using a clustered-sparse temporal acquisition, Hemodynamics Unrelated to Sounds of Hardware (HUSH). Stimulus is presented for the first 6 seconds, followed by acquisition of three image volumes with a TR of 2 seconds. This is repeated for all 60 word-pair stimuli for 12 minutes and a total of 180 image volumes. (HRF: Hemodynamic response function).

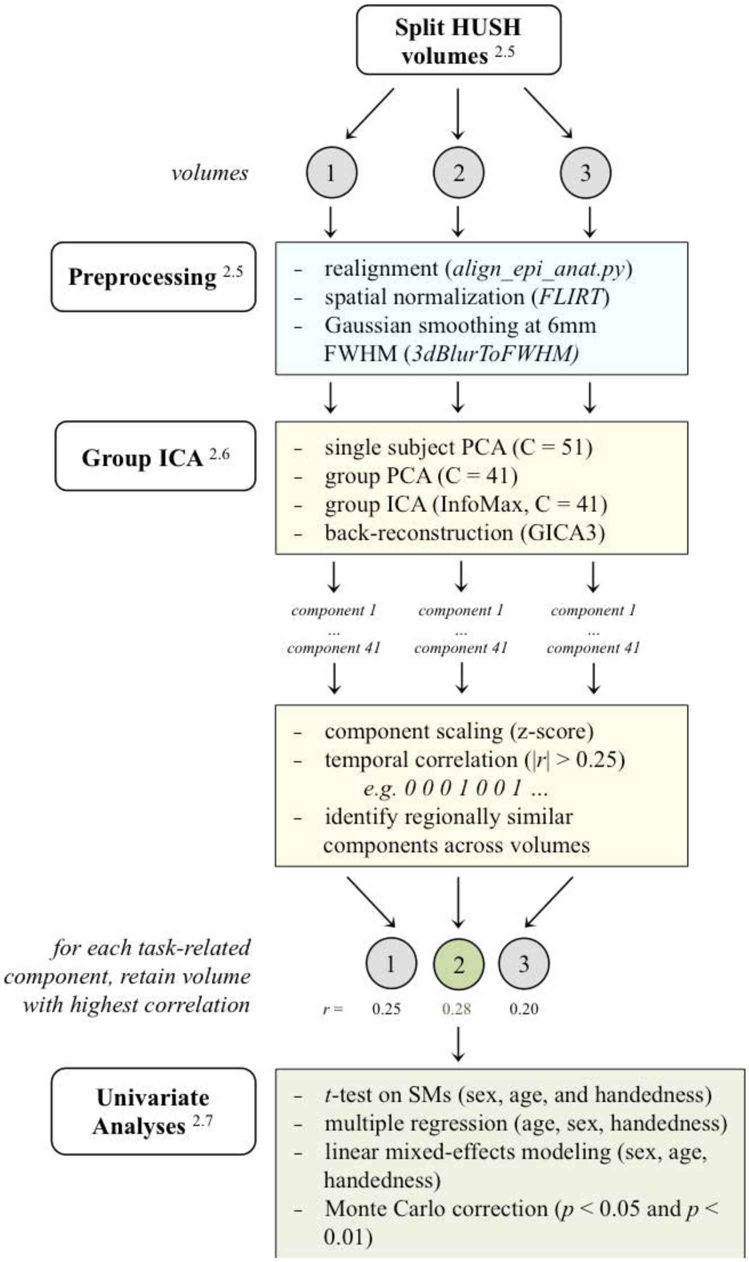
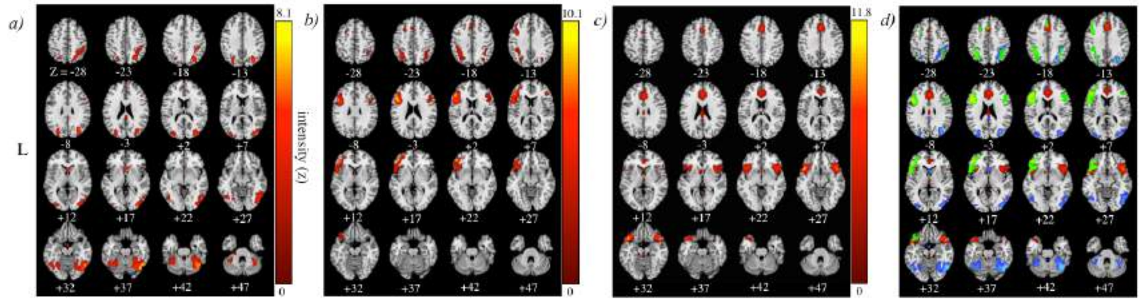


Figure 3. A schematic of the analysis pipeline. HUSH volumes were split into the 3 volumes acquired, and subsequent preprocessing and analysis in GIFT (PCA/ICA) was applied to volumes separately. After sorting components using the binary task time series, regionally similar components were identified across the three analyses and the volume with the highest correlated to the task time series was retained for further analyses. (Superscripts correspond to sections in the methods that further describe that stage in the analysis. HUSH: Hemodynamics Unrelated to Sounds of Hardware; FLIRT: FMRIB's linear image registration tool; FWHM: full width at half maximum; PCA: principle component analysis; ICA: independent component analysis; SMs: spatial maps).

Task-positive components (correlated with the *generate* condition; $r > 0.25$)



Task-negative components (correlated with the *read* condition; $r < -0.25$)

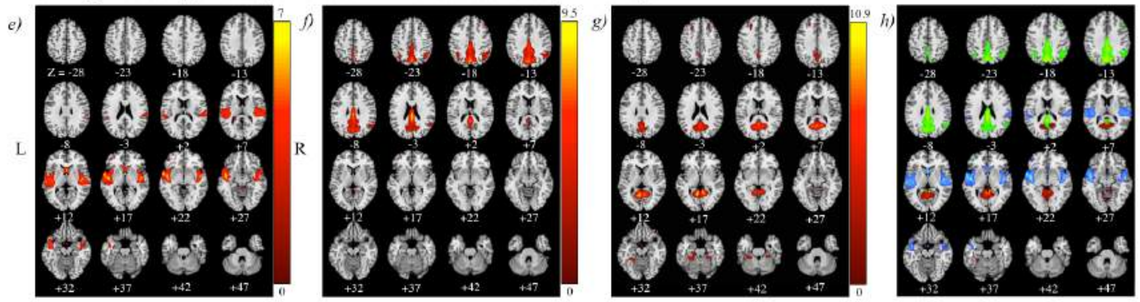
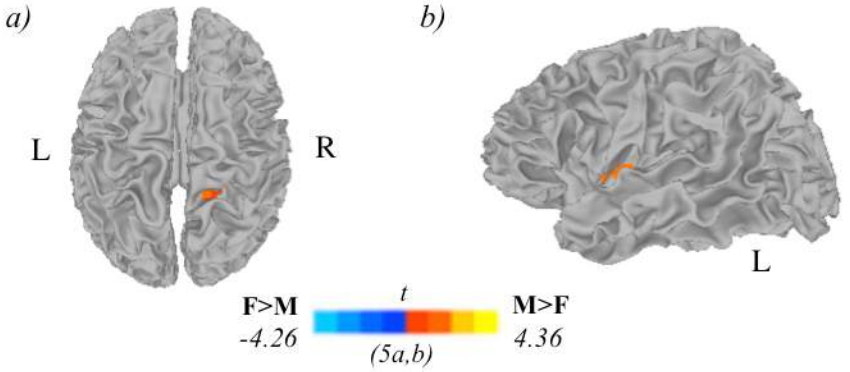


Figure 4. Task-positive and task-negative components (correlated with the *generate* and *read* conditions |r| > 0.25). Images are presented in neurological orientation (R=R). Group average independent components positively correlated ($r > 0.25$), *3a-c*, and negatively correlated ($r < -0.25$), *3e-g,* with the task timecourse, along with composite images for task-positive (*3d*) and task-negative (*3h*) components presented below. Components span the following brain regions: *a)* bilateral occipital; *b)* bilateral (left-lateralized) inferior frontal gyrus and precentral gyrus; *c)* anterior insula and superior temporal gyrus; *d)* composite image of task-positive components (*3a-c*); *e)* bilateral superior temporal gyrus; *f)* bilateral precuneus and posterior cingulate cortex; *g)* posterior cingulate cortex and culmen; *h)* composite image of task-negative components (*3e-g*).

Task-positive components:



Task-negative components:

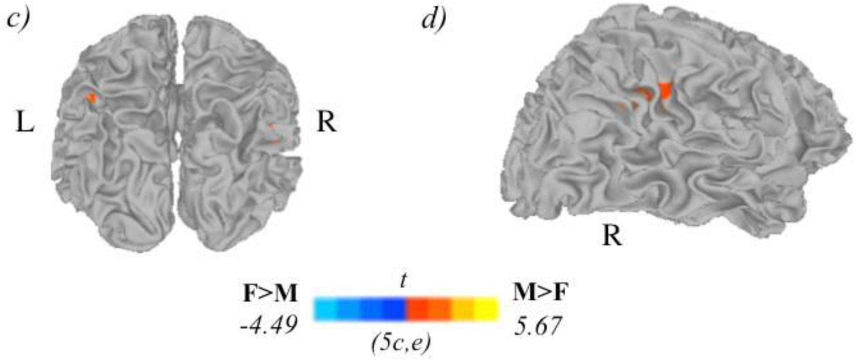


Figure 5. Relationships between sex and task-related components: Two-sample t-tests between males and females in task-positive components (4a-b) and task-negative components (4c-d) reveal males recruit additional brain areas during active encoding compared to females: a) right postcentral gyrus, b) left insula; and during passive encoding: c) left supramarginal gyrus, d) right superior temporal gyrus (F: females, M: males; $p<0.05$ corrected).

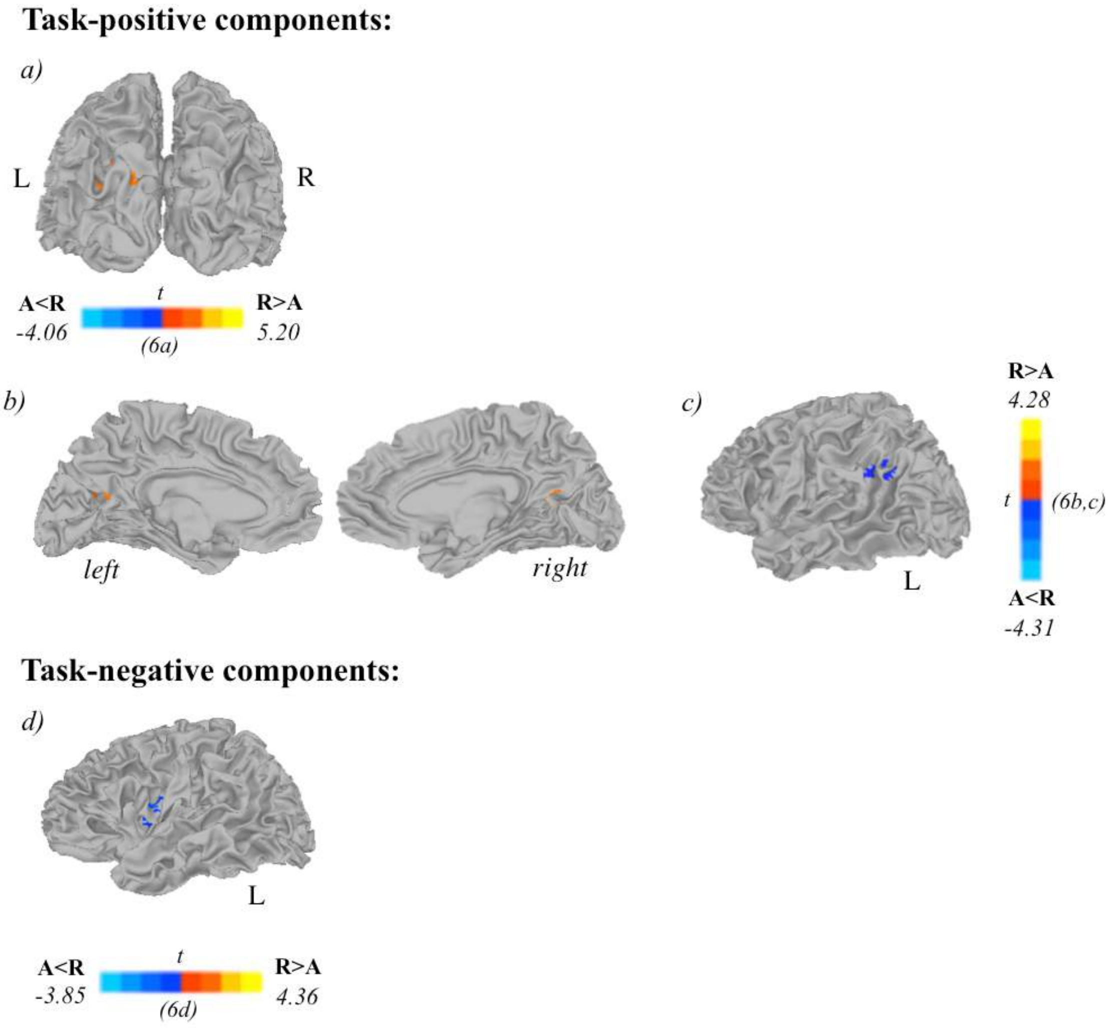


Figure 6. Relationships between handedness and task-related components. Two-sample t-tests reveal differences between atypically-handed and right-handed individuals in task-positive components (5a-c) and task-negative components (5d). In terms of spatial extent of task-related activation, atypical-handers and right-handed individuals recruited additional regions during active encoding: a) left cuneus, b) posterior cingulate cortex, c) left angular gyrus; and during passive encoding: d) left insula. Orange depicts areas where atypical-handers task-related extent was greater than right-handed individuals, and blue depicts areas where right-handed individuals task-related extent was greater than atypical-handers (A: atypical-handed, R: right-handed; p<0.05 corrected)

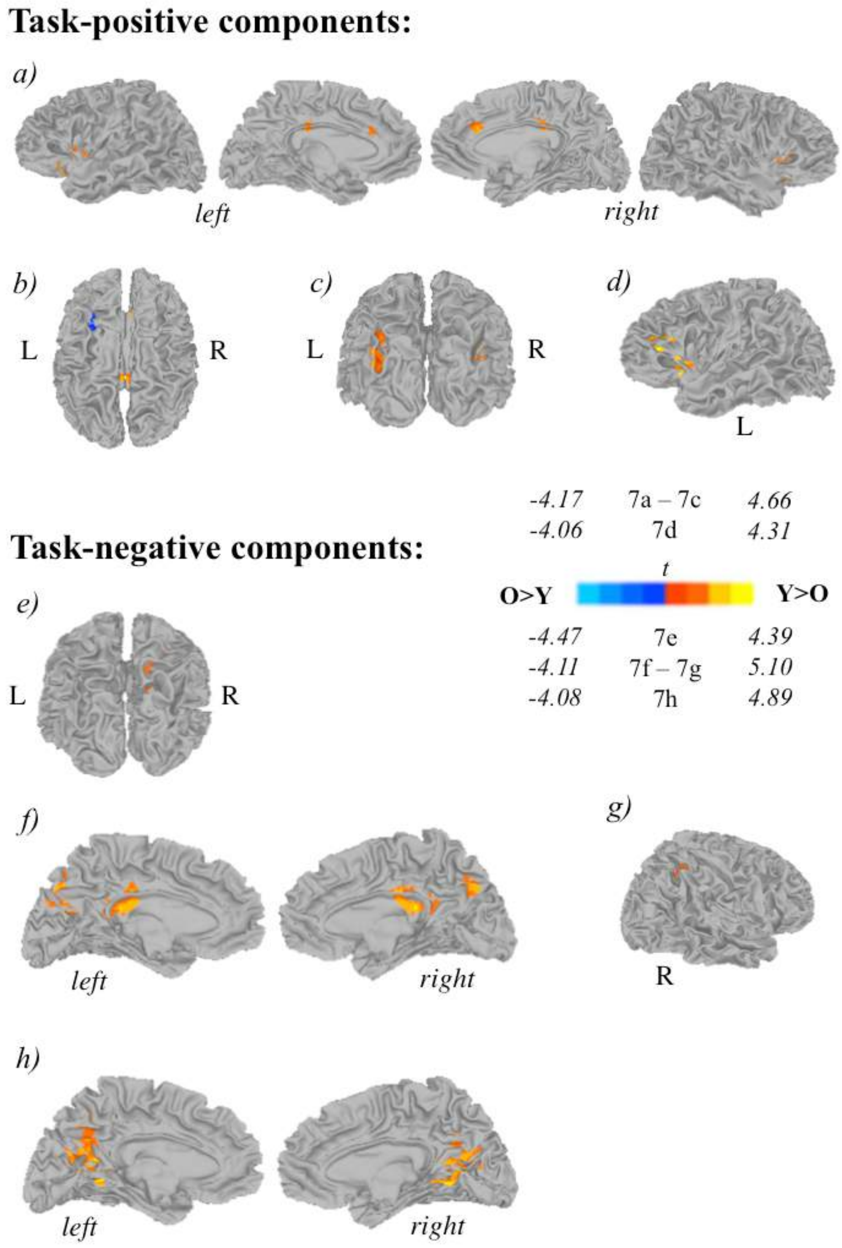


Figure 7. Relationships between age and task-related components. Two-sample t-tests reveal differences between younger (<50 y.o.) and older (≥50 y.o.) adults in task-positive components (6a-d) and task-negative components (6e-f). Recruitment among young adults seemed more widespread compared to older adults during self-generation, with greater recruitment across a) bilateral insula, anterior and middle cingulate cortices, and left inferior frontal gyrus, c) bilateral middle occipital gyrus, d) left inferior frontal gyrus and left insula. During self-generation, older adults showed greater recruitment compared to younger adults in b) left middle frontal gyrus. During reading, younger adults showed greater activity compared to older adults across: e) right precuneus, f) bilateral precuneus

and PCC, g) right inferior parietal lobe, and h) bilateral PCC (Y: younger adults (<50 y.o.), O: older adults (≥50 y.o.); *p*<0.05 corrected).

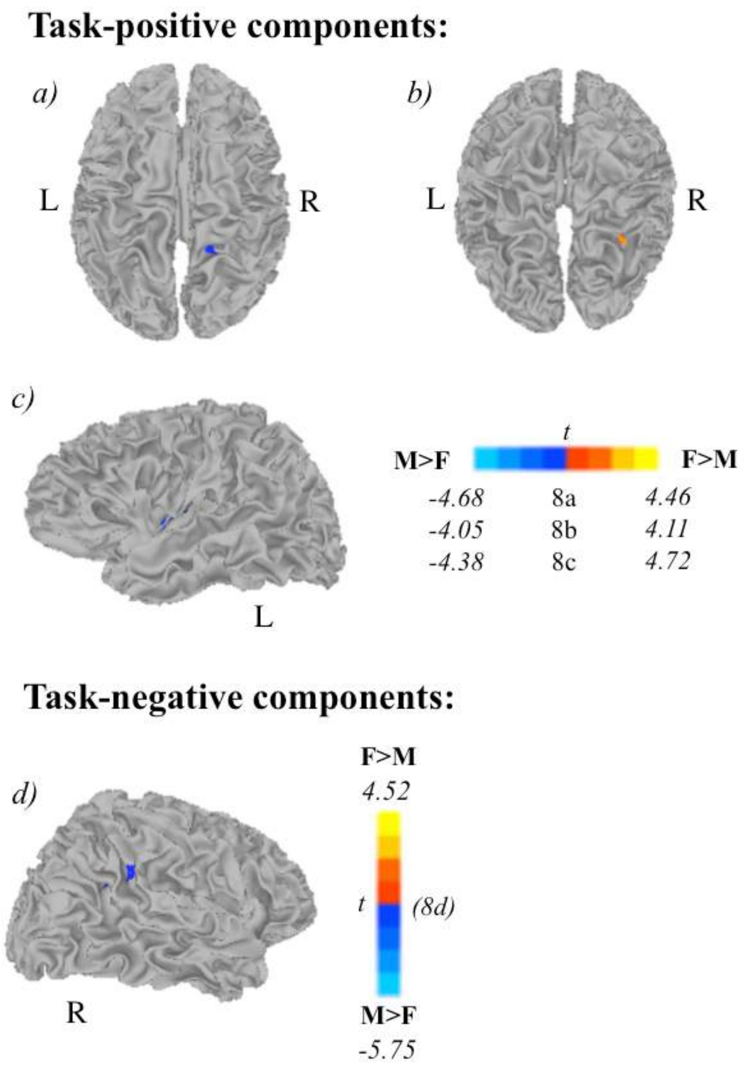


Figure 8. Relationship between sex and task-related components, controlling for scanner, age, and handedness. Males show greater task-positive network extent when controlling for scanner, age, and handedness in a) right paracentral lobe and c) left insula during self-generation and greater task-negative network extent in d) right supramarginal gyrus / STG during passive reading. Females show greater task-positive recruitment during self-generation of b) right middle temporal gyrus (F: females, M: males; $p<0.01$ corrected).

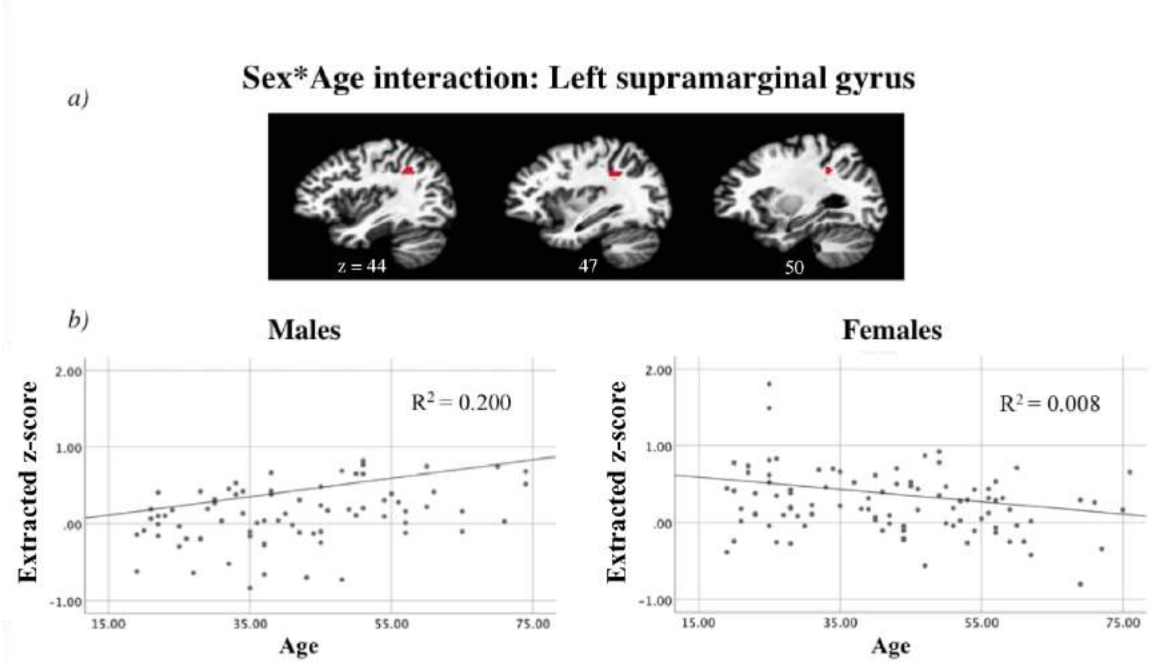


Figure 9. Linear mixed-effects model revealed a) an interaction between sex and age while controlling for scanner and handedness in the left supramarginal gyrus in a task-positive component. Correlations between subjects mean z-score for the left supramarginal gyrus ROI and age suggests that b) as age increases, males show increased recruitment of left SMG during passive reading while females show a decline in BOLD signal intensity as age increases (p<0.01 corrected).

DYNAMIC BRAIN ACTIVITY DURING ASSOCIATIVE LEARNING EXAMINED WITH MEG/FMRI CO-PROCESSING

by

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Under review at *Journal of Neuroscience Methods*

Format adapted for dissertation

CHAPTER 2

DYNAMIC BRAIN ACTIVITY DURING ASSOCIATIVE LEARNING EXAMINED WITH MEG/FMRI CO-PROCESSING

Abstract

Due to limitations of individual neuroimaging methods we examine spatial and temporal contributions to self-generation using multimodality imaging with functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG) within the Bayesian framework Multiple Sparse Priors (MSP). 24 healthy participants performed an fMRI and MEG paired-associate learning task. FMRI data were processed within Group ICA fMRI Toolbox. Independent components (ICs) were temporally sorted by task time series (|r|>0.30 threshold identified task-related ICs). Task-positive (“generate”) ICs were retained as spatial priors for MEG analyses. MEG data were processed by averaging trials to increase the signal-to-noise ratio within subjects and with an event-related theta power approach. MEG source reconstructions were constrained within the task-positive ICs for both analytical approaches.

For fMRI, five networks were identified as task-related. Four ICs underlying active generation spanned bilateral parietal, orbitofrontal, medial frontal and superior temporal regions, and occipital lobe. FMRI-constrained MEG source reconstructions yielded early visual cortex activity followed by left inferior frontal gyrus (IFG) and orbito-frontal cortex (OFC) recruitment to coalesce in the left inferior temporal lobe. For

the event-related theta approach, reconstructions showed a progression of activity from bilateral temporal areas to left OFC and middle temporal gyrus, followed by right IFG. MSP analyses informed by fMRI produced more focused regional activity than reconstructions without priors suggesting increased attention and maintenance when selecting relevant semantic information during active generation. Constraining MEG source reconstruction to fMRI priors during active generation implicates interconnected fronto-temporal and fronto-parietal networks across time.

INTRODUCTION

The processes behind acquiring new knowledge are broadly divided into two learning styles: passive and active (Mcdaniel, Waddill, and Einstein 1988; Olofsson and Nilsson 1992; Pugh et al. 1996). Passive learning is conceptualized as a one-way transference of information. Individuals are meant to passively absorb and retain new knowledge through traditional approaches like lectures, presentations, and reading. In contrast, active learning requires engagement and participation from the individual such as group discussions, hands-on workshops, or interactive games (Prince 2004). As these two styles of learning require different contributions from the individual in terms of cognitive mechanisms including attention and depth of processing, they also present specific strengths in various settings. The benefits of active learning have been widely studied across a range of metrics, including improved retention of information, academic achievement, and self-esteem (Mcdaniel et al. 1988; Olofsson and Nilsson 1992). Enhanced memory of active learning, for example, with self-generating content, has been hypothesized to be a result of the increased distinctiveness of the target word (Otten, Henson, and Rugg 2001a).

The neurological processes underlying both passive and active learning recruit distinct and overlapping brain networks. There have been recent efforts to evaluate neuroanatomical and functional contributions to verbal learning in healthy and diseased populations using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) (Binder et al. 2009), as well as contributions from the electrophysiological literature outlining stereotyped responses across groups (Marinković 2004). However, such approaches are hampered by either the poor temporal resolution of fMRI or poor spatial resolution of PET or electrophysiology techniques. In fMRI, the blood oxygen level dependent (BOLD) responses are sensitive to functional changes in response to a specific task. Although fMRI is often utilized for its high spatial resolution, the method is limited in what information it can provide within the temporal domain. As neuronal activity takes place in the order of milliseconds, considerably faster than any associated vascular changes at roughly 5-7 seconds of the hemodynamic response function (HRF) (Hawco et al. 2007; de Munck et al. 2007), fMRI is unable to preserve the temporal resolution of neuronal activity and thus is not widely used to explore the timing and information flow of cognitive processes. Previously mentioned fMRI studies of healthy controls identify distributed networks that underlie various verbal memory processes (encoding and retrieval), but little is known about the dynamic communication between nodes in these networks (Baker et al. 2001; Buckner, Kelley, and Petersen 1999; Kim 2011).

Bioelectric-based methods, including electroencephalography (EEG) and magnetoencephalography (MEG), are sensitive to electromagnetic fields generated by synaptic currents in the brain. These techniques offer insight into neuronal activity with an especially high temporal resolution, allowing for evaluation of activity as it unfolds across milliseconds. As such, bioelectric and electromagnetic techniques are particularly well suited to explore questions around the dynamics of brain activity and information transfer. While both EEG and MEG noninvasively measure electromagnetic fields at the scalp surface and retain valuable temporal information, EEG is unable to resolve the location of the source of any measured activity. This “inverse problem” is primarily driven by the heterogeneous layers of tissue, skull, and scalp with varying conductivities between the brain and scalp (i.e., between the source and measurement device). The electrical potentials measured at the scalp surface are in turn, distorted across the scalp, and without the ability to accurately model the conductivities of different layers of tissue, it is difficult to localize the measured signals across the brain. MEG is described as the magnetic equivalent to EEG due to the specific properties of magnetic fields. MEG is impacted by the inverse problem to a lesser degree compared to EEG as the measured magnetic field is not distorted by heterogeneous layers of tissue between the brain and the measuring device (Hämäläinen 1992). Source localization is considerably easier with MEG compared to EEG and there exist many possible “solutions” to the inverse problem via equivalent dipole fitting, beamforming, and Bayesian methods. However, the shortcoming of MEG is that it is only sensitive to currents tangential to the scalp surface as only these currents produce magnetic fields detectable outside the head (Hämäläinen 1992; Singh 2014). Further, activity from deep or subcortical sources is challenging to resolve with MEG. In whole, this distinction makes determining sources from MEG recordings preferred over EEG, though the spatial resolution of both of these techniques is limited compared to fMRI.

Because fMRI and MEG visualize different neural sources and measure different aspects of brain function, these methods are complementary (Wang and Holland 2014; Wang, Holland, and Vannest 2012). FMRI measures metabolic processes that drive neural firing and is able to identify primary brain regions and networks involved with different tasks with millimeter accuracy, but its poor temporal resolution limits its use to determine directional information flow within a network. MEG directly reflects magnetic fields generated by postsynaptic neural activity and preserves the millisecond time-scale of neurophysiologic activity, but unlike hemodynamic methods, it has limited spatial resolution. Implementing a multi-modal approach by combining hemodynamic and electrophysiological functional connectivity methods capitalizes on the advantages of both modalities. We are able to develop complete models of verbal memory in healthy populations by characterizing neuroanatomical contributions alongside sequential and dynamic aspects of verbal encoding with high spatiotemporal resolution. The ability to capture and describe the differential recruitment of contributing brain areas during a task is especially relevant during working memory, as the time scale of brain activity during verbal memory is known to be fast (Marinković 2004).

Successful studies combining the strengths of both MEG and fMRI have mainly focused on sensory or motor processing (Ahlfors et al. 1999; Auranen et al. 2009; Schulz et al. 2004; Stippich et al. 1998; Tuunanen et al. 2003) and rest (Lottman et al. 2019). Studies investigating higher cognitive functions are limited (Wang et al. 2012). It is especially challenging for MEG to resolve source localization that involves complex and distributed neural processes: inducted activity is not likely to be time-locked to stimuli across subjects, may arise from multiple generators across the cortex, and thus can be difficult to isolate (Lopes da Silva 2013; Takeda et al. 2014). When examining distributed responses during a cognitive task, certain considerations should be discussed. Experimental paradigms evaluating sensory responses, including visual, auditory, motor, and somatosensory responses, typically involve very short paradigms (and, in turn, have high signal-to-noise ratio (SNR) due to averaging hundreds of trials). However, it is substantially more difficult to reach similar SNR among paradigms associated with high-order cognitive tasks due to the duration of each trial (Wang and Holland 2021). Additionally, averaging across trials when investigating induced activity has the potential to weaken SNR when responses are not time-locked to the stimulus across runs, unlike consistently identified event-related potentials (ERPs) of sensory stimuli and related evoked activity (Hillebrand et al. 2005; Takeda et al. 2014).

The main goal of our study was to develop a processing stream that combines information from fMRI and MEG during a verbal memory learning and attention task to maximize the strengths of each modality. FMRI's spatial resolution and MEG's temporal resolution may be resolved together within a Bayesian framework by applying the Multiple Sparse Prior (MSP) algorithm (Friston et al. 2008a; Henson et al. 2011, 2019). We used this pipeline to identify spatiotemporal characteristics of active encoding with improved spatial and temporal resolution when compared to fMRI or MEG approaches alone.

METHODS

Participants

We recruited 24 healthy native English-speaking adults (13 female, 4 atypically handed, ages 18-39 years*)* with no history of neurological or psychiatric disorders (Table 1). Participation included attending two separate sessions of scanning approximately one week apart. Of the 24 participants, 23 completed all study procedures and are included in the analyses. The Institutional Review Board at the University of Alabama at

Birmingham approved this project, and all participants provided written informed consent. Participants completed the MRI scanning session during their first visit and the MEG scanning session during their second visit (Nair et al. 2019; Vannest et al. 2015).

Table 1

Participant demographics

	Male participants (*N* = 11)	Female participants (*N* = 13)	All participants (*N* = 24)
Age			
mean (sd)	25.73 (6.2)	24.46 (3.9)	25.04 (5.0)
min - max	20 - 39	18 - 30	18 - 39
Handedness (#)			
Right	10	10	20
Aytpical	1	3	4

Paired-Associate Learning Task

During both fMRI and MEG sessions, related word pairs were presented to participants during the verbal paired-associate learning task (Schefft et al. 2008). All word pairs selected for the present study were all under 6 letters in length and were chosen from previous studies (Schefft et al. 2008; Siegel et al. 2012). Word pairs were distributed across 5 relationship classes: associates (e.g., *lock – key*), category members (e.g., *saucer – bowl*), synonyms (e.g., *street – road*), antonyms (e.g., *hot – cold*), and rhymes (e.g., *care – dare*) (Siegel et al. 2012). To ensure comprehension regarding task procedures, participants practiced a version of the task before their first scanning session. During fMRI scanning, 60 word pairs were presented either in full (e.g., *spider – web*), or with the second word partially missing (e.g., *bed – p******), and participants were instructed to either passively read or actively self-generate the second word out loud. During MEG scanning, 200 word pairs were presented, but only with the second word partially missing and participants were instructed to *covertly* generate the target word for each trial. There was no overlap in the word pairs used in the fMRI and MEG versions of the task. For all but three participants, fMRI scanning sessions preceded MEG scanning sessions by several weeks.

Data Acquisition

MRI Acquisition. Anatomical and fMRI data were acquired on a Siemens Magnetom Prisma 3.0T whole-body MRI system during approximately one hour-long scanning session. High-resolution T1-weighted anatomical images were acquired (TR: 2400ms, TE: 2.22ms, FOV: 25.6x24.0x16.7cm, matrix 256x240, flip angle: 8 degrees, slice thickness: 0.8mm, voxel size: 0.8x0.8x0.8mm). During the in-scanner pairs encoding task, functional T2*-weighted images were obtained using a partially silent event-related task design (TR: 1990ms, TE: 35ms, FOV: 240x240x129mm, flip angle: 70 degrees, matrix 240x240, slice thickness: 4mm, axial slices, voxel size: 3.8x3.8x4mm). This clustered-sparse temporal acquisition technique (HUSH; Schmithorst and Holland 2004) allows for recording overt responses during scanning while taking advantage of the intrinsic delayed response of the HRF. The HUSH technique captures activity taking place seconds preceding data collection, as the positive peak of the HRF occurs around 4 to 6 seconds following stimulus presentation (Buxton et al., 2004).

MEG Acquisition. MEG recordings (sampling frequency of 291 Hz) were collected in a magnetically shielded room using a 148-channel whole head magnetometer (MagnesTM 2500 WH, 4-D Neuroimaging). Fiducial head-sensor coils and head shape data using a 3D digitizer were collected to monitor head position and for co-registration between participant's MEG data and anatomical MRI. Collection of task and a resting-state scans was counterbalanced.

FMRI Data Processing

We have outlined the co-processing pipeline for clarity in Figure 1, and annotated MATLAB scripts (.mat) for the entire pipeline are available to share (directory creation, fMRI and MEG preprocessing and second level analyses). These can be adapted to suit various task designs. Preprocessing of event-related fMRI data was performed with SPM12 (http://www.fil.ion.ucl.ac.uk/spm/). To account for any signal intensity changes in the HRF across three volumes acquired via sparse acquisition, functional image volumes were split into three separate HUSH parts (Schmithorst and Holland, 2004), realigned and coregistered to individual participant's anatomical before normalization to the MNI152 template atlas. All functional image volumes were then spatially smoothed to an effective smoothness of a Gaussian FWHM of 6mm. There were no additional filtering or artifact regression steps prior to Group ICA (Calhoun et al., 2001). All trials were retained for analysis as participants attempted to reach semantic and contextual integration during the task, and thus are assumed to undergo the process of encoding word pair associates regardless of whether they produce the correct word during the task (Marinkovik, 2004). Further details regarding fMRI preprocessing of HUSH data, including a broad schematic of the developed analysis pipeline, can be found in our previously published work (Nair et al. 2019).

Group-level spatial independent component analysis (ICA) was carried out using Group ICA fMRI Toolbox, v4.0b (GIFT; http://mialab.mrn.org/software/gift) implemented in MATLAB (Calhoun et al. 2001). Functional image volumes were not subject to any additional filtering or artifact regression prior to Group ICA (Calhoun et al. 2001). First, two rounds of subject-specific principle component analysis (PCAs) were conducted for data reduction for each of the three HUSH image volumes. The first round of PCA at the individual subject level yielded 51 components, and the second yielded 41 components (Calhoun et al. 2001; Erhardt et al. 2011). A high model order of 41 independent components was selected using Infomax algorithm to aid in segmenting task-related brain activity into functionally distinct and noise-related sources (Hutchison and Morton 2015; Ray et al. 2013; Saliasi et al. 2014; Ystad et al. 2010) consistent with similar studies from our group (Nair et al. 2019; Vannest et al. 2015). Using GIFT's GICA3 back-reconstruction method, subject-specific time courses and spatial maps (SMs) were estimated from matrices derived in previous PCA steps (Calhoun et al. 2001; Erhardt et al. 2011). GIFT yields these spatial maps that can be interpreted as networks of similar BOLD activity, related to various aspects of processing (Calhoun et al., 2001; McKeown et al., 2003). We used GIFT's temporal sorting tool to classify components by comparing the model's time course to the time courses of all 41 ICs using a correlation function (Rachakonda et al. 2007). The model time course was inputted as a binary task time series, where a "1" was used to designate the active encoding condition (task-positive trials), and a "0" identified passive reading (task-negative) trials. Components with a correlation coefficient of |r|>0.30 were selected as task-related (Gaston et al. 2017; Nair et al. 2019; Vannest et al. 2015). After temporal sorting, components are arranged based on correlation with the binary time series, and those with positive and negative correlations that meet threshold are visually examined. Of the 41 components identified, 4 components met threshold for task-positive relatedness, and 1 component was identified as task-negative. For the active encoding condition, component correlations were *r*>0.30 and for the passive reading condition, correlations were *r*>-0.30. Components with a correlation coefficient between -0.30>*r*>0.30 were excluded from any further analyses.

To resolve any discrepancies using the HUSH sparse acquisition paradigm and three GIFT analyses, task-related components were visually inspected to identify similar regional activity across HUSH parts. When a component met task-relatedness threshold across more than one volume, then the volume with the highest correlation to the task time series was selected. Once components were selected as meeting threshold for both task-positive and -negative conditions, masks were directly created from group ICA NIFTI files using AFNI's 'Save Mask' tool in the graphical user interface.

MEG Data Processing

MEG raw data in 4D/BTI format were first converted using SPM's convert function (spm_eeg_convert), and headshape points were incorporated (spm_eeg_prep). An ERP approach was employed in order to identify early sensory responses to active generation, and an approach isolating theta frequency band (4-7Hz) was employed due to the lexical-semantic retrieval nature of the task (Bastiaansen et al. 2005; Klimesch 1999; Pu et al. 2020; Raghavachari et al. 2006).

ERP approach. A series of filters was applied to the converted raw data (spm_eeg_filter): a high pass filter at 0.6Hz, followed by a notch filter to remove line noise (60Hz, 120Hz), and a low pass filter at 30Hz. Data were epoched (spm_eeg_epochs), trials were averaged (spm_eeg_average), and a low pass filter at 30Hz was applied once more due to the potential introduction of high frequencies after averaging (Litvak et al. 2011).

Theta power approach. To analyze event-related theta power, additional analyses averaging power across the time-frequency window (4-7Hz) were conducted (Henson et al. 2019). For these data, a high pass filter at 0.6Hz, notch filters at 60Hz and 120Hz, and a low pass filter at 60Hz were applied. To preserve cognitive activity that is not likely time-locked across trials, within subject epochs were not averaged before moving forward with source localization.

For both approaches, artefact detection was conducted using SPM's threshold z-scored data detection algorithm with the threshold set at z=3 (spm_eeg_artefact). Artefacts were marked as events with an excision window around each event of 100ms. Channels with more than 80% of trials with detected artefacts were declared as bad. Data were epoched using a trial definition file that establishes a condition label, event type, event value, and trial shift.

Multiple Sparse Priors: fMRI Constrained MEG

Combining data from two modalities with different neural sources is challenging. At present, there is no optimal solution for integrating MEG and fMRI data. We employed a hierarchical Bayesian approach, Multiple Sparse Prior (MSP) to approximate current density and determine possible source solutions for a verbal memory task (Friston et al. 2008a; Henson et al. 2010, 2011, 2019; Litvak et al. 2011). We used the fMRI task-positive independent components outlined in Section 2.4 as spatial priors to constrain MEG source estimations within MSP.

The MEG imaging pipeline for source analysis is divided into four steps, three of which are executed in the "g_source_reconstruction.m" script. First, source space modeling created a head model based on an individual's structural image and corresponding spatial deformation field. A nonlinear transformation was applied to create individual cortical meshes in the designated template space using a "normal" cortical mesh size (5124 vertices). Next, data co-registration utilized the fiducials by projecting the MEG data onto each participant's anatomical MRI using a rigid-body transformation (Henson et al. 2010). When a subject's structural MRI is available, it is recommended to specify fiducial points but not use the head shape information (Litvak et al. 2011). Forward volume head modeling of the projected magnetic field was determined by using a single-shell (surface) fit to the individual's scalp mesh. Lead field matrices calculated during this stage are later used for inversions. Following source space modeling and co-registration and forward computation variables are created for each fMRI prior (four task-positive IC's). Source reconstruction takes place during the model inversion stage of processing, using multiple sparse priors for each prior using greedy search (GS) inversion type, with a full time-frequency window of [-100 to 1200 ms] and a prior mask (.nii) for each prior derived fMRI components from section 2.4.3.

In the final stage of source analysis, inverse reconstruction, time-frequency contrasts were created by inverting the epoch of interest (across listed frequencies) to localize the effects within the cortical mesh (Henson et al. 2019). For the ERP approach, time windows analyzed (in ms) included [0 150], [100 250], [300 450], [350 500], [500 650], [600 750], and [700 850], and a baseline condition at [-150 0]. For the theta approach, time windows included [100 250], [300 450], [450 600], [600 750], [750 900], [900 1050], [1050 1200] with frequencies restricted to 4-7 Hz.

To examine spatial projections at the group level, paired two-sample t-tests were conducted for each prior and for each time window of interest, contrasting the active generation condition with a baseline condition (stats.factorial_design).

RESULTS

Group ICA: Task-related components from fMRI data

Five components met threshold for task-relatedness out of the 41 components identified using Group ICA (Table 2, Figure 2). Four were the active generation condition (positive correlation with task time course) and one was the passive reading condition (negative correlation with task time course). The component with the highest task correlation (IC19; r=0.4142) included regions spanning right supramarginal gyrus, postcentral gyrus, and middle frontal gyrus, bilateral superior and inferior parietal lobes (IPL), and precuneus (Figure 2a). The component with the second highest task-positive correlation (IC13; r=0.3674) included regions spanning bilateral inferior, medial, and middle frontal gyri, supramarginal gyri, inferior and superior parietal lobes, left superior temporal gyrus (STG) and middle temporal gyrus (MTG), superior frontal gyrus, precentral gyrus, and precuneus (Figure 2b). The third component (IC4; *r*=0.3652) included bilateral cuneus, inferior and middle occipital gyri, lingual gyri, and supramarginal gyri (Figure 2c). The fourth task-positive component (IC26; *r*=0.3319)

Table 2

Group level task-related ICs from fMRI (Figure 2) and the location, volume and MNI coordinates (x, y, z) for each IC cluster's center of mass. L, left; R, right

Component	Location	Volume (cc)	x	y	z
	Task-positive components (active generation)				
IC19	R supramarginal gyrus	7.1	26	-58	58
(r=0.41418)	R precuneus	6.7	12	-66	62
	R superior parietal lobe	6.5	30	-58	60
	R inferior parietal lobe	6.1	34	-54	58
	L inferior parietal lobe	5.6	-32	-54	58
	L precuneus	5.6	-20	-66	52
	L superior parietal lobe	5.1	-22	-66	58
	R postcentral gyrus	3.5	14	-58	66
	R middle frontal gyrus	1.4	40	0	54
IC13	L middle frontal gyrus	15	-52	14	30
(r=0.36739)	L inferior frontal gyrus	10.9	-52	18	28
	L supramarginal gyrus	7.6	-46	24	24
	L inferior parietal lobe	5.4	-32	-62	48
	R middle frontal gyrus	5	52	22	28
	R inferior frontal gyrus	4.5	50	26	24
	L superior parietal lobe	2.8	-30	-66	46
	R supramarginal gyrus	2.5	46	26	22
	L precuneus	2.5	-28	-68	42
	L medial frontal gyrus	1.9	-2	28	42
	L precentral gyrus	1.8	-44	4	38
	L superior frontal gyrus	1.7	-30	58	2

	R superior parietal lobe	1.6	34	-62	50
	R inferior parietal lobe	1.5	34	-60	46
	R medial frontal gyrus	1.2	2	24	44
	L middle temporal gyrus	1.1	-58	-50	4
	L superior temporal gyrus	1.1	-60	-48	8
IC4 (r=0.36521)	R middle occipital gyrus	9.7	26	-94	6
	L middle occipital gyrus	6.7	-24	-96	0
	R cuneus	6.5	14	-94	-8
	L lingual gyrus	5.4	-8	-98	-6
	L cuneus	5.1	-12	-98	-6
	R lingual gyrus	3.3	15	-94	-8
	L inferior occipital gyrus	3.3	-28	-92	-12
	R supramarginal gyrus	2.3	24	-92	-8
	R inferior occipital gyrus	1.5	30	-90	-12
	L supramarginal gyrus	1	-22	-94	-8
IC26 (r=0.3319)	R inferior frontal gyrus	7.4	44	18	-10
	R superior frontal gyrus	6.5	4	14	54
	L inferior frontal gyrus	5.7	-44	16	-8
	R anterior cingulate cortex	5.6	6	30	26
	L anterior cingulate cortex	4.8	-2	30	28
	R cingulate gyrus	3.8	2	30	30
	L medial frontal gyrus	3.3	-4	12	50
	R medial frontal gyrus	3.2	2	24	46
	L superior frontal gyrus	3.1	0	12	56
	L cingulate gyrus	3	0	24	34
	R middle frontal gyrus	3	32	54	22
	R insula	2.6	36	24	2
	L superior temporal gyrus	2.5	-44	16	-12
	R superior temporal gyrus	2.4	48	18	-8
	L insula	2.1	-40	14	-4
	L extra-nuclear	1.3	-32	26	8
	R extra-nuclear	1.3	36	16	-10
	R caudate	1.2	8	6	4
Task-negative components (passive reading)					
IC38 (r= -0.34658)	L precuneus	10.2	0	-64	32
	R precuneus	7.2	4	-64	30
	L posterior cingulate cortex	4.6	0	-54	20

R posterior cingulate cortex	4.6	5	-52	20
L cingulate gyrus	4.5	0	-64	28
L middle temporal gyrus	3.7	-48	-70	28
R cingulate gyrus	3.5	4	-64	26
L superior temporal gyrus	2.4	-46	-62	28
R superior temporal gyrus	2.3	50	-60	28
R inferior parietal lobe	2.2	44	-66	40
L angular gyrus	2.2	-44	-70	36
R middle temporal gyrus	2	50	-64	26
L middle frontal gyrus	2	-22	26	44
R angular gyrus	1.9	50	-64	30
L superior frontal gyrus	1.9	-22	28	48
L inferior parietal lobe	1.5	-42	-70	40
L superior parietal lobe	1.3	-34	-74	44
R supramarginal gyrus	1.3	50	-60	32
R superior parietal lobe	1.1	38	-70	46
R extra-nuclear	1	16	-54	18

spans bilateral inferior and superior frontal gyri, insula, anterior cingulate cortex (ACC) and medial frontal gyri, STG, and extra-nuclear areas, and right middle frontal gyrus and caudate (Figure 2d). The one component meeting task-relatedness for passive reading (IC38; *r*=-0.3466) spans bilateral precuneus, cingulate and posterior cingulate cortices (PCC), angular gyri, STG and MTG, inferior and superior parietal lobe, and left superior and middle frontal gyri, and right supramarginal gyrus and extra-nuclear areas (Figure 2e). All four task-positive components were retained as fMRI priors (binarized masks) for MEG source reconstruction, and the distributed cortical solutions for each prior's model inversion are listed below.

MEG Source Reconstruction

Source reconstruction was performed in standardized MNI space for each fMRI prior resulting in summarized images (Figures 3 and 4). Reconstructions were run for all four fMRI priors (independent components meeting task-positive threshold) for each subject, producing individual subject spatial maps. Results from the paired two-sample t-test contrasting the active generation condition to baseline period are presented in Figures 3b-c, 4b-c. Source reconstruction maps were also generated without fMRI priors for the ERP and theta power (Figures 3a, 4a) approaches. All results are corrected for multiple comparisons at $p<0.05$.

IC19 (Figure 3b). Source reconstruction results using the ERP approach for IC19 using fMRI prior that spans bilateral parietal areas are presented in Figure 3b and Table 3. Early activity in the first 150ms across bilateral occipital and left inferior temporal gyri, followed by recruitment of bilateral inferior temporal gyri, superior orbitofrontal and medial frontal gyri between 100 and 250ms. Between 350 and 500ms, group activity spans medial and inferior frontal gyri, right parahippocampal gyrus, and left inferior temporal gyrus, and between 500 and 650ms, sustained activity in bilateral medial frontal gyrus right medial orbitofrontal cortex (OFC), and fusiform gyrus.

IC13 (Figure 4b). Source reconstruction images for our theta power approach for IC13 using fMRI prior that includes bilateral frontal gyri and left parietal lobe are presented in Figure 4b and Table 3. Early activity between 300 and 450ms in left inferior temporal gyrus and MTG, followed by right inferior temporal gyri and left middle temporal pole between 450 and 600ms. Within the next 150ms, left MTG joins right middle temporal pole. The time window between 750 and 900ms yielded broad, bilateral temporal activity and left inferior OFG. From 900 to 1050ms, we see right fusiform and left inferior temporal gyri contributions.

IC4 (Figure 3c). Source reconstruction results using the ERP approach for IC4 using fMRI prior that spans bilateral occipital areas are presented in Figure 3c and Table 3. Activity within bilateral fusiform gyri, MTG, right middle frontal gyri, and strong middle occipital gyrus contributions are present within the first 150ms, with bilateral

Table 3

MEG source reconstruction results for each fMRI prior using the ERP approach (Figure 3) and the theta-power approach (Figure 4). For each time window, the location and MNI coordinates (x, y, z) for each source location's center of mass are provided. L, left; R, right

fMRI Prior	Time window (ms)	Location	x	y	z
		ERP approach			
No fMRI priors	0-150	R parahippocampal gyrus	32	-20	-28
		L calcarine gyrus	-4	-92	-10
		R inferior occipital gyrus	34	-92	-10
		R inferior occipital gyrus	48	-76	-4
		L medial orbitofrontal cortex	-6	54	-8
		R middle temporal gyrus	64	-40	-2
		L superior occipital gyrus	-16	-80	40
	100-250	R medial frontal gyrus	-6	54	20
		L medial orbitofrontal cortex	-6	54	-8
		R inferior occipital gyrus	44	-70	-14

		R superior orbitofrontal cortex	24	44	-14
		L inferior frontal gyrus, opercular part	-50	10	2
		R middle frontal gyrus	40	44	18
		R superior medial frontal gyrus	8	56	18
	350-500	R parahippocampal gyrus	24	-14	-30
		L inferior temporal gyrus	-44	-26	-24
		R medial frontal gyrus	8	60	-18
		L medial orbitofrontal cortex	-6	62	-12
		L middle temporal gyrus	-52	-38	0
		R middle temporal gyrus	50	-38	-2
		L inferior frontal gyrus, opercular part	-48	12	4
	500-650	R medial orbitofrontal cortex	10	52	-4
		L inferior orbitofrontal cortex	-46	24	-12
		L medial orbitofrontal cortex	-6	54	-10
		L middle temporal gyrus	-64	-36	0
		L superior medial frontal gyrus	-8	54	18
IC19	0-150	R fusiform gyrus	38	-26	-26
		L calcarine gyrus	-6	-92	-10
		L inferior temporal gyrus	-54	-58	-20
		R inferior occipital gyrus	30	-88	-8
		L middle occipital gyrus	-48	-78	0
		L middle occipital gyrus	-32	-84	30
		L superior occipital gyrus	-16	-82	40
	100-250	L inferior temporal gyrus	-58	-54	-22
		R superior orbitofrontal cortex	8	52	-24
		R inferior occipital gyrus	38	-82	-16
		L superior orbitofrontal cortex	-6	54	-10
		L rolandic operculum	-44	-4	12
		R superior medial frontal gyrus	8	54	18
		L superior medial frontal gyrus	-8	58	20
	350-500	R parahippocampal gyrus	28	-20	-28
		R superior orbitofrontal cortex	10	56	-22
		L inferior temporal gyrus	-58	-54	-22
		L inferior orbitofrontal cortex	-46	26	-12
		L middle orbitofrontal cortex	-24	40	-12
		L inferior frontal gyrus, opercular part	-44	10	6
		L superior medial frontal gyrus	-8	56	18
		R superior medial frontal gyrus	8	54	18

	500-650	R fusiform gyrus	44	-36	-22
		R medial orbitofrontal cortex	10	44	-12
		L superior medial frontal gyrus	-8	54	18
		R superior medial frontal gyrus	8	54	16
IC4	0-150	R fusiform gyrus	38	-28	-26
		L fusiform gyrus	-44	-48	-20
		L middle occipital gyrus	-48	-78	0
		L middle temporal gyrus	-64	-36	0
		R middle temporal gyrus	64	-40	-2
		R middle frontal gyrus	42	44	4
		L middle occipital gyrus	-32	-84	30
		R middle frontal gyrus	38	42	18
	100-250	R parahippocampal gyrus	30	-22	-28
		L parahippocampal gyrus	-22	-18	-28
		R medial frontal gyrus	6	54	-20
		L fusiform gyrus	-30	-82	-18
		L medial orbitofrontal cortex	-6	54	-8
		R inferior occipital gyrus	30	-88	-8
		R middle orbitofrontal cortex	26	42	-14
		R inferior temporal gyrus	40	-52	-14
		R middle frontal gyrus	40	44	18
		L middle frontal gyrus	-42	38	16
		R superior medial frontal gyrus	8	56	18
		L superior medial frontal gyrus	-8	54	18
	350-500	L inferior temporal gyrus	-40	-38	-18
		R medial orbitofrontal cortex	8	40	-10
		L inferior orbitofrontal cortex	-40	28	-12
		L medial orbitofrontal cortex	-6	54	-10
		L middle temporal gyrus	-56	-38	0
		R middle temporal gyrus	62	-42	2
		R superior medial frontal gyrus	8	56	18
	500-650	R parahippocampal gyrus	26	-10	-32
		R fusiform gyrus	38	-28	-24
		R medial frontal gyrus	8	58	-18
		L inferior orbitofrontal cortex	-46	24	-12
		L medial orbitofrontal cortex	-6	54	-10
		L middle temporal gyrus	-66	-34	-2
		R middle temporal gyrus	62	-42	2

		L superior medial frontal gyrus	-8	56	18
		R superior medial frontal gyrus	8	54	16
		Theta power approach			
No fMRI priors	300-450	L inferior temporal gyrus	-36	4	-42
	450-600	L inferior temporal gyrus	-32	4	-40
		R middle temporal pole	30	6	-42
		L inferior temporal gyrus	-42	-28	-20
		L middle temporal gyrus	-60	-14	-24
	600-750	R fusiform gyrus	28	2	-42
		L middle temporal pole	-38	4	-44
	750-900	R inferior temporal gyrus	40	2	-38
		L inferior temporal gyrus	-40	2	-44
		L middle temporal gyrus	-60	-14	-22
		L inferior orbitofrontal cortex	-16	20	-24
		R middle temporal gyrus	62	-12	-20
	900-1050	R inferior temporal gyrus	42	2	-38
		L inferior temporal gyrus	-40	2	-44
		L middle temporal gyrus	-60	-14	-24
IC13	300-450	L inferior temporal gyrus	-34	6	-42
		L middle temporal gyrus	-64	-18	-10
	450-600	R inferior temporal gyrus	40	2	-38
		L middle temporal pole	-38	4	-44
		L middle temporal gyrus	-60	-14	-16
	600-750	R middle temporal pole	34	4	-38
		L inferior temporal gyrus	-32	2	-40
		L lateral inferior temporal gyrus	-60	-12	-26
	750-900	R middle temporal pole	30	6	-42
		L middle temporal pole	-38	4	-44
		L middle temporal gyrus	-60	-14	-16
		L inferior orbitofrontal cortex	-24	8	-18
	900-1050	R fusiform gyrus	26	0	-44
		L inferior temporal gyrus	-32	4	-40
IC26	450-600	R fusiform gyrus	26	6	-42
		L inferior temporal gyrus	-34	4	-42
		L middle temporal gyrus	-64	-18	-10
	600-750	R inferior temporal gyrus	28	8	-44
		L middle temporal gyrus	-60	-14	-16

	L insula	-26	8	-18
750-900	L inferior orbitofrontal cortex	-28	16	-24
	L middle temporal gyrus	-64	-18	-10
900-1050	L middle temporal pole	-30	6	-40
	L inferior orbitofrontal cortex	-16	18	-24
	L middle temporal gyrus	-62	-14	-14
	R pars triangularis	52	24	0

parahippocampal gyrus, superior medial and middle frontal gyri and orbitofrontal gyri following between 100-250ms. Within the 350 to 500ms window, we see bilateral MTG recruited, along with left inferior and medial orbitofrontal gyri, and right superior medial frontal gyrus. Within 500 to 650ms, there is still recruitment of bilateral MTG and superior medial frontal areas, along with right fusiform gyrus.

IC26 (Figure 4c). Source reconstruction images for the theta power approach for IC26 using fMRI prior within bilateral inferior frontal gyrus and anterior cingulate cortices are presented in Figure 4c and Table 3. The earliest significant activity is within the time window of 450-600ms within left inferior temporal gyrus and MTG, and right fusiform gyrus. Between 600 and 750ms, there is recruitment of right inferior temporal gyrus along with left MTG and left insula, followed by left inferior OFG and left MTG within 750 and 900ms. Activity within the left middle temporal pole, inferior OFG, and MTG, along with right pars triangularis is present within the 900 to 1050ms window.

DISCUSSION

The aim of the present study was to develop a processing pipeline that would integrate fMRI and MEG data and to use this pipeline to analyze a paired associate learning task conducted with the same group of subjects. By first establishing spatial contributions to active generation using fMRI, we are able to constrain MEG source space solutions to specific volumes of interest (Friston et al. 2008b; Henson et al. 2019).

FMRI: Spatial contributions to active generation

The four independent components meeting a task-positive threshold of $r > 0.30$ broadly capture various aspects of active encoding. The network with the highest correlation with the task, IC19 (Figure 3b), includes bilateral inferior and superior parietal areas, which have been shown to be recruited during tasks involving maintaining visual and cognitive attention (Otten, Henson, and Rugg 2001b). The inferior parietal lobe (IPL) is thought to play a substantial role in maintaining attention (Rueckert and Grafman 1998; Rushworth, Krams, and Passingham 2001). In the present study, IPL contributions seen during self-generation (Figures 2a-b) suggest that attentional demands may be greater when actively encoding the second word in the word pair compared to passive reading.

The network with the second highest correlation with the task, IC13 (Figure 4b), is the only component meeting threshold that showed a left-lateralization effect within a broad fronto-parietal network. There is evidence suggesting the middle frontal gyri's (MFG) role in integrating between dorsal and ventral attention streams, aiding in reorienting attention towards relevant task demands (Christensen et al. 2012; Japee et al. 2015). In the case of active generation, top-down modulation is necessary in the mental search for target words using cues, and frontal contributions likely play an integrative role during the present task. In addition to dynamic interactions with posterior brain areas, the MFG (Miller and Cohen 2001), and more broadly the dorsolateral prefrontal cortex (dlPFC), has been long affiliated with working memory processes and retrieval (D'Esposito et al. 1997; Thompson-Schill et al. 1997).

Another task-positive network with frontal contributions, IC26 (Figure 4c), shows bilateral frontal and superior temporal activity at the group level, along with ACC. This is largely consistent with previous studies of self-generation effects, where the ACC, a part of the salience network, may be playing a role in the present task when internally monitoring potential responses to the task demands (Nair et al. 2019; Rosner, Elman, and Shimamura 2013; Vannest et al. 2015). Additionally, there is recent evidence that activity within the ACC and left inferior frontal gyrus (IFG), along with superior parietal areas, may be modulated by the complexity of processing during a semantic task (Moss et al. 2011). In the present study, all three regions are implicated within two task-positive networks, suggesting increased task demand within self-generation compared to passive reading. Our findings of bilateral superior temporal gyrus involvement is also consistent with previous work on word and pseudoword recognition (Simos et al. 2000).

The third task-positive network spans bilateral visual areas, including middle and inferior occipital gyri, lingual and supramarginal gyri, and cuneus. Our findings of an extended visual network recruited during self-generation are important considering the visual nature of the task presented (Nair et al. 2019). Additionally, the differences in stimuli for passive reading and active generation may contribute to this network meeting task-relatedness as well: while the "read" condition fully presented two related word pairs on screen, the "generate" condition replaced letters in the second word pair with asterisks characters, possibly introducing variability in the visual complexity between stimuli utilized in the two conditions.

Together, brain areas associated with the default mode network (DMN) are thought to contribute to internal processing, and studies of self-generation have implicated certain areas of the DMN (IPL, medial PFC, and precuneus) to aspects of internally generating semantic information (Rosner et al. 2013). Here, we also note contributions from bilateral IPL, medial PFC, and precuneus across task-positive networks (Figures 2a-b, d) during self-generation suggesting aspects of the task encourage internal mediation perhaps during semantic and conceptual processing while searching for the correct word pair.

The only task-negative component to meet threshold for passive reading implicated a temporo-parietal network spanning PCC, superior and middle temporal gyri, inferior and superior parietal lobes. This network appears more classically aligned with the DMN, with strong activation in bilateral precuneus, IPL, and PCC, and is consistent with previous work examining brain networks associated with reading and generating (Rosner et al. 2013). In terms of the differential DMN contributions during self-generation and passive reading, it is plausible that various aspects of internal processing may recruit regionally specific areas of the DMN depending on task demands (Buckner and Carroll 2007; Shimamura 2011; Spreng, Mar, and Kim 2009).

MEG: ERP approach to active generation

MEG source reconstructions for the evoked approach constrained using fMRI priors (Figure 3a) and without priors (Figures 3b-c), all show early primary visual activity, followed by left inferior frontal gyrus and left inferior temporal lobe. Left IFG activity is more pronounced in the reconstruction for IC19, the fMRI network that spans bilateral parietal areas (Figure 2a) within 100-250ms. The left IFG has been long implicated in studies involving categorization of words (Demb et al. 1995; Kapur et al. 2016), and when identifying words among competing alternatives (Thompson-Schill et al. 1997; Thompson-Schill, D'Esposito, and Kan 1999). Despite parietal activity being absent from MEG reconstructions, these findings also suggest early communication within a frontoparietal network during active generation. This network has been historically associated sustained attention during a task (Ptak 2012), and has been implicated in stimulus-driven action (Corbetta, Patel, and Shulman 2008), rule-learning (de Diego Balaguer et al. 2007), and recently been found to respond to cue-related stimuli (Macaluso and Doricchi 2013).

Activity in the left OFC is more robust within 350-500ms in reconstructions for IC4 (Figure 3c), the prior spanning primary visual areas, compared to other evoked reconstructions. The timing of this activity is consistent with MEG findings of distributed, left-lateralized activity within frontopolar areas during semantic processing around 400ms (Halgren et al. 2002). These findings also support previous work suggesting prefrontal areas play a role in modulating sensory cortices during learning in a top-down fashion (Gilbert and Li 2013; Liu et al. 2020; Poort et al. 2015; Zhang et al. 2014).

MEG: Event-related Theta Power

Source reconstructions for the theta power approach with (Figure 4a) and without fMRI priors (Figures 4b-c) all show early left ITG activity within the first 600ms, but fMRI constrained reconstructions seemed to elucidate dynamics and information transfer more clearly than the reconstructions not informed by fMRI priors. Reconstructed time windows loosely constrained to IC26 (Figure 4c), the bilateral network including IFG, medial frontal cortex, and STG, suggest recruitment of a broad frontotemporal network during active generation. There is a clear progression of early activity from bilateral inferior temporal areas to sustained left inferior OFC and MTG activity at around 750ms, and right IFG activity after 900ms.

In relation to language processing and the generation effect, the left ITG is a critical region in the semantic system (Binder et al. 2009; Kim et al. 2011), involved in image generation (D'Esposito et al. 1997), and implicated as playing a role in stimulus encoding during visual working memory tasks (Woloszyn and Sheinberg 2009). Our findings correspond with previous work both within the temporal window and spatial characteristics of left ITG (Dhond et al. 2001; Marinkovic et al. 2012), and work suggesting left temporal theta may be modulated by retrieving lexical-semantic properties of specific words (Bastiaansen et al. 2005). The later involvement of left OFC suggests increased attention and maintenance of semantic or lexical information (Rosner et al. 2013; Tops and Boksem 2011), and along with bilateral temporal activity may represent communication underlying response selection and decision making (Young and Shapiro 2011) during active generation.

Some caution should be used when interpreting timing associated with theta-related effects, as the temporal resolution of lower frequencies is poorer than higher frequencies by roughly a few hundred milliseconds (Knösche and Bastiaansen 2002), which may contribute to the sustained activity in bilateral temporal areas across time windows (IC13, Figure 4b).

Differences between MSP with and without priors

Previous work examining the impact of fMRI priors on reconstructed MEG source activity has yielded mixed findings, with the MSP framework demonstrating greater model evidence compared to other techniques (Friston et al. 2008b; López et al. 2014; R.N. Henson et al. 2009), with the use of both consistent and inconsistent fMRI priors still increasing the accuracy of MEG source reconstruction (Henson et al. 2011; Wang and eHolland 2021), and priors derived from a meta-analysis also improving MEG source reconstruction (Suzuki and Yamashita 2021).

Previously, Wang and colleagues had demonstrated both spatial concordance and disagreement between MEG and fMRI among different brain areas (Wang et al. 2012). These findings suggest a model integrating the two modalities must prove robust against invalid fMRI spatial priors. MSP addresses this concern by applying a "soft" constraint of priors, which allows for disagreement between the two sources (Wang and Holland 2014). A recent study from the same group found improvement in induced activity over evoked activity during a high-order cognitive paradigm when incorporating fMRI priors into the MEG inversion solution (Wang and Holland 2021). These findings together highlight the ability of MSP to select either a sparse solution or multiple, distributed cortical sources automatically in a data driven way, using empirical priors.

In the current study, source reconstructions without fMRI priors yielded more distributed solutions (Figure 2) compared to reconstructions constrained by fMRI priors. Overall, MSP solutions for both ERP and theta-power approaches produced more focused regions that were largely, but not entirely, present in solutions without priors. This can be seen with early, sustained (0-500ms) left inferior temporal gyrus activity in solutions from bilateral parietal prior (IC19, Figure 3b) where left ITG activity is not present until 350ms in the no priors approach. Another instance where a constrained solution with fMRI prior seems to elucidate a more detailed pattern of activity is with theta-power approach: while the bilateral frontal network fMRI prior (IC26, Figure 4c) seemed to capture stronger and sustained left orbitofrontal cortex activity, along with less pronounced left ITG contributions compared to no prior approach. The left lateralized fronto-parietal fMRI prior (IC13, Figure 4b) does capture sustained left ITG activity similar to the no prior approach. Additionally, with the occipital prior (IC4, Figure 3c), the early posterior activity is sustained longer than without the prior approach (0-250ms).

A model of dynamic processing across all priors

The event-related active generation fMRI paradigm implicated four broad networks that, when integrated within the MSP framework for MEG source reconstruction, yielded distributed solutions across peristimulus time. Within the first 250ms, solutions constrained to the primary occipital prior (Figure 2c) showed inferior and middle occipital activity within the first 250ms (Figure 3c), followed by left inferior temporal gyrus and orbitofrontal cortex activity (350-500ms). These specific fronto-temporal contributions were apparent within earlier time windows within the MSP reconstruction for the bilateral inferior parietal prior (Figure 2a). With an event-related theta-power approach, the left-lateralized (Figure 2b) and bilateral frontal priors (Figure 2d) displayed sustained inferior temporal gyrus and middle temporal pole (450ms+), along with delayed left OFC activity (750ms+) within the bilateral frontal prior (Figure 4c).

The lack of parietal effects across all MSP reconstructions that is present in fMRI spatial ICA results may suggest parietal contributions may be too scattered temporally to be present in the group analysis, or perhaps that this particular approach may not be sensitive enough to detect these effects within MEG at the group level.

Other considerations

Another important MEG processing consideration that has a potential impact on SNR and interpretability involves treatment of artifacts and characterization of “bad” data. As public sharing of electrophysiological data gains popularity alongside large databases of fMRI data, the MEG/EEG community has continued to build upon methods to improve replicability of experiments. While frequency filtering can address low frequency artifacts, high frequency artifacts like muscle activity, and line noise artifacts, these methods are not able to suppress broadband artifacts and data often require additional inspection. Though many of the widely used software packages (Brainstorm, FieldTrip, MNE, SPM) have ready to use tools that can identify and reject segments of data based on basic metrics, like peak-to-peak signal amplitude differences used here, modern and more advanced methods include identifying bad sensors using Signal Space Separation methods (Jas et al. 2017). There are benefits to automated techniques to identify and reject ‘bad’ data, including reproducibility of data processing across sites and studies, though barriers to successful implementation of these techniques exist, especially when using 4d/BTI MEG data as in the current study.

Conclusions

In summary, the present study built a MEG/fMRI data co-processing pipeline and found four major networks associated with self-generation using fMRI, along with differential progression of activity across multiple sparse priors MEG source reconstruction solutions. Across fMRI priors, evoked responses begin bilaterally across lateral and medial occipital cortex, spreading to inferior frontal, orbitofrontal, and inferior temporal areas. No early significant activity (< 300ms) was captured across analyses examining event-related theta power, and bilateral temporal activity was left lateralized within 750ms. Inclusion of fMRI priors to the MSP framework seemed to produce similar, but more detailed accounts of distributed activity across the cortex.

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FIGURES

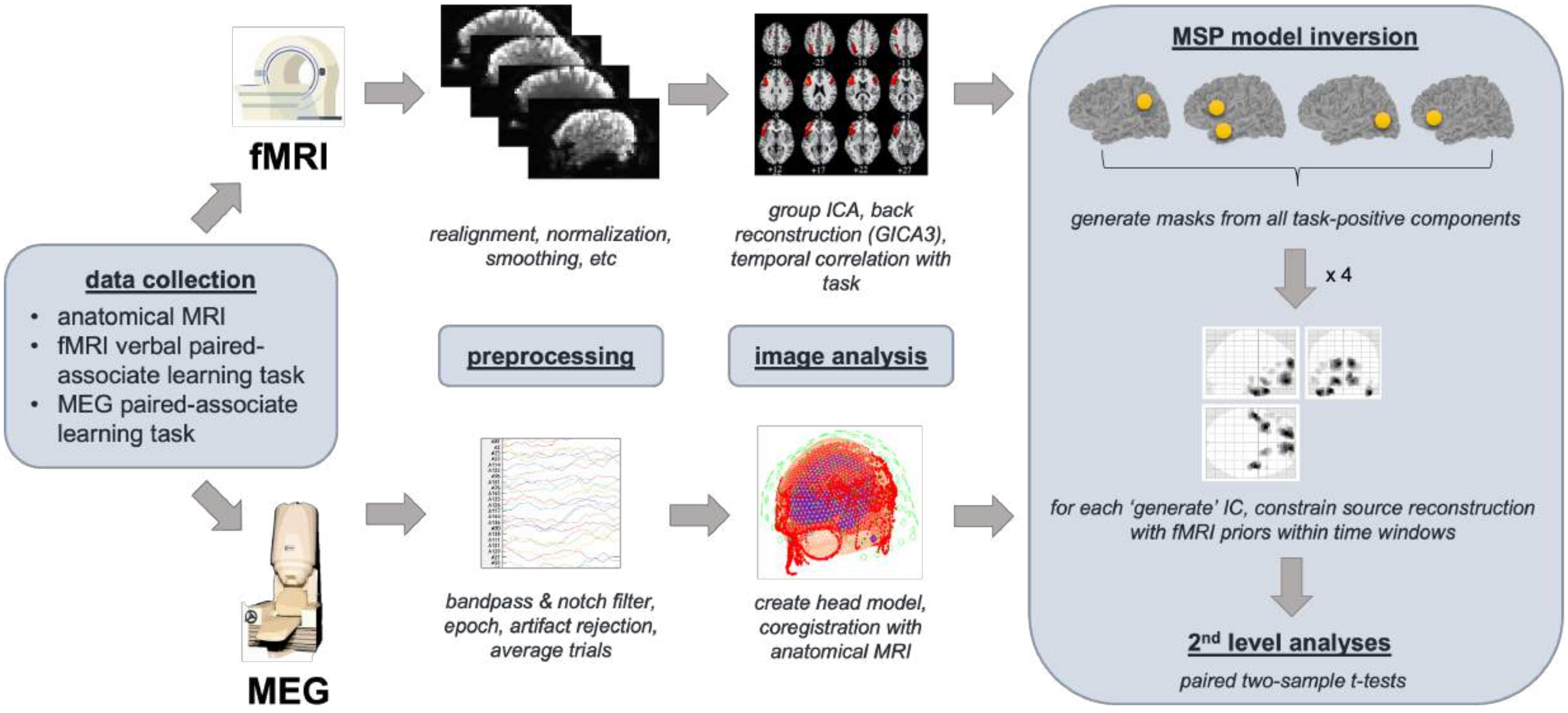

Figure 1. Co-processing pipeline overview/schematic. Data collection (section 2.3), preprocessing fMRI (2.4.1) and MEG (2.5.1), group level fMRI analysis using group ICA (2.4.2) and MEG image analysis (2.5.2), MSP model inversion steps (2.4.2 and 2.5.2), and second level analysis comparing ”generate” and “baseline” conditions (2.5.3)

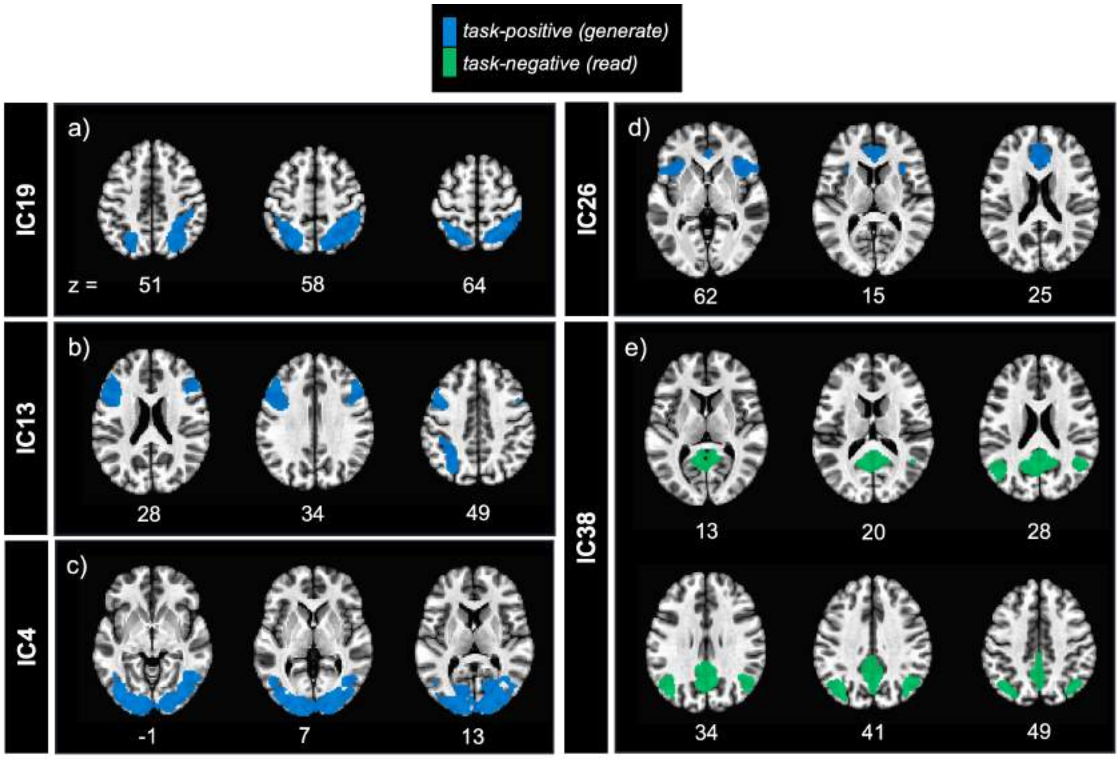

Figure 2. Task-related fMRI components. Images are presented in neurological orientation (right in the image is right in the brain). (A-F) are group average independent components positively correlated (r>0.25) and (G) is negatively correlated (r<0.25) with the time course. Components span: (A) bilateral SPL and IPL, precuneus, middle occipital gyri, and right supramarginal gyrus (IC19); (B) bilateral IFG, precentral gyri, left superior frontal gyrus, middle orbital gyrus, IPL, middle occipital gyrus (IC13); (C) bilateral calcarine gyri, fusiform gyri, lingual gyri, middle occipital gyri, inferior temporal gyri (IC4); (D) bilateral IFG, insula, ACC, MCC, supplementary motor area (IC26); (E) bilateral precuneus, MCC, calcarine and angular gyri, PCC, middle occipital gyri, MTG (IC38). SPL: superior parietal lobe; IPL: inferior parietal lobe; IFG: inferior frontal gyrus; ACC: anterior cingulate cortex; MCC: middle cingulate cortex; MTG: middle temporal gyrus; PCC: posterior cingulate cortex

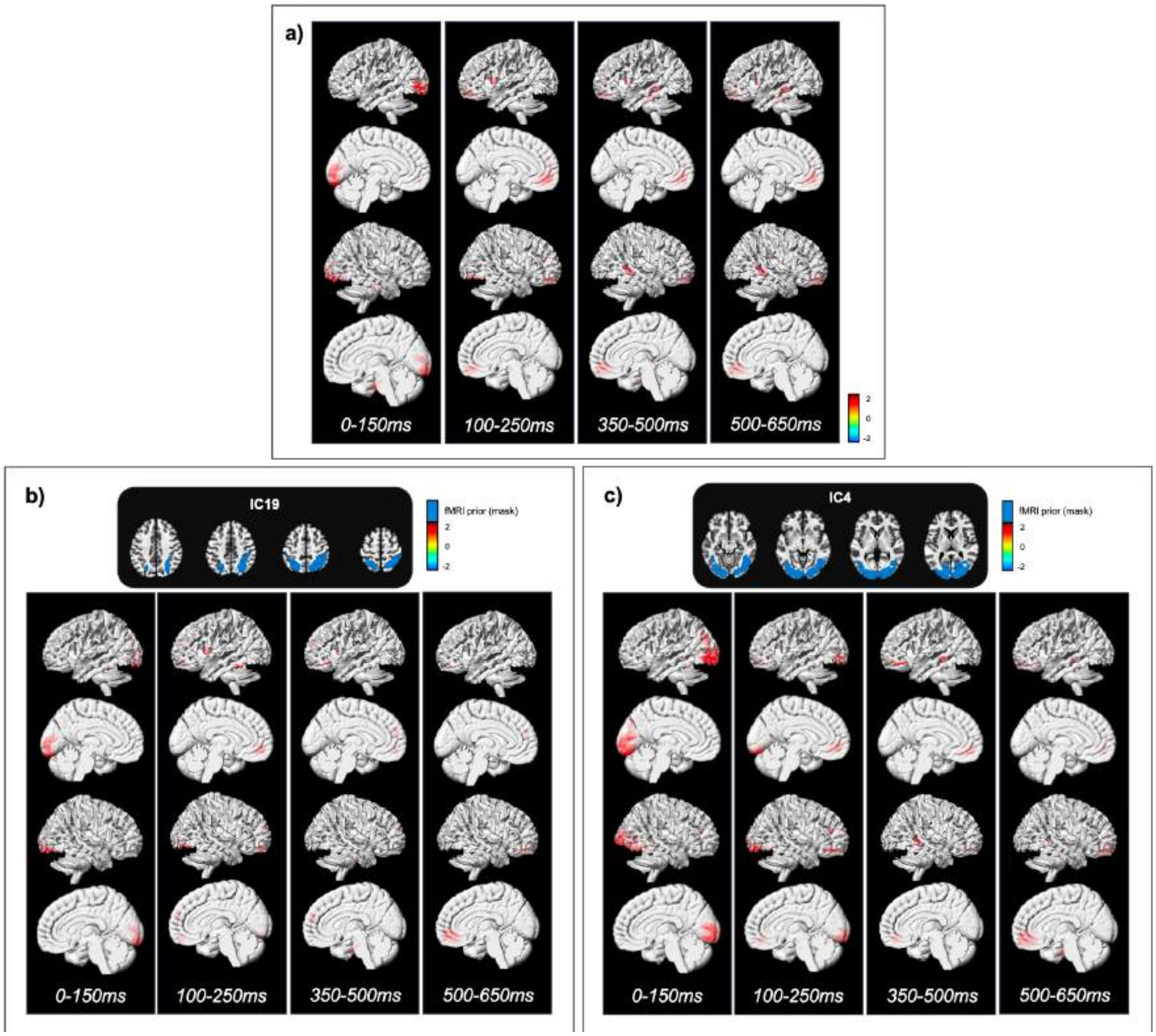

Figure 3. Multiple sparse priors (MSP) for ERP approach. (a) no priors approach, (b) IC19 constrained source reconstructions, (c) IC4 constrained reconstructions. Images are presented in neurological orientation (R=R).

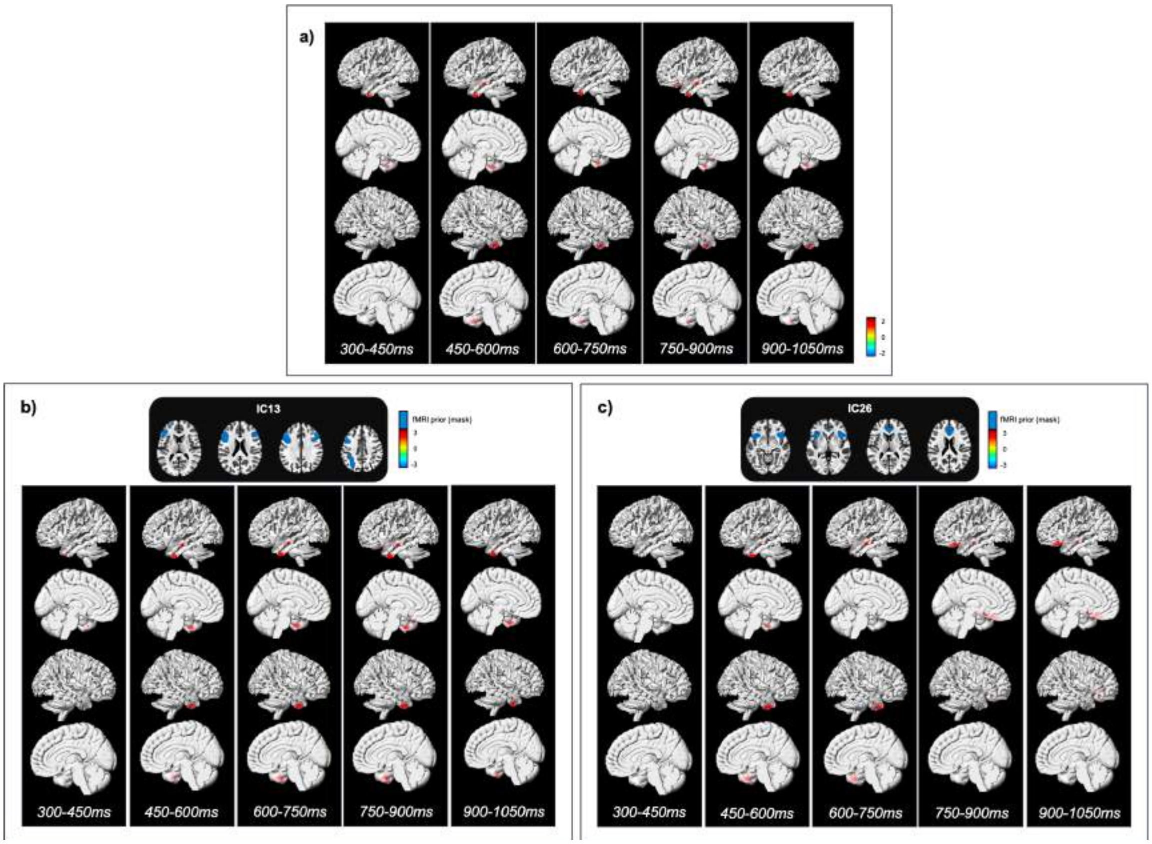

Figure 4. Multiple sparse priors (MSP) for event-related theta-power approach. (a) no priors approach, (b) IC13 constrained source reconstructions, (c) IC26 constrained reconstructions. Images are presented in neurological orientation (R=R).

EVALUATING DYNAMICS WITHIN NETWORKS UNDERLYING WORKING MEMORY USING MULTIPLE SPARSE PRIORS

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In preparation for *Journal of Clinical Neurophysiology*

Format adapted for dissertation

CHAPTER 3

EVALUATING DYNAMICS WITHIN NETWORKS UNDERLYING WORKING MEMORY USING MULTIPLE SPARSE PRIORS

Abstract

FMRI of working memory has documented aspects of the learning and memory processes but it is unable to resolve their dynamics. FMRI and MEG co-processing may improve our understanding of the spatio-temporal characteristics of brain networks. We investigated the dynamics of working memory network using Multiple Sparse Priors (MSP) derived from fMRI to constrain the MEG source reconstruction across time. 24 healthy participants were presented with a modified Sternberg task during fMRI and MEG scanning sessions. Task-related Independent Components (ICs) were derived from fMRI data using Group ICA fMRI Toolbox (GIFT), identifying networks underlying encoding and retrieval working memory processes. Conjunction masks were created combining across ICs for encoding (7 ICs) and retrieval (6 ICs). These were then used to constrain MEG source reconstructions using Multiple Sparse Priors (MSP) across time windows spanning 50sec from 1750-2450ms for encoding and 350-850ms for retrieval. Time windows were also reconstructed without fMRI priors. ICs that met task-relatedness for encoding and retrieval spanned bilateral fronto-parietal areas. During encoding, the use of fMRI priors revealed dynamic brain activity across bilateral middle temporal regions within the first 2 seconds, followed by recruitment of the left

supramarginal and bilateral inferior frontal gyri that were not visible without priors. During retrieval, constrained source reconstructions yielded early bilateral activity within orbitofrontal cortex, followed by right-lateralized engagement and robust bilateral inferior frontal recruitment not seen in analyses without fMRI priors. Across conditions, there was an advantage of applying fMRI spatial priors to MEG source reconstruction. Co-processing of data revealed additional brain regions underlying working memory, and expanded on the dynamic communication between relevant brain areas. The use of fMRI spatial priors on MEG inverse solutions provided a better understanding of the spatiotemporal relationships for encoding and retrieval than the use of MEG alone.

INTRODUCTION

The learning and memory processes are complicated as they comprise of concurrent and sequential events involving several brain structures including bilateral pre/frontal cortices, cingulate, and medial and lateral temporal regions and their connections, all of which are important for successful encoding and retrieval (Krause et al. 1999; Mottaghy et al. 1999). Working memory is typically modeled across three phases: initial encoding of information, maintenance of the information during some delay, and retrieval of the information amid response selection (Repovs and Baddeley 2006). Recent efforts have focused on evaluating the neuroanatomical and functional underpinnings of memory processes in the normative population. The temporal and frontal lobes play a particular role in the encoding process as brain regions that either mediate or induce complex associations between mood and cognition (Helmstaedter and Kurthen 2001) which is likely due to their interconnections (Hermann, Wyler, and Richey 1988; Lieb et al. 1991). While various brain areas are thought to participate in the learning process, hippocampi, parahippocampal gyri, dorsolateral prefrontal and lateral temporo-parietal cortex are most frequently identified in these studies (Dupont et al. 2002; R. N. A. Henson, Burgess, and Frith 2000; Konishi et al. 2000; Krause et al. 1999).

Specialized whole-brain networks comprised of distributed, interconnected regions play a critical role in higher-order cognitive functions (e.g., language processing, attention, and developing strategies for learning and retrieval (Fair et al. 2009; Shaywitz et al. 1995)). Functional magnetic resonance imaging (fMRI) is a widely used tool to identify neural contributions underlying a range of somatosensory and cognitive processes, including working memory, and a wide body of work using this technique has contributed greatly to our understanding of healthy network organization throughout development and aging (Bressler and Menon 2010; Cabeza et al. 1997; Fair et al. 2009; Sporns 2013).

Neuroimaging studies of encoding and retrieval have documented differential effects of various disease states on the learning and memory processes, but the dynamics of these processes are not fully understood. Filling this knowledge gap is important for understanding the distributed processes of working memory and developing interventions that may alleviate abnormalities within those networks. Though approaches to estimate temporal information from fMRI exist, such approaches are still limited by the intrinsic lag of the hemodynamic response function and measured blood oxygenation level dependent (BOLD) signal, and thus are constrained by assumptions and simplifications inherent to the limitation (Buxton 2013; Buxton et al. 2004).

Magnetoencephalography (MEG) directly measures magnetic fields generated by postsynaptic neural activity, preserving the millisecond time-scale of neurophysiological activity. Though MEG boasts specific strengths in the temporal domain, unlike hemodynamic methods, it has a poor spatial resolution. Although fMRI and MEG represent different neural sources and measure different aspects of brain function, these methods can be seen as complementary (Coombes 2010; Lottman et al. 2019; Schulz et al. 2004; Stippich et al. 1998; Wang, Holland, and Vannest 2012). Due to the relative strengths and weaknesses of fMRI and MEG across spatio-temporal domains, finding an optimal solution to integrate data from both modalities may provide a more detailed estimation of functional networks supporting working memory by characterizing sequential and dynamic aspects of encoding and retrieval.

We aimed to identify brain networks underlying working memory in healthy controls using fMRI, and to evaluate the dynamics of encoding and retrieval within relevant brain areas with MEG. To address this, we implemented a recently developed co-processing pipeline (Nair et al. 2021) that integrates fMRI and MEG task data within a hierarchical Bayesian framework by using task-derived independent components from a modified Sternberg task to constrain MEG source reconstructions using Multiple Sparse Priors (MSP). We hypothesized that the MSP approach would allow for increased granularity of the dynamic spatial and temporal aspects of encoding and retrieval during working memory.

METHODS

Participants

A total of 24 healthy native English-speaking adults (13 female, 4 atypically handed, ages 18-39 years) with no history of neurological or psychiatric disorders were recruited. Across two in-person visits, all participants completed the MRI scanning session and 23 participants completed the MEG scanning session due to a participant moving away (Nair et al. 2021). For all but 3 participants, the fMRI session preceded the MEG session. The Institutional Review Board at the University of Alabama at Birmingham approved this project, and all participants provided written informed consent.

Modified Sternberg Working Memory Task

During the fMRI sessions, in the modified Sternberg visual working memory task, participants were presented with a string of either 2 or 6 letters on a screen, followed by a delay of either 4s or 12s, and then presented with one single letter (Gaston et al. 2020; Sternberg 1966). Individuals were instructed to remember the letter series from the previous slide and, via button box press, to respond either "yes" or "no" whether they remembered the single letter presented in the previous series. The task was completed across 2 functional scans spanning 9:38 minutes each, comprising of 64 trials in total. The task was pseudorandomized across the load, delay, and correct responses.

During the MEG scanning session, a total of 200 stimuli were presented across one run, with the total duration typically ranging from 30-45 minutes (dependent on participant response times). Minor differences in the task compared to fMRI included presentation of an alpha-numeric string of 1, 3, 5, or 7 letters and the delay jittered between 2 and 2.5 seconds. There was a 1-back format across both task designs, as participants were not instructed to remember subsequent trials. A schematic of the fMRI and MEG tasks is provided in Figure 1.

Image Acquisition

Anatomical and functional MRI data were collected on a Siemens Magnetom Prisma 3.0T whole-body MRI system. High-resolution T1-weighted anatomical images were obtained (TR: 2400ms, TE: 2.22ms, FOV: 25.6x24.0x16.7cm, matrix 256x240, flip angle: 8 degrees, slice thickness: 0.8mm, voxel size: 0.8x0.8x0.8mm). Functional T2*-

weighted images were acquired using an event-related task design (TR: 2000ms, TE: 35ms, FOV: 240x240, flip angle: 90 degrees, matrix 64x64, slice thickness: 4mm, axial slices, voxel size: 3.8x3.8x4mm) across two runs of 9 minutes and 40 seconds each.

MEG recordings were acquired with a MagnesTM 2500WH, 4-D Neuroimaging, 148-channel whole-head magnetometer system with a sampling frequency of 291 Hz. A 3D digitizer and fiducial head-sensor coils were used to collect head shape data for co-registration between an individual's MEG data and anatomical MRI.

Data Processing

All preprocessing of event-related fMRI and 4D/BTI MEG data was performed with SPM12 (http://www.fil.ion.ucl.ac.uk/spm/). The co-processing pipeline implemented in the present study and outlined below is described in detail in our recent publication(Nair et al. 2021).

FMRI Processing and Group Level Analyses

For both runs of the task, functional image volumes underwent realignment and co-registration to each participant's corresponding anatomical MRI, followed by normalization to the MNI152 template atlas using participant-specific deformation fields derived during co-registration, and spatial smoothing to an effective smoothness of a Gaussian FWHM of 6mm. Overall accuracy was relatively high across all subjects (mean overall runs: 84.2%), and all trials were retained for the following analyses.

Group-level spatial independent component analysis (ICA) was carried out in MATLAB using Group ICA fMRI Toolbox, v4.0b (GIFT;

http://mialab.mrn.org/software/gift)(Calhoun et al. 2001). Two rounds of subject-specific principal component analysis (PCA) were conducted at the individual subject level for each run prior to ICA, with the first and second runs of PCA yielding 51 and 41 components, respectively. PCA is often conducted prior to ICA for data reduction purposes, identifying and selecting components that account for the most variance in the dataset (Chen, Calhoun, and Liu 2012). Next, a model order of 41 independent components (ICs) was selected using the Infomax algorithm.

Subject-specific time courses and corresponding spatial maps were generated using GICA3, a back-reconstruction method offered within GIFT that allows for the interpretation at the group level much like networks of similar BOLD activity (Calhoun et al. 2001; McKeown, Hansen, and Sejnowsk 2003). As a data-driven, blind source separation method, ICA is unable to order source signals without additional task-relevant information. We used GIFT's temporal sorting tool to order components according to the correlation between the model's time course to the time courses of all 41 ICs (Rachakonda et al. 2007). Once sorted by binary task time series for both encoding and retrieval, components were visually inspected and ICs with the highest correlation for each condition were identified as task-related. For both conditions, component correlations of $r>0.071$ were excluded from further analyses (Gaston et al. 2017; Nair et al. 2019; Vannest et al. 2015). ICs that met task-relatedness were then combined into one conjunction mask within each condition (7 ICs for encoding, 6 ICs for retrieval), to be later used in MEG source space modeling.

MEG Preprocessing and Source Reconstruction

Due to the length of the MEG task, some sessions were incomplete due to technical or subject-related reasons. As such,15 of the 23 participants undergoing the scanning session had complete data for the Sternberg task as determined by a minimum of 160 completed trials (80% of total trials). For preprocessing, MEG data were converted, headshape points were integrated, and a series of high (0.6 Hz), notch (60 Hz, 120 Hz), and low pass filters (30 Hz) was applied. Data were then epoched (baseline, encoding, retrieval), and trials for each condition were averaged. A low pass filter at 30Hz was applied once more following averaging trials(Litvak et al. 2011). Finally, artifact detection was employed with a threshold z-scored data detection algorithm (z=3), and individual channels with >80% of "bad" trials were declared as bad and excluded from further analysis.

Source space modeling of preprocessed data included head model creation, co-registration using individual participant's anatomical MRI, and forward modeling using a single-shell. There are many different algorithms that can be employed during the model inversion stage that vary in assumptions made regarding prior information. Here, we used a technique within an Empirical Bayesian framework, to evaluate source solutions underlying encoding and retrieval during the Sternberg task (Friston et al. 2008a; R. N. Henson et al. 2010). Advantages of the MSP approach include the ability to incorporate information from fMRI as spatial priors to guide, or constrain, MEG source estimations while still accounting for inconsistencies between the modalities (R. N. Henson et al. 2011; López et al. 2014; Wang and Holland 2021).

Source reconstruction was conducted for each condition using the Greedy Search MSP inversion type and constrained to the fMRI spatial prior (conjunction mask) for encoding and retrieval. In order to derive maps of spatial projections within the cortical mesh, inverse reconstruction was conducted in 50ms intervals, totaling thirteen time-windows of interest for encoding between 1750ms and 2400ms peri-stimulus time, and ten time-windows for retrieval between 350ms and 850ms. Paired two-sample t-tests were conducted for each time-window within each condition to evaluate dynamic activity across time at the group level.

RESULTS

Group ICA: Task-related components from fMRI data

Previous work evaluating neural correlates of working memory has found that signal intensity in contributing brain regions is modulated by load of stimuli through greater demands placed on individuals (Manoach et al. 1997). Studies have shown that the brain regions underlying encoding and retrieval are largely similar in spatial organization regardless of load (Gaston et al. 2020; Speer, Jacoby, and Braver 2003). Thus, we investigated encoding and retrieval irrespective of the load to identify whole-brain networks associated with these related cognitive processes. For encoding, the 7 components that met task-relatedness (seen in Figure 2a) are listed from highest to lowest correlation: The IC with the highest correlation with encoding ($r = 0.083$; IC7) spanned bilateral inferior frontal gyrus (IFG) and orbitofrontal cortex (OFC), followed by a right-lateralized network including precentral and postcentral gyri, Rolandic operculum, and middle cingulate cortex ($r = 0.082$; IC3). A left-lateralized network across IFG, middle temporal gyrus (MTG), insula, supramarginal gyrus (SMG), precentral gyrus, and supplementary motor area (SMA) was the third highest correlation (*r* = 0.080; IC15) with encoding. The final four components for encoding that met task-relatedness all showed bilateral activity: an IC spanning bilateral cuneus (*r* = 0.080; IC41), an IC spanning inferior parietal lobe (IPL) and postcentral gyrus (*r* = 0.079; IC20), a network across anterior cingulate cortex (ACC) and superior medial gyrus (*r* = 0.075; IC23), and an IC comprised of IFG, superior medial gyrus, left IPL and middle occipital gyrus (*r* = 0.071; IC27).

The 6 ICs that met task-relatedness (seen in Figure 2c) for retrieval are as follows: a left-lateralized network displayed the highest correlation with retrieval (*r* = 0.081; IC21b), spanning angular gyrus, IPL, superior parietal lobe (SPL), IFG, middle and superior frontal gyrus, and middle orbital gyrus. A right-lateralized network with the second highest correlation (*r* = 0.079; IC14) included IPL, SPL, middle and superior frontal gyrus, superior medial gyrus, IFG, and middle orbital gyrus, followed by a left-lateralized network across precentral and postcentral gyrus, IPL and SMA (*r* = 0.078; IC35). The final three components for retrieval that met task-relatedness all showed largely bilateral activity: an IC spanning bilateral medial gyrus and ACC (*r* = 0.077; IC36), an IC across cuneus and precuneus (*r* = 0.077; IC21a), and a network comprised of bilateral precuneus and superior temporal gyrus (STG), along with right superior frontal gyrus and SMG (*r* = 0.071; IC3).

Two conjunction masks were derived for both conditions, combining across 7 encoding and 6 retrieval task-related components (seen in Figure 2b & 2d, respectively, along with a list of brain areas and coordinates of center of mass for each cluster comprising the two conjunction maps in Table 1).

Table 1

Group level task-related ICs from fMRI, along with the location and MNI coordinates (x, y, z) for each cluster's center of mass. L, left; R, right.

location	ICs	x	y	z
Encoding				
L superior medial gyrus	IC23	-2	-39	39
R precentral gyrus	IC3	37	23	55
L inferior frontal gyrus	IC7, IC15, IC27	-47	-20	14
R inferior frontal gyrus	IC7, IC27	49	-27	15
L middle temporal gyrus	IC15	-56	40	4
L inferior parietal lobe	IC20, IC27	-51	29	45
L superior parietal lobe	IC15, IC27	-31	60	45
L cuneus	IC41	3	90	28
R supplementary motor area	IC15	5	18	49
L supramarginal gyrus	IC15	-54	47	28
R rolandic operculum	IC3	47	18	16
Retrieval				
L precuneus	IC21a	-5	51	50
L middle cingulate cortex	IC21b	2	-40	37
L middle orbital gyrus	IC21b	-38	-50	-4
R supramarginal gyrus	IC14	58	25	24
L superior temporal gyrus	IC3	-58	31	20
R middle orbital gyrus	IC14	43	-52	-5
L supplementary motor area	IC35	-3	9	52
R superior frontal gyrus	IC14	25	5	68
L cuneus	IC21a	-2	94	-19
L inferior frontal gyrus	IC21b	-44	-38	13
R superior temporal gyrus	IC3	60	26	15
R inferior frontal gyrus	IC14	48	-36	11

MEG Source Reconstructions

The two conjunction masks combining across task-related ICs for encoding and retrieval were used as fMRI spatial priors to constrain MEG source solutions using MSP in separate inverse reconstructions for each condition, all performed in standardized MNI space. Additionally, source reconstruction maps were generated without fMRI priors for encoding and retrieval to evaluate the impact of including fMRI priors during an event-related Sternberg task.

Encoding: With and Without fMRI Priors

Source reconstructions for encoding with and without spatial priors are displayed for all time-windows with activity that met threshold at $p<0.15$ from 2050ms - 2450ms (Figure 3, Table 2). This threshold level was selected of visualize a broad pattern of activity rather than specific, focal areas of sustained activity across time. For the no fMRI priors approach, there was little to no activity in earlier time-windows (1750-2150ms), with sustained left MTG contributions beginning at 2150ms throughout all time-windows of interest. This activity was followed by sustained right STG from 2250ms-2400ms, and shortly by right IFG and left inferior OFC from 2300-2450ms. Activity across bilateral MTG, middle temporal pole, and STG was the most pronounced across the two time-windows spanning 2300-2400ms.

The MSP with fMRI priors approach using the IC conjunction mask to constrain source reconstruction for encoding yielded bilateral activity across middle temporal pole and MTG beginning at 2050ms, joined by left ITG at 2100ms, left SMG at 2150ms, and left IFG at 2200ms, all sustained until roughly 2250ms. From 2250ms onwards, there still

Table 2

MEG source reconstruction results for encoding with and without fMRI priors. For each time window, the location and MNI coordinates (x, y, z) for each source location's center of mass are provided. L, left; R, right.

ENCODING: no priors					ENCODING: fMRI priors				
Time window (ms)	*Location*	*x*	*y*	*z*	*Time window (ms)*	*Location*	*x*	*y*	*z*
2050-2100	*none*				2050-2100	L middle temporal pole	-34	6	-42
						R middle temporal pole	30	8	-40
2100-2150	*none*				2100-2150	L inferior temporal gyrus	-34	6	-42
						R middle temporal pole	30	10	-40
2150-2200	L middle temporal gyrus	-58	-14	-20	2150-2200	L inferior temporal gyrus	-32	8	-42
						R middle temporal pole	30	8	-40
						L supramarginal gyrus	-52	-42	26
2200-2250	L middle temporal gyrus	-60	-14	-16	2200-2250	L inferior temporal gyrus	-36	4	-42
						R middle temporal pole	30	8	-42
						L inferior frontal gyrus	-40	32	-4
						R rolandic operculum	48	-18	18
						L supramarginal gyrus	-52	-42	26
2250-2300	L middle temporal gyrus	-60	-14	-16	2250-2300	L middle temporal gyrus	-50	-48	16

	R superior temporal gyrus	32	8	-32		R middle temporal pole	30	8	-42
						L inferior frontal gyrus	-38	32	-4
						L inferior frontal gyrus, tri. part	-36	32	14
						R rolandic operculum	46	-16	18
						L supramarginal gyrus	-54	-34	32
2300-2350	R middle temporal pole	32	14	-36	2300-2350	R middle temporal pole	30	6	-42
	R superior temporal gyrus	42	16	-28		R middle temporal pole	32	6	-38
	L superior temporal gyrus	-46	2	-26		L middle temporal gyrus	-48	-4	-24
	R inferior frontal gyrus	20	32	-18		R inferior orbitofrontal gyrus	44	36	-16
	L middle temporal gyrus	-60	-14	-18		L middle temporal gyrus	-50	-48	20
	L inferior orbitofrontal gyrus	-48	28	-10		L inferior orbitofrontal gyrus	-42	32	-16
						L supramarginal gyrus	-52	-34	32
2350-2400	L middle temporal gyrus	-46	0	-26	2350-2400	L middle temporal gyrus	-50	12	-22
	R superior temporal gyrus	42	16	-28		R superior temporal gyrus	48	14	-22
	R inferior frontal gyrus	20	32	-18		R inferior frontal gyrus	20	40	-18
	L inferior orbitofrontal gyrus	-48	26	-10		L inferior orbitofrontal gyrus	-44	30	-16
						R inferior orbitofrontal gyrus	44	40	-14
						R inferior frontal gyrus, tri. part	52	24	0
						L inferior frontal gyrus, tri. Part	-36	32	14
2400-2450	R middle temporal pole	32	8	-38	2400-2450	R middle temporal pole	32	6	-38
	L middle temporal gyrus	-60	-14	-26		L middle temporal gyrus	-58	-6	-26
	R inferior frontal gyrus	16	14	-22		R inferior frontal gyrus	26	4	-14
	L inferior orbitofrontal	-48	28	-10		L inferior orbitofrontal gyrus	-46	28	-14

gyrus				
	L superior orbitofrontal gyrus	-20	46	-16
	R middle orbitofrontal gyrus	20	40	-18
	R inferior orbitofrontal gyrus	46	34	-14
	L precentral gyrus	-40	2	42

were substantial contributions from right MTG along with right Rolandic operculum, left IFG and SMG. There was a more robust pattern of activity within these areas in the following two time-windows, along with bilateral inferior OFC and left MTG activity (from 2300-2400ms), though left SMG is only seen until 2350ms.From 2350-2400ms, there was sustained left MTG and right middle temporal pole activity, along with increased activity across bilateral frontal areas (including bilateral inferior OFC, left IFG, right middle OFC, left superior OFC) and left precentral gyrus.

Retrieval: With and without fMRI Priors

MEG source reconstructions for retrieval with and without spatial priors are displayed for all time-windows of interest (p<0.15) from 350-850ms (Figure 4, Table 3). Source reconstruction maps without fMRI priors yielded early, robust activity within left IFG at 350ms until roughly 600ms, with some contributions from right-lateralized areas (amygdala from 450-500ms, parahippocampal gyrus and IFG from 500-600ms). This was followed by increased activity in right-lateralized brain areas including parahippocampal gyrus, IFG, superior OFC, and inferior OFC from 500-650ms. Sustained right parahippocampal gyrus activity was joined by left fusiform gyrus (700-800ms), left IFG (800ms), right inferior OFC (700ms), right IFG and right middle temporal pole (800ms) contributions until 850ms.

Table 3

MEG source reconstruction results for retrieval with and without fMRI priors. For each time window, the location and MNI coordinates (x, y, z) for each source location's center of mass are provided. L, left; R, right.

RETRIEVAL: no priors				
Time window (ms)	*Location*	*x*	*y*	*z*
350-400	R parahippocampal gyrus	22	-10	-30
	L inferior frontal gyrus	-22	4	-16
	R inferior frontal gyrus, tri. part	52	24	0
400-450	L parahippocampal gyrus	-28	-16	-28
	L inferior frontal gyrus	-22	2	-14

RETRIEVAL: fMRI priors				
Time window (ms)	*Location*	*x*	*y*	*z*
350-400	R superior temporal pole	48	14	-22
	L inferior frontal gyrus, tri. part	-50	32	-2
	R inferior frontal gyrus, tri. part	52	24	0
	L superior temporal pole	-50	12	-22
	R amygdala	34	2	-26
	L inferior orbitofrontal gyrus	-28	16	-24
400-450	L superior temporal pole	-50	12	-22
	L inferior frontal gyrus, tri. part	-48	26	-2
	L inferior orbitofrontal gyrus	-26	12	-22
	R amygdala	34	2	-26
	R inferior frontal gyrus	24	30	-12
	R inferior frontal gyrus, tri. part	52	24	0

450-500	L fusiform gyrus	-30	-18	-28
	L inferior frontal gyrus	-24	2	-14
	R amygdala	26	2	-14
500-550	R parahippocampal gyrus	30	-12	-36
	L inferior frontal gyrus	-24	2	-14
	R inferior frontal gyrus	24	8	-16
550-600	R parahippocampal gyrus	22	-10	-30
	L amygdala	-24	0	-14
	R superior orbitofrontal gyrus	18	22	-20
600-650	R superior orbitofrontal gyrus	18	22	-20
	R parahippocampal gyrus	22	-10	-28
650-700	R parahippocampal gyrus	22	-6	-32
700-	R parahippocampal gyrus	24	-6	-32

450-500	L inferior frontal gyrus	-26	4	-16
	R superior orbitofrontal gyrus	22	26	-16
	R inferior frontal gyrus, tri. part	52	24	0
	L inferior orbitofrontal gyrus	-44	22	-12
	L inferior frontal gyrus, tri. part	-48	26	-2
500-550	R parahippocampal gyrus	22	-6	-32
	L inferior frontal gyrus	-24	4	-16
	R inferior frontal gyrus	22	4	-14
	R inferior frontal gyrus, tri. part	52	24	0
550-600	R parahippocampal gyrus	22	-6	-32
	R superior orbitofrontal gyrus	18	18	-22
	R inferior orbitofrontal gyrus	-24	24	-18
	R inferior frontal gyrus, tri. part	52	24	0
600-650	R superior orbitofrontal gyrus	22	26	-16
650-700	R middle temporal gyrus	46	0	-24
700-	R superior temporal pole	46	0	-24

750				
	R inferior orbitofrontal gyrus	34	36	-14
	L fusiform gyrus	-40	-62	-12
750-800	R parahippocampal gyrus	24	-8	-32
	R inferior orbitofrontal gyrus	34	36	-14
	L fusiform gyrus	-40	-62	-12
800-850	R parahippocampal gyrus	24	-8	-32
	L inferior frontal gyrus	-22	4	-16
	R middle temporal pole	40	10	-40
	R inferior frontal gyrus	22	4	-14
	R inferior orbitofrontal gyrus	34	36	-14

750				
	R middle orbitofrontal gyrus	36	38	-14
750-800				
	R inferior orbitofrontal gyrus	44	34	-16
	L superior orbitofrontal gyrus	-24	60	-4
	L inferior orbitofrontal gyrus	-38	34	-16
800-850	R parahippocampal gyrus	24	-4	-32
	L inferior orbitofrontal gyrus	-40	38	-16
	R superior temporal pole	48	14	-22
	R middle orbitofrontal gyrus	40	52	-10
	R medial orbitofrontal gyrus	10	66	-2
	L superior temporal pole	-50	12	-22

For MEG reconstructions using fMRI priors, there was early bilateral superior temporal pole activity (350-400ms), along with sustained activity across left IFG and inferior OFC areas (350-550ms), and right amygdala (350-450ms). This was accompanied by early activity in right frontal areas (IFG, inferior and superior OFC) sustained until roughly 650ms. After 700ms, there was a steady increase across bilateral OFC areas (left middle OFC from 700-750ms and 800-850ms, left superior OFC from 750-800ms, left inferior OFC from 750-850ms, and right medial OFC from 800-850ms).

DISCUSSION

Our study employed a recently developed co-processing pipeline to investigate spatiotemporal characteristics of visual WM processes in healthy individuals using a modified Sternberg task (Gaston et al. 2020; Nair et al. 2021; Sternberg 1966). Group independent component analysis of fMRI data yielded 7 ICs for encoding (Figure 2a, b) and 6 ICs for retrieval (Figure 2c, d) that together implicate broad, fronto-parietal networks including various regions across temporal areas that are typical for this task (Gaston et al. 2020; Jimura et al. 2018; H. Kim 2011; Smith and Jonides 1997).

The networks underlying encoding and retrieval derived from fMRI were then used as spatial priors to localize MEG neuronal activity using MSP, an approach aimed to highlight the spatial and temporal strengths of each modality (Friston et al. 2008b; R. N. Henson et al. 2019; Wang and Holland 2021). Previous work examined spatial concordance between fMRI and MEG results and found consistencies and disagreements between the two modalities (Wang, Holland, and Vannest 2012). As fMRI and MEG are sensitive to different aspects of underlying brain activity, disparate patterns of activation between the two modalities are expected and have been seen in other studies of multimodal approaches to high-level cognitive tasks (Vartiainen et al. 2011). Further work found that improvements, when constraining MEG source solutions with fMRI priors, were more pronounced when evaluating induced activity over during a high-order cognitive paradigm (Wang and Holland 2021). These authors attributed this benefit to the complexity of induced responses, as there is typically more variability across trials compared to evoked responses, which are phase-locked to trial onset.

MEG results for Encoding

MEG source reconstructions for encoding in Figure 3 revealed additional brain areas with the inclusion of fMRI spatial priors compared to without. The gains associated with the use of fMRI spatial priors on source reconstructions are more pronounced during encoding than retrieval. Areas where MEG results with fMRI spatial priors yield additional cortical contributions include the left precentral gyrus, SMG, inferior frontal gyrus, and inferior temporal gyrus during encoding and across bilateral fronto-temporal areas during retrieval. These gains, attributed to the use of fMRI spatial priors, are depicted by blue ellipses in Figures 3c and 5a for encoding, and highlight the potential advantages of this co-processing technique in high-order cognitive tasks.

Involvement of the SMG and IPL during encoding, seen only in reconstructions with fMRI priors, suggests reliance on storage and retrieval of phonological information (R. N. A. Henson, Burgess, and Frith 2000) and rehearsal processes (Paulesu et al. 1997) (Figures 3c). The absence of any parietal activity from MEG only localizations suggest that the involvement of IPL may be difficult to detect without additional constraints. This may be in part due to the temporal variability of induced activity across trials (Wang and Holland 2021), which is supported by the timing of SMG activity seen in the fMRI constrained approach. Additionally, the specific timing of SMG during encoding (between 2150ms-2250ms and then from 2300-2350ms, see Figure 5a) suggest dynamic communication between areas responsible for phonological storage and lexical-semantic processing (R. N. A. Henson, Burgess, and Frith 2000; Vandenberghe et al. 1996) and may be representative of storing task-relevant information. Meanwhile, consistent activity within left and right inferior frontal areas was more robust when constraining reconstructions with fMRI (Figure 5a), suggesting bilateral contributions underlying rehearsal and overall executive control during encoding that were not visible across reconstructions without priors (Huang et al. 2015).

Overall, the pattern of neural activity following encoding revealed with fMRI constrained analyses showed sustained, bilateral temporal lobe activity characteristic of short-term storage of visual and object information (Smith and Jonides 1997), progressing towards left-lateralized fronto-parietal areas underlying attention (Christensen et al. 2012), manipulating stored information (C. Kim et al. 2015; Poort et al. 2015; Zhang et al. 2014), and followed by sustained inferior frontal contributions related to complexity of processing during semantic tasks (Moss et al. 2011).

MEG results for Retrieval

MEG source reconstructions across time windows for retrieval in Figure 4 revealed additional contributing brain regions using a constrained approach. Improvements in estimating cortical generators underlying retrieval were seen largely across left orbitofrontal cortex, right middle temporal gyrus, and bilateral superior temporal pole (Figures 4c and 5b, depicted by blue ellipses). OFC function has been largely understood as relevant in emotional decision making and reward-related behaviors (Adolphs 2002; Kringelbach 2005), but is also implicated in some studies of response selection (Duarte et al. 2010; Young and Shapiro 2011) and memory performance (Frey and Petrides 2002; Ranganath et al. 2005). Moreover, studies of nonhuman primates suggest there may be substantial communication between the OFC and medial temporal areas (Petrides 2007). Interestingly, bilateral temporal contributions were among the regions seen only within fMRI constrained analyses across early windows (350ms-450ms) and later time-windows (650ms-850ms). This activity is seen alongside bilateral OFC activity (Figure 5b), suggesting dynamic communication within these areas.

These findings enhance our understanding of encoding and retrieval processes by elucidating relevant nodes of task-related networks (seen during encoding, Figure 3c), and by expanding on the communication between brain areas (seen during retrieval, Figure 5b). Taken together, the effects of fMRI priors on MEG data indicate the usefulness of this approach and ability to better characterize the spatiotemporal features of the memory encoding and retrieval processes.

The effects of fMRI priors on MEG source solutions were also investigated in previous work of an associative learning task that developed the co-processing pipeline implemented here (Nair et al. 2021). Specific spatial gains associated with spatial priors are not as robust as seen here, though constrained solutions do produce more focused regions with a more detailed pattern of activity across time (Nair et al. 2021). Differences in improvements associated with the use of fMRI spatial priors within the MSP framework may be attributed to the flexible nature of this inversion scheme: using empirical priors, this approach selects either a sparse solution or distributed sources automatically, yielding solutions largely dependent on the data itself (Friston et al. 2008b). In sum, approaches applying fMRI priors to constrain MEG inverse solutions yield additional information in terms of contributing brain areas, but also specific timing of task-related activity and communication within relevant memory networks.

Conclusions

Spatial contributions to working memory processes implicate broad fronto-parietal networks for encoding and retrieval, with encoding recruiting more bilateral and left-lateralized frontal areas and retrieval relying more on inferior parietal and superior temporal regions. In terms of dynamics, constraining MEG with fMRI priors for encoding after 2s showed a progression of activity from bilateral temporal areas to prefrontal areas, with consistent SMG involvement. For retrieval, source reconstructions after 350ms show activity moving from left-lateralized to right-lateralized orbitofrontal areas, with robust bilateral prefrontal and right temporal activity after 700ms. Additionally, specific brain areas and dynamic patterns of activity between nodes were noted only after constraining MEG inverse solutions with fMRI priors, suggesting the MSP approach is beneficial in evaluating spatiotemporal characteristics underlying working memory. Future work is needed to identify differences within these networks, or communication within relevant brain areas, among patients with epilepsy.

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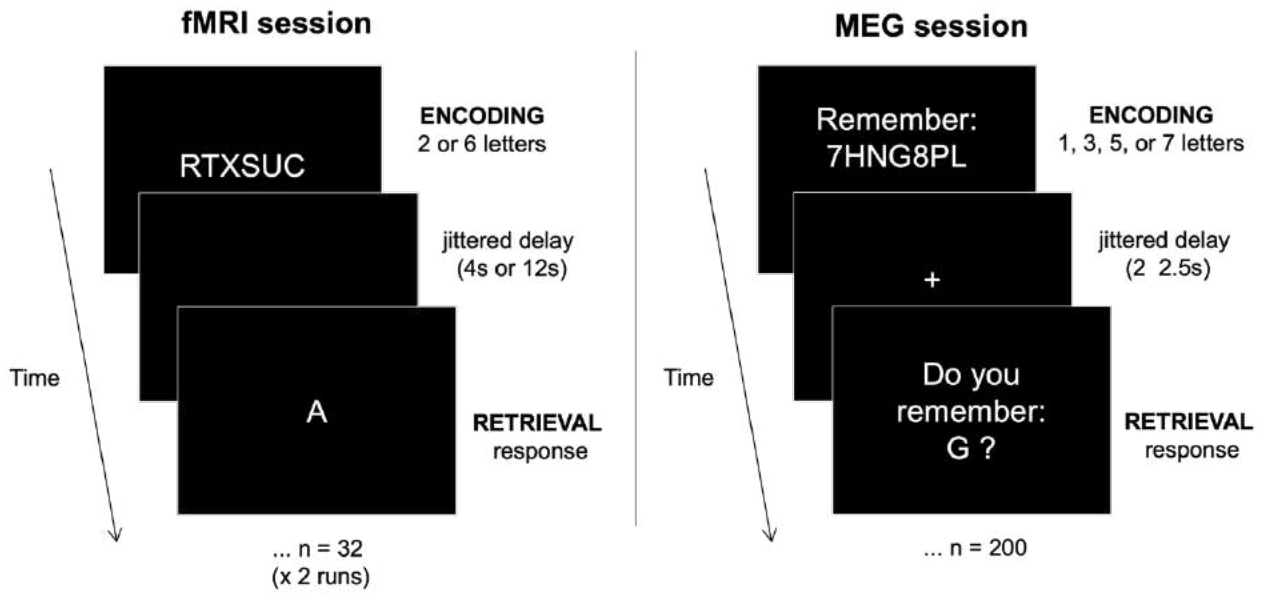

FIGURES

Figure 1. Modified Sternberg task paradigm presentation during fMRI and MEG scanning sessions. For the fMRI session, the modified Sternberg task was presented across two consecutive runs of 9:38 minute each. Character strings of either 2 or 6 letters were presented on screen, followed by a jittered delay of either 4 or 12 seconds, and a single letter probe during retrieval totaling 64 trials across runs. The MEG paradigm slightly differed from the fMRI task design: alphanumeric strings were presented that were either 1, 3, 5, or 7 characters, followed by a delay of 2 or 2.5 seconds, and a single letter probe during retrieval totaling 200 trials. There were no repeated stimuli across sessions, and all stimuli were pseudorandomized across load, delay, and correct responses.

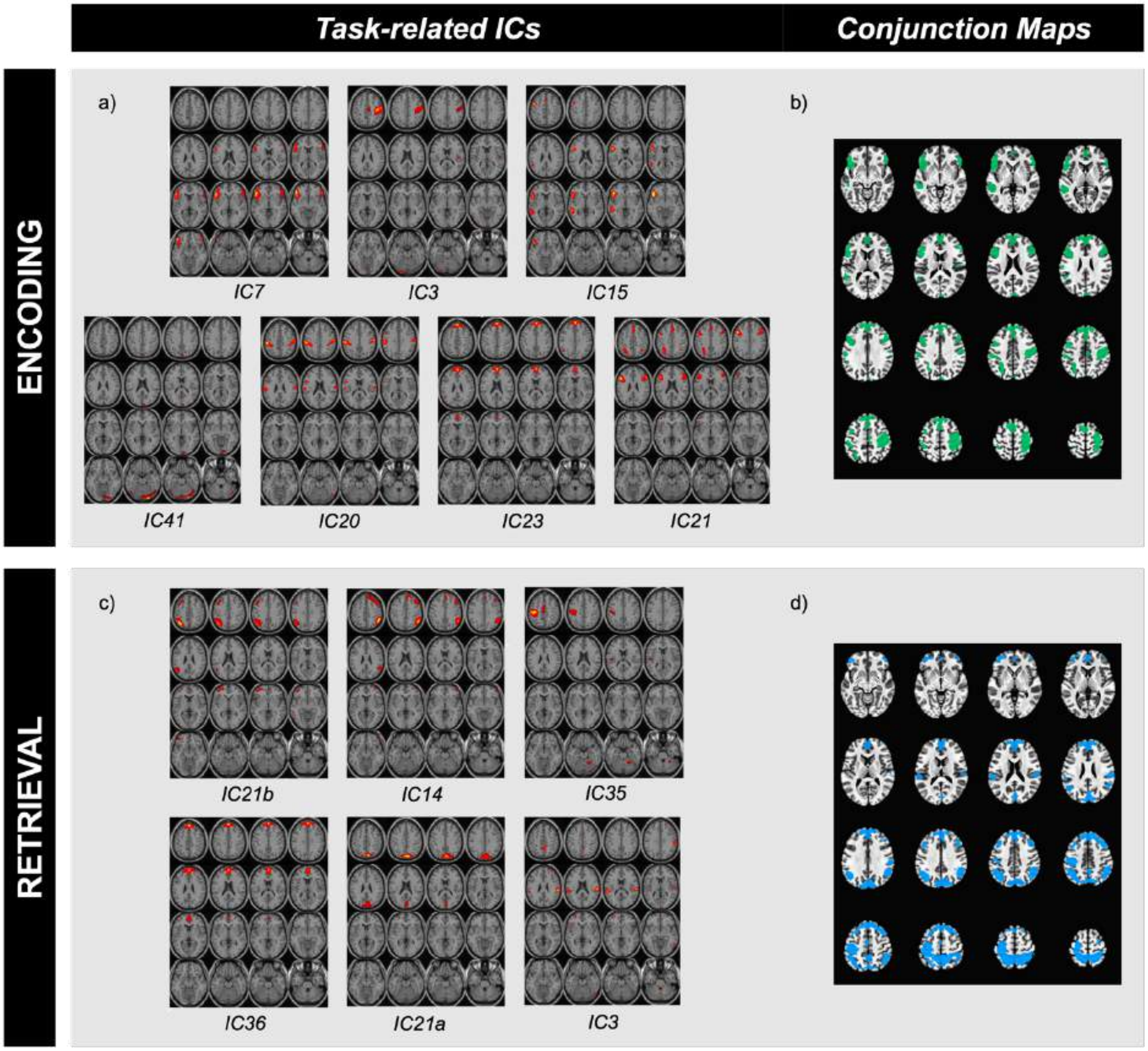

Figure 2. Task-related independent components derived from fMRI data. Images are presented in neurological orientation (right in the image is right in the brain). (A) and (C) are all task-related ICs for encoding and retrieval. Conjunction maps of all ICs for (B) encoding and (D) retrieval.

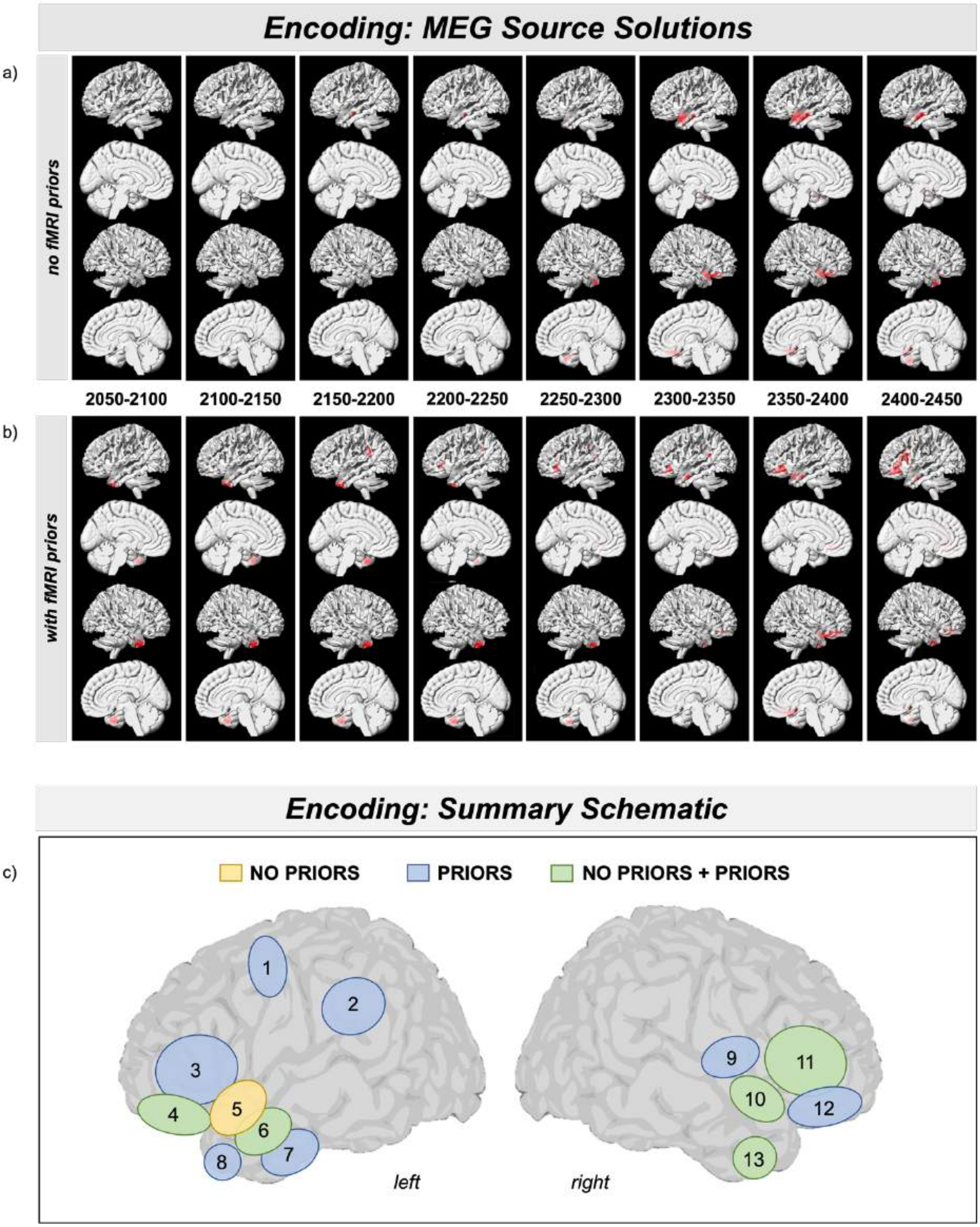

Figure 3. MEG source reconstructions using MSP without (A) and with (B) fMRI priors for encoding within eight time-windows of interest spanning 50ms each, from 2050ms-

2450ms. (C) A diagram summarizing brain regions identified by source reconstructions across time-windows without fMRI priors (yellow ellipses), with fMRI priors (blue ellipses), and areas implicated across analyses (green ellipses). Brain regions within the left hemisphere are as follows: (1) precentral gyrus, (2) supramarginal gyrus, (3) inferior frontal gyrus, (4) orbitofrontal gyrus, (5) superior temporal gyrus, (6) middle temporal gyrus, (7) inferior temporal gyrus and (8) middle temporal pole. Brain regions within the right hemisphere are as follows: (9) Rolandic operculum, (10) superior temporal gyrus, (11) inferior frontal gyrus, (12) orbitofrontal gyrus and (13) middle temporal pole.

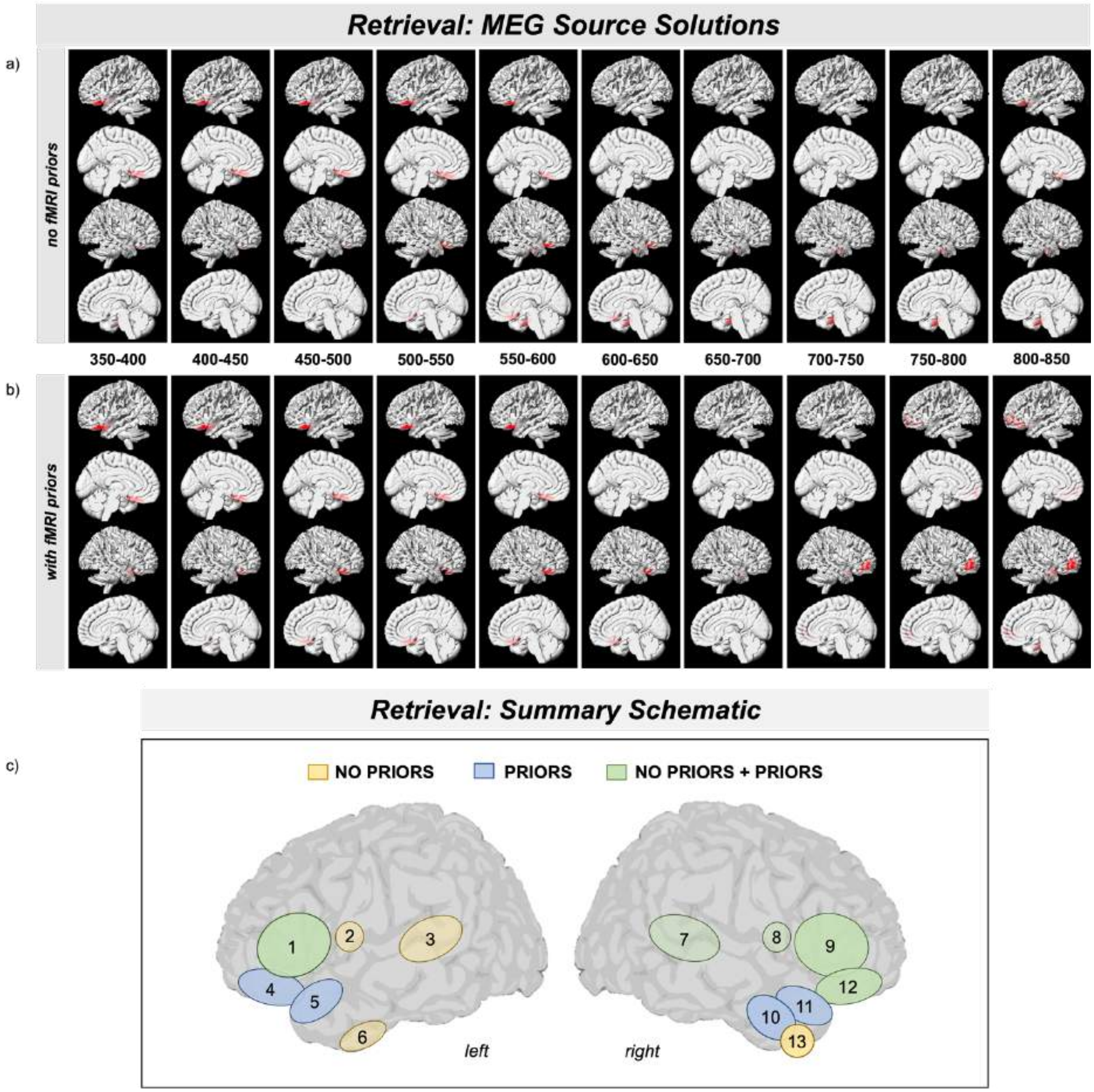

Figure 4. MEG source reconstructions using MSP without (A) and with (B) fMRI priors for retrieval within ten time-windows of interest spanning 50ms each, from 350ms-850ms. (C) A diagram summarizing brain regions identified by source reconstructions across time-windows without fMRI priors (yellow ellipses), with fMRI priors (blue ellipses), and areas implicated across analyses (green ellipses). Brain regions within the left hemisphere are as follows: (1) inferior frontal gyrus, (2) amygdala, (3) parahippocampal gyrus, (4) orbitofrontal cortex, (5) superior temporal pole and (6) fusiform gyrus. Brain regions within the right hemisphere are as follows: (7) parahippocampal gyrus, (8) amygdala, (9) inferior frontal gyrus, (10) middle temporal gyrus, (11) superior temporal pole, (12) orbitofrontal cortex and (13) middle temporal pole.

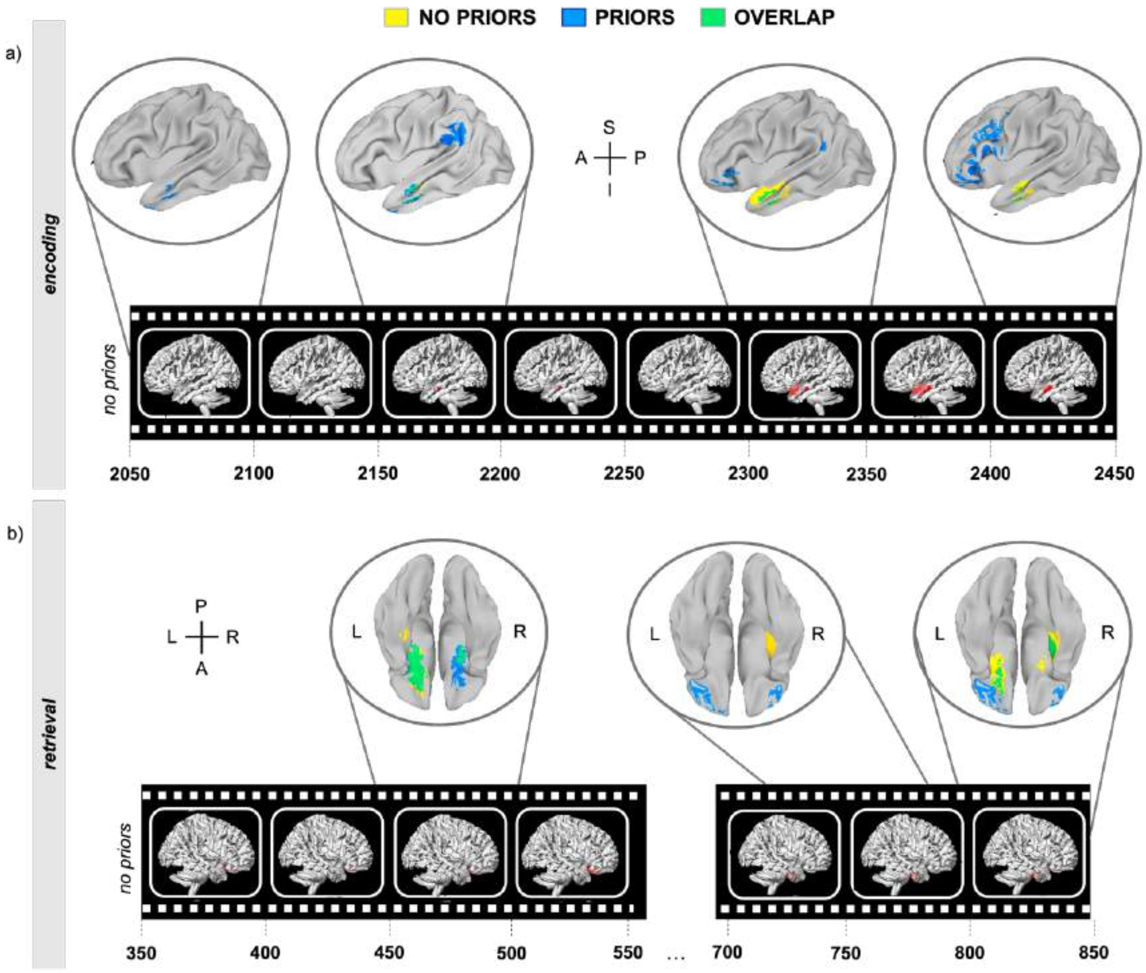

Figure 5. Schematic of MEG source reconstructions across time, depicting regions identified by MEG only localizations (no priors), localizations incorporating fMRI spatial priors, and areas of overlap between the two approaches across (A) encoding and (B) retrieval.

CONCLUSIONS

"Progress lies not in enhancing what is, but in advancing toward what will be."

– Khalil Gibran

FMRI is a popular neuroimaging approach used to studying healthy cognition, identify biomarkers associated with health and disease, and monitor effects of therapy and intervention (Martin et al. 2019b; Gaston et al. 2019). Alongside its non-invasive nature and widespread availability, fMRI boasts excellent spatial resolution within the order of millimeters. However, in investigations of dynamic brain activity fMRI falls short. By their nature, hemodynamic techniques are limited by the delayed time-scale of the HRF in relation to brain activity (Buxton 2013; Buxton et al. 2004; Brown et al. 2007). As large part of communication within the brain is characterized by electrical signaling, electrophysiological techniques able to preserve the timing of neuronal activity and are especially appropriate for studies that require higher temporal resolution (Hillebrand et al. 2005).

High-level cognitive tasks involving language, decision making, and memory often involve distributed, interconnected networks characterized by dynamic communication within and between relevant brain areas. The poor temporal resolution offered by fMRI alone limits its use to determine directional information flow within a network, but a multimodal approach to MEG source reconstruction, implemented in Manuscripts 2 and

3, was able to reveal additional spatiotemporal characteristics of task-related brain areas and, thus, provide a more nuanced and compete picture of the networks underlying associative learning and nonverbal memory processes. The purpose of the present work was to characterize dynamics of brain networks underlying associative learning and working memory among healthy controls by integrating fMRI and MEG data. We aimed to maximize strengths from each method across spatiotemporal domains by constraining MEG source reconstruction with fMRI spatial priors using the flexible, data-driven framework of MSP.

First, we identified neural correlates of active and passive encoding using a large (n=174), existing dataset of healthy individuals. This work is outlined within the first chapter (manuscript 1). We employed a data-driven blind source separation technique, group independent components analysis (GIFT), to isolate task-related networks and examine any differences in spatial extent between sexes (male vs. female), handedness (atypical vs. right), and age (<50 vs. >50 years old).

Handedness is known to play a significant role in hemispheric language dominance (Szaflarski et al. 2002; Szaflarski et al. 2012), and differences between left- and atypical-handers were identified within the left angular gyrus. The angular gyrus has been long associated with language ability (Van Ettinger-Veenstra et al. 2016), semantic processing (Seghier 2012; Hartwigsen et al. 2016), and more recently, understood as playing an integrative role across domains, including attention and problem solving (Seghier 2012). During active generation, differential recruitment of the left angular gyrus among right-handers may be related to increased reliance on left dominant brain areas, a pattern of activity previously suggested by work revealing left-lateralized patterns of activity among right handed individuals during a semantic task of Chinese characters (Gao et al. 2015).

In terms of age, we found significant differences within memory of read (p=0.014) and generated (p=0.008) words among older (>50) and younger adults. These behavioral effects were accompanied by differences in spatial extent of networks underlying self-generation and reading: Older adults showed reduced recruitment of left inferior frontal gyrus, bilateral insula, and middle occipital gyrus compared to younger adults. Specifically, findings of left IFG recruitment during active generation present among younger adults but absent among older adults support an existing model of age-related reduced lateralization underlying task-related activity (Roberto Cabeza 2002). The proposed hemispheric asymmetry reduction in older adults (HAROLD) model has been challenged by work evaluating the effects of age, sex and handedness on language lateralization (Nenert et al. 2017). Significant decreases in lateralization indices with age were only seen in right-handed men, and effects were limited to temporo-parietal brain areas (Nenert et al. 2017).

To further investigate the relationship between age, sex and associative learning, we used a linear mixed-effects modeling approach to examine the effect of age and sex differences across all task-related components. Several components showed age-related effects across self-generation and passive reading, indicating that as age increases, there are marked decreases in activity across specific frontal, temporal, and parietal brain areas. Additionally, sex and age seemed to modulate activity within left supramarginal gyrus: as age increased males showed increased recruitment of left SMG during passive reading while females showed a decline in activity. These differences within SMG suggest differential reliance on storage and retrieval of language-related information (Henson, Burgess, and Frith 2000; Vandenberghe et al. 1996), and partially support previous findings of sex modulating age-related differences in language-related brain areas (Nenert et al. 2017).

In sum, the work outlined in the first paper evaluated neural correlates of active and passive learning and yielded networks largely consistent with previous functional imaging studies (Kim 2011; Otten, Henson, and Rugg 2001; Vannest et al. 2012). This work also established an fMRI processing pipeline aimed to extract task-related brain areas using data acquired with HUSH, providing us with confidence in using ICA to evaluate spatial characteristics of networks derived from sparse acquisition datasets. Though there is correspondence within these networks with a wide body of associative learning and depth of processing literature, dynamics between relevant nodes are not well understood within a comprehensive model.

The remaining body of work aims to integrate fMRI and MEG to capitalize on the spatiotemporal strengths offered by both methods individually. We collected new fMRI and MEG data on a sample of healthy participants (n=24) during a range of tasks across two sessions.

In manuscript 2, we used group ICA to confirm the presence of these same verbal paired associate learning networks previously identified in manuscript 1, within in our smaller sample of individuals. Using fMRI alone, the four ICs meeting task-relatedness for active generation seemed to capture various aspects of active generation: the presence of bilateral parietal areas along with medial frontal areas suggests maintenance of cognitive attention, as well as internal monitoring of task demands and responses

(Rosner, Elman, and Shimamura 2013; Siegel et al. 2012; Rushworth, Krams, and Passingham 2001). Middle frontal and inferior frontal gyrus activity suggests demands associated with top-down modulation, integrating various sources of relevant information across the brain, and reorienting attention towards task demands (Christensen et al. 2012; Japee et al. 2015).

We then developed a data processing pipeline in SPM that integrates data across both modalities: We created masks from task-related ICs that were subsequently used as constraints during MEG inverse reconstruction within a data-driven, Parametric Empirical Bayesian framework. We used two approaches to isolate sources contributing to active learning: an ERP approach was used to identify early responses to active generation by averaging epoched trials to increase SNR across trials. An event-related theta power approach was also employed to preserve cognitive activity that is not likely time-locked across trials and may be lost via averaging approaches.

The ERP approach revealed early inferior and middle occipital activity within the first 250ms that was followed by bilateral fronto-temporal contributions across priors. The timing of activity across left orbitofrontal cortex between 350ms-500ms seen in fMRI constrained reconstructions is in line with Halgren et al, where left-lateralized activity across anterior orbitofrontal areas was revealed around 400ms during a semantic congruency task (Halgren et al. 2002). With the theta power approach, we saw a clear progression of early activity from bilateral inferior temporal gyri to left orbitofrontal and middle temporal activity around 750m, followed by right IFG contributions after 900ms. This progression of activity across both approaches suggests a top-down, integrative role of prefrontal areas in searching for target words using presented cues during active generation (Miller and Cohen 2001; Sharon L. Thompson-Schill et al. 1997).

Overall, in manuscript 2, we found that source solutions informed by fMRI yielded more focused regional activity compared to solutions without prior information from fMRI, which allowed for a more detailed understanding of information flow within task-positive networks.

In manuscript 3, we tested the co-processing pipeline developed in manuscript 2 on fMRI and MEG data using a modified Sternberg working memory task to evaluate dynamics of encoding and retrieval processes (Gaston et al. 2020; Sternberg 1966). We also investigated the impact of fMRI priors on MEG source reconstructions across time for both conditions. Here, we found co-processing data produced additional brain regions underlying working memory and revealed communication between relevant areas. For example, recruitment of SMG during encoding was only visible in fMRI constrained source reconstructions, and intermittently within specific time-windows, suggesting dynamic correspondence between brain areas underlying phonological storage and lexical-semantic processing (R. N. A. Henson, Burgess, and Frith 2000; Vandenberghe et al. 1996). We also noted improvements in temporal visualization during retrieval using this co-processing approach: bilateral orbitofrontal cortex and temporal gyri contributions were noted only in reconstructions informed by fMRI. These gains are consistent with evidence of substantial connectivity between these areas during response selection (Young and Shapiro 2011; Duarte et al. 2010) and memory performance (Frey and Petrides 2002; Ranganath et al. 2005). Further, the progression of activity seen using fMRI priors compared to that without priors indicates that bilateral fronto-temporal contributions are present at various stages of the retrieval process. The effects of fMRI priors on MEG data highlighting additional brain areas were seen clearly during encoding, and the impact of fMRI priors expanding on timing and communication between brain areas is especially evident during retrieval.

Across the two studies implementing this co-processing approach, we see improvements in spatiotemporal visualization of networks underlying associative learning and working memory. It is important to note that the MSP framework is a flexible, data-driven inversion scheme and improvements (or lack thereof) in source reconstruction are largely dependent on the quality and information to be gained from the prior data itself (Friston et al. 2008; Wang and Holland 2021). Though MSP will select a sparse or distributed solution automatically, previous study by Wang et al. found gains associated with fMRI priors were more pronounced when evaluating induced activity due to greater temporal variability across trials with induced responses compared to evoked responses (Wang and Holland 2021). Thus, suggesting this co-processing approach is especially useful in investigations of high-level cognitive functions.

We were able to characterize the dynamics of associative learning and working memory in healthy individuals using fMRI-informed MEG localizing techniques. Understanding healthy learning and memory circuits can inform abnormalities in clinical populations, for example how divergent persons with epilepsy may be from normative processing during memory encoding and retrieval. This work serves to further overall goals of the UAB Epilepsy Research Center by providing a flexible, multimodal framework to better assess dynamic characteristics of memory in disease states. Network-based approaches to focal epilepsies provide a more comprehensive view of atypical whole-brain neural synchronization, allowing the identification of regions beyond the ictal onset zone that may produce various neurological effects and/or behavioral deficits. Applying a network perspective to characterize deficits within these populations has the potential to inform intervention approaches that address difficulties with memory and thus improve quality of life among patients with such impairments.

Together, these experiments provide a greater understanding of the spatiotemporal underpinnings of associative learning and working memory. This work also provided an implementable framework to merge these datasets and shed light on what information may be gained by constraining MEG inverse solutions with fMRI spatial priors. Overall, this project provides support for the use of multimodal datasets within a hierarchical Bayesian model as an approach to evaluating spatiotemporal characteristics of task-related networks. Some benefits to adding fMRI spatial information into MEG source reconstruction include the ability to detect additional contributing brain areas during learning and memory, and to better characterize information flow between relevant brain areas. During a time where clinical neuroimaging research has increased substantially over decades, it is especially important to approach studies of brain function with the aim to maximize the strengths of any selected modalities.

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APPENDIX

IRB APPROVAL FORM

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM
Office of the Institutional Review Board for Human Use

470 Administration Building
701 20th Street South
Birmingham, AL 35294-0104
205.934.3789 | Fax 205.934.1301 | irb@uab.edu

APPROVAL LETTER

TO: Nair, Sangeeta

FROM: University of Alabama at Birmingham Institutional Review Board
Federalwide Assurance # FWA00005960
IORG Registration # IRB00000196 (IRB 01)
IORG Registration # IRB00000726 (IRB 02)
IORG Registration # IRB00012550 (IRB 03)

DATE: 29-May-2021

RE: IRB-170601002
Combining MEG and fMRI to Examine Dynamic Brain Activity During Verbal Generation (Encoding) Task with High Spatiotemporal Resolution (Probing and Understanding the Brain: Micro and Macro Dynamics of Seizure and Memory Networks)

The IRB reviewed and approved the Revision/Amendment submitted on 27-May-2021 for the above referenced project. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services.

Type of Review:	Expedited
Expedited Categories:	4, 6, 7,
Determination:	Approved
Approval Date:	29-May-2021
Expiration Date:	27-Apr-2022

The following apply to this project related to informed consent and/or assent:

- Waiver (Partial) of HIPAA

Documents Included in Review:

- REVISION/AMENDMENT EFORM

To access stamped consent/assent forms (full and expedited protocols only) and/or other approved documents:
1. Open your protocol in IRAP.
2. On the Submissions page, open the submission corresponding to this approval letter. NOTE: