# SEX DIFFERENCES IN THE BRAIN DURING LONG-TERM MEMORY

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A dissertation
submitted to the Faculty of
the Department of Psychology
and Neuroscience in partial
fulfillment of the requirements
for the degree of
Doctor of Philosophy

Boston College
Morrissey College of Arts and Sciences
Graduate School

May 2021

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**LONG-TERM MEMORY**

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Sex differences exist in both brain anatomy and neurochemistry (Cahill, 2006). Many differences have been identified in brain regions associated with long-term memory including the dorsolateral prefrontal cortex, hippocampus, and visual processing regions (Andreano & Cahill, 2009). There is, however, a paucity of research investigating whether and how these differences translate into differences in functional activity. Part 1 investigated sex differences in the patterns of functional activity in the brain during spatial long-term memory, item memory, memory confidence, and false memory. In addition, a meta-analysis was conducted to identify whether there were consistent sex differences in the brain across different long-term memory types. Part 2 determined whether there were sex differences in the patterns of functional connectivity in the brain during spatial long-term memory. Specifically, differences in functional connectivity between the hippocampus and the rest of the brain in addition to the thalamus and the rest of the brain were investigated. Finally, Part 3 investigated whether the observed differences in the patterns of activity (identified in Chapter 1) had sufficient information to classify the sex of individual participants. The results of Part 3 argue against the popular notion that the average female brain and average male brain are not significantly different (Joel et al., 2015). More broadly, the studies presented in this dissertation argue against the widespread practice of collapsing across sex in cognitive neuroscience.

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**ACKNOWLEDGEMENTS**

To the faculty and graduate students of the Boston College Psychology and Neuroscience Department – thank you for the stimulating discussions and support throughout the years.

To Dr. Elizabeth Kensinger, Dr. Gorica Petrovich, and Dr. Jessica Karanian – thank you for serving on my committee and for always taking the time to provide me with support, feedback, and new ideas.

To Dr. Scott Slotnick – thank you for teaching "The Cognitive Neuroscience of Human Memory" in the Fall of 2016. I would not be here if you didn't. That class sparked an interest in me I didn't know I had. I cannot believe how much I have learned and how much we have accomplished together in the past five years. You are truly the best mentor I could have asked for, in all respects.

To the members of AMP Lab (past and present) – you have all contributed to my education in some invaluable way. More than that, I've made friendships that I believe I will have for the rest of my life.

To Michael Janson – thank you for making life fun, your endless support, and for always encouraging me to think outside the box.

To Ashley, Lexie, and Rob Spets – thank you for a lifetime of support. Most importantly, thank you for always keeping me laughing.

To David and Katherine Spets – thank you for the decades of support in all areas of my life. I am so lucky to have you two as parents.

To Morgan, Piper, and Luke – thank you for inspiring the inner kid in me every day.

*To my mother, Elizabeth O'Connor, and Dorothy Nelson.*
*Among so much else, you instilled in me an insatiable passion to study and advocate for women's health.*

# GENERAL INTRODUCTION

Long-term memory enables us to revisit the past, to build skills, to plan for the future, and to know who we are. Decades of research in cognitive neuroscience has identified several brain regions responsible for our ability to remember distant events. Medial temporal lobe structures (including the hippocampus and parahippocampal cortex), control regions (including the dorsolateral prefrontal cortex and parietal cortex), and sensory regions (including visual cortex) all play critical roles in long-term memory processes (Slotnick, 2017).

Whether or not sex differences exist in the brain has been studied for over a century (Swaab & Hofman, 1984; Hofman & Swaab, 1991). Presently, there is sufficient evidence that sex differences exist in both brain anatomy and neurochemistry (Cahill, 2006). Many anatomical and neurochemical sex differences have been identified in regions implicated in long-term memory, such as the dorsolateral prefrontal cortex and the hippocampus that, corrected for brain size, both have relatively larger volumes in women (Andreano & Cahill, 2009). Moreover, the magnitude of the sex differences in these, and other, regions has been found to correlate with the expression of sex-steroid receptors in these regions during development (Goldstein et al., 2001). Related to this is the finding that levels of circulating sex hormones modulate cognition. In females, suppression of ovarian hormones has been found to affect performance on verbal memory and working memory tasks, and in males, testosterone replacement has been found to affect performance on spatial memory, verbal memory, and working memory tasks (Andreano & Cahill, 2009). Despite sufficient evidence that sex differences exist in brain anatomy and neurochemistry, research investigating how these differences influence the functional activity associated with long-term memory is wanting. Recently, we identified only seven functional magnetic resonance imaging (fMRI) studies (without confounded results) that investigated sex influences on brain activity during long-term memory (Spets & Slotnick, in press).

Some fMRI studies have identified sex differences in brain activity across different memory types including object recognition (Canli et al., 2002; Banks et al., 2012; Frings et al., 2006), autobiographical memory (St. Jacques et al., 2011; Young et al., 2013), and spatial navigation (Gron et al., 2000). However, there is little consistency in the sex specificity of regions that are reported between studies. Some studies, for example, have reported greater magnitudes of activity in the prefrontal cortex for males (Canli et al., 2002; Ino et al., 2010; Sneider et al., 2011; St. Jacques et al., 2011) while others have reported greater magnitudes of activity in this region for females (Hazlett et al., 2010; Young et al., 2012). Mixed results have also been reported in the parietal cortex (Ino et al., 2010; Young et al., 2012). There are, however, two regions that seem to be more consistently activated in males compared to females: visual processing cortex and the hippocampus (Banks et al., 2012; Canli et al., 2002; Haut & Barch, 2006; Persson et al., 2013; St. Jacques et al., 2011). Based on the variability of the results from these studies, it is likely that regions producing sex differences are based on a combination of variables including the type of stimuli and task employed (see Spets & Slotnick, in press).

Although there is evidence that sex differences exist in the patterns of brain activity during long-term memory, the aforementioned studies are not without limitations. Many, for example, utilized a blocked design (Banks et al., 2012; Bell et al, 2006; Frings et al., 2006; Gron et al., 2000; St. Jacques et al., 2011), which can introduce vigilance confounds due to differences in the processing demands across blocks. Others did not sufficiently isolate the cognitive process of long-term memory. If, for example, emotional stimuli are used to probe long-term memory, the differences observed may actually reflect sex differences in emotional processing rather than long-term memory (Cahill, 2006). Because memory plays such a vital role in our everyday lives and because it is implicated in many diseases, gaining a better understanding of how sex influences memory remains an important to-be-studied topic.

In Part 1, we investigated sex differences in the patterns of brain activity during long-term memory. Critically, we employed an event-related paradigm with neutral stimuli in which

there was no behavioral difference between the sexes (Rahman, 2011). By utilizing neutral stimuli and an event related design, we were able to isolate the cognitive process of long-term memory (without other confounds). Part 1 concludes with a meta-analysis looking at whether there are consistent sex differences in the brain across different memory types. In Part 2, we investigated sex differences in patterns of functional connectivity. Specifically, we looked at whether there were sex differences in connectivity between the hippocampus and the rest of the brain in addition to the thalamus and the rest of the brain during long-term memory. Lastly, in Part 3, we investigated whether the differences in multivoxel patterns observed between the sexes were consistent enough to classify sex on an individual-participant basis. These findings are in direct opposition to the notion that individual differences supersede sex differences in the brain (Joel et al., 2015), and lend support to the idea that the average female brain and the average male brain are significantly different.

# PART 1

## SEX DIFFERENCES IN THE PATTERS OF BRAIN ACTIVITY DURING LONG-TERM MEMORY

## CHAPTER 1

Different patterns of cortical activity in the brain during spatial long-term memory
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Published in *Neuroimage*
DOI: 10.1016/j.neuroimage.2019.06.027

It is generally assumed that identical neural regions mediate the same cognitive functions in females and males. However, anatomic and molecular sex differences exist in the brain, including in regions associated with long-term memory, which suggests there may be functional differences. The present functional magnetic resonance imaging (fMRI) investigation aimed to identify the differences and similarities in brain activity between females and males during spatial long-term memory. During encoding, abstract shapes were presented to the left or right of fixation. During retrieval, shapes were presented at fixation and participants made "old-left" or "old-right" judgments. For both females and males, spatial memory hits versus misses produced activity in regions commonly associated with visual long-term memory; however, the activations were almost completely distinct between the sexes. An interaction analysis revealed sex-specific activity for males in visual processing regions, the left putamen, the right caudate nucleus, and bilateral cerebellum, and sex-specific activity for females in the parietal cortex. A targeted anatomic region-of-interest (ROI) analysis identified sex-specific activity for males and females in the left hippocampus and language processing cortex, respectively. A multi-voxel pattern correlation analysis within functional ROIs between all pairs of participants showed greater within-sex than between-sex correlations, indicating the differential activations were due to sex differences rather than other individual differences between groups. These results indicate that spatial long-term memory is mediated by largely different brain regions in females and males. These findings have major implications for the field of cognitive neuroscience, where it is common practice to collapse across sex.

Females and males are known to differ in their behavioral performance across a variety of long-term memory tasks (Cahill, 2006). Females often show an advantage in tasks in which it is helpful to utilize verbal strategies, such as list recall, associative memory, recognition of faces, and autobiographical memory, whereas males often show an advantage in tasks requiring visuospatial processing, such as mental rotation and navigation (Andreano and Cahill, 2009; Herlitz and Rehnman, 2008). Overall, females excel in long-term memory tasks, which may be explained, in part, by anatomical and neurochemical sex differences in the brain (Andreano and Cahill, 2009; Cahill, 2006). For example, corrected for brain size, females have greater overall cortical volume compared to males including greater volumes of the hippocampus and the dorsolateral prefrontal cortex (Andreano and Cahill, 2009; Goldstein et al., 2001), two regions associated with long-term memory (Slotnick, 2017b). Females also have a greater number of estrogen receptors in the hippocampus and the dorsolateral prefrontal cortex, potentially making these regions more easily activated (Cahill, 2006). Moreover, females have larger volumes of language processing cortex, which could account for their advantage in tasks in which verbal strategies can be employed (Goldstein et al., 2001). Sex differences in anatomical and neurochemical makeup within regions critical for long-term memory would be expected to translate into sex differences in functional activity within these regions.

Sex differences in functional activity have been reported in control regions associated within long-term memory, which include the prefrontal cortex, the parietal cortex, and the hippocampus within the medial temporal lobe (Slotnick, 2017b). For example, one functional magnetic resonance imaging (fMRI) study investigated sex differences while navigating a three-dimensional maze, which can be assumed to involve spatial long-term memory encoding. Females had greater activity than males in the prefrontal cortex, the inferior parietal lobule, and the superior parietal lobule. Males had greater activity than females in the hippocampus and the parahippocampal gyrus (Gron et al., 2000). Functional sex differences were also reported in an fMRI study investigating the neural basis of autobiographical memory (St. Jacques et al., 2011).

Behavioral data were collected using a SenseCam worn by participants that recorded visual scenes while they walked around during everyday life. During retrieval, participants were either shown images from the SenseCam or were given verbal cues to recall one of the previous visual scenes. The contrast of SenseCam cues versus verbal cues produced activity in males within the inferior prefrontal cortex, the hippocampus, and the retrosplenial cortex and produced activity in females within the occipital cortex (St. Jacques et al., 2011).

The findings from the previous studies suggest the presence of functional sex differences during long-term memory. However, many of these studies utilized a blocked design (Banks et al., 2012; Bell et al., 2006; Frings et al., 2006; Gron et al., 2000; St. Jacques et al., 2011), where multiple events occur during individual epochs and participants alternate between epochs of different event types. Blocked designs introduce a possible vigilance confound due to certain types of task blocks having greater processing demands. In addition, multiple studies that have investigated sex differences may not have isolated a single cognitive process. For instance, sex differences in emotional long-term memory may reflect differences in long-term memory but may alternatively reflect differences in emotional stimulus processing, as females and males are known to respond differently to emotional stimuli (Cahill, 2006). Related to this, other studies have investigated neural sex differences during short-term memory, but nearly all of these studies have utilized the n-back task (Hill et al., 2015; Speck et al., 2000), where participants are continuously presented with stimuli (usually letters or numbers) at the center of the screen and indicate when the same stimulus appeared ‘n’ stimuli previously. The n-back task requires working memory but also requires shifting attention such that working memory is not isolated. Finally, many studies that have investigated sex differences during working memory or long-term memory did not equate behavioral performance between females and males (Goldstein et al., 2001; Guillem and Mograss, 2005; Speck et al., 2000) such that differences in functional activity may have reflected differences in task difficulty.

Of additional relevance, there is anatomic evidence suggesting that classifying brains as "female" or "male" is an over simplification of the intricate differences that occur both between sexes and among individuals (Joel et al., 2015). According to this view, most brains exist on a continuum, sharing more aspects of morphology and connectivity with females, sharing more aspects of morphology and connectivity with males, or sharing aspects of morphology and connectivity with females and males. As such, it can be difficult to assess whether functional differences between groups are attributable to sex or other individual differences.

The aim of the present fMRI investigation was to identify the differences and similarities in brain activity between females and males during spatial long-term memory. To do so, we reanalyzed data from two spatial long-term memory studies that used similar experimental protocols. In both studies, we employed abstract shapes as stimuli, as such stimuli have been shown to produce similar spatial memory performance for females and males (Rahman et al., 2011). Across the two studies there were 40 female and 18 male participants. To ensure similar statistical power between the two groups, we selected 18 females using a matching procedure such that there was similar memory accuracy and variance between the two groups. During the study phase, shapes were presented in the left or right visual field (Fig. 1, left). During the test phase, shapes were presented at fixation and participants made an "old-left" or "old-right" judgment (Fig. 1, right). By employing neutral stimuli, a task that does not produce behavioral sex differences, selecting participants to closely match behavioral accuracy, and an event-related design, we were able to isolate the cognitive process of spatial long-term memory. Furthermore, to address whether spatial long-term memory activation differences were attributable to sex differences, rather than other individual differences, multi-voxel pattern correlation analysis was conducted — by correlating the patterns of activity of each participant with all other participants — to identify if the patterns of activity were more similar within sex than between sex.

There is a large body of evidence indicating that the hippocampus binds item and context information, including spatial information, during long-term memory (Diana et al., 2007;

Eichenbaum et al., 2007; Slotnick, 2013). In many long-term memory tasks, males are known to utilize spatial strategies to a greater degree than females, while females are known to utilize verbal strategies to a greater degree than males (Cahill, 2006; Frings et al., 2006). Therefore, we predicted males would produce greater activity than females in the hippocampus and females would produce greater activity than males in language processing cortex. As this is the first event-related fMRI study that has investigated sex differences during spatial long-term memory, it is difficult to predict whether the overall patterns of brain activity in females and males would be more similar or different.

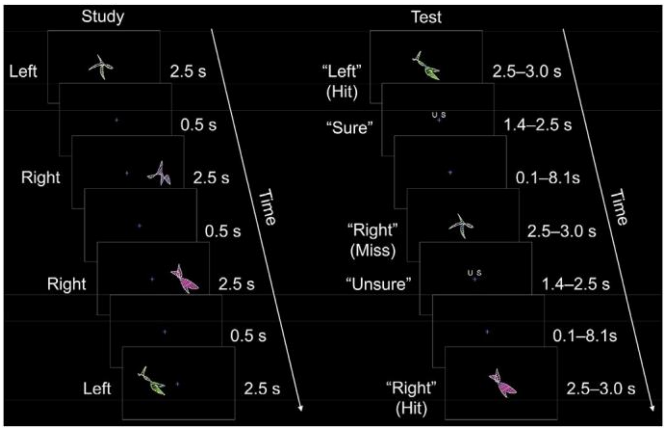


Fig. 1. Stimulus and response protocol. During the study phase, abstract shapes were presented for 2.5 s to the left or right of fixation followed by a fixation period of 0.5 s (labeled to the left). During the test phase, old shapes were presented at fixation for 2.5–3.0 s followed by a confidence rating reminder screen for 1.4–2.5 s and a fixation period of 0.1–8.1 s (see Methods for experiment-specific details). Participants indicated whether the shapes were previously on the "left" or "right" and made an "unsure"–"sure" confidence rating. Example responses are shown to the left (corresponding response types are shown in parentheses).

## Methods

The present study reanalyzed the data from two spatial long-term memory studies (Jeye et al., 2018; Slotnick and Schacter, 2004). Each of these studies was comprised of two experiments (below, the experiments in Slotnick and Schacter, 2004, are referred to as

Experiments 1 and 2 and the experiments in Jeye et al., 2018, are referred to as Experiments 3 and 4).

*Participants*

Twelve individuals from the Harvard University community were included in the analysis of Experiment 1 (7 females, age range 18–22 years). Fourteen individuals from the Harvard University community were included in the analysis of Experiment 2 (8 females, age range 18–25 years). Sixteen individuals from the Boston College community were included in the analysis of Experiment 3 (12 females, age range 22–28 years). Sixteen individuals from the Boston College community were included in the analysis of Experiment 4 (13 females, age range 20–29 years). All participants self-reported having normal or corrected-to-normal vision and being right handed.

Across the four experiments, 18 females were selected from 40 female participants that best matched the spatial memory accuracy and variance of all 18 male participants (spatial accuracy matching procedure details are outlined below). The number of participants in the present study (total N = 36) is on the high end of previously published fMRI studies that have investigated long-term memory sex differences (range = 20–44, mean ± 1 SE = 27.63 ± 2.89; Banks et al., 2012; Canli et al., 2002; Compere et al., 2016; Frings et al., 2006; Garn et al., 2009; Gron et al., 2000; St. Jacques et al., 2011; Manns et al., 2018). A power analysis indicated that the number of participants in each group (N = 18) was sufficient to identify spatial long-term memory activity within each group and between groups, particularly in language processing cortex and the hippocampus (the hypothesized regions of activation for females and males, respectively). Specifically, assuming a value for power of 0.8, Cohen's d effect size of 0.85 (which is reasonable given that these regions are consistently activated during context memory, Slotnick, 2013, and language processing, Price, 2000), and an alpha value of 0.05, at least 12 participants per group are required to produce spatial long-term memory activity within each group and at least 18

participants per group are required to identify differential activity between groups. Critically, as spatial long-term memory activity was observed within each group and differential activity was observed between groups (see the Results), the present study had adequate power. There was no significant difference between the ages of the 18 selected female participants (22.54 ± 0.68 years) and the 18 male participants (22.28 ± 0.61 years, $t(34) < 1$) and no significant difference in handedness between the selected female participants (86.13 ± 3.52) and the male participants (81.27 ± 5.87, $t(33) < 1$; handedness laterality quotient ranged from −100 to +100 indicating completely left handed and completely right handed, respectively, computed based on responses to the Edinburgh handedness inventory; Oldfield, 1971). Handedness data was not available for one female participant. Study 1 (Slotnick and Schacter, 2004) was approved by the Harvard University Institutional Review Board (for the training protocol) and the Massachusetts General Hospital Institutional Review Board (for the imaging protocol) and Study 2 (Jeye et al., 2018) was approved by the Boston College Institutional Review Board. Informed consent was obtained prior to each session. Participants received $10 for the training session and $25 per hour for the fMRI session.

*Spatial accuracy matching procedure*

In Experiment 1, we selected five females from the original seven to best match the spatial memory accuracy of the five males. We selected these females on an individual basis such that the spatial memory accuracy of each selected female was closely matched to the spatial memory accuracy of a single male participant (i.e., a matched-pair procedure was employed). We followed the same matched-pair selection procedure for the remaining experiments. In Experiment 2, six females were selected from eight to match the six males. In Experiment 3, four females were selected from twelve to match the four males. In Experiment 4, three females were selected from thirteen to match the three males. For each experiment, following selection, we ran independent samples t-tests to determine whether there were any significant differences in spatial

memory accuracy between the groups. Using an iterative procedure, if the average accuracy of one group was marginally higher than the other or the variances deviated from one another, we selected alternative female participants and ran another t-test until we determined a combination of female and male participants that were best matched on both spatial accuracy and variance.

*Stimulus protocol and task*

Across all experiments, each participant completed a behavioral training session prior to the scanning session (experiment-specific stimulus protocol and task procedure details are outlined below). Each participant completed a single anatomic scan and three to eight study-test runs. During the study phase, abstract shapes were presented in randomized order to the left or right of the fixation cross (Fig. 1, left). Participants were instructed to remember each shape and its spatial location while maintaining fixation. During the test phase, shapes were presented at fixation. Shape sets were randomized such that no more than 3 shapes of a given type were presented. For each shape, participants made an "old-left" or "old-right" judgment with their left hand (Fig. 1, right) followed by an "unsure" or "sure" judgment. Shapes sets were counterbalanced across participants using a Latin Square design. Shapes were never repeated and color/line orientation was never repeated within a run, with the exception of old items that were repeated during the test phase.

*Experiment 1*

In Experiment 1, participants completed a training session at Harvard University that was identical to the imaging session at Massachusetts General Hospital. Each session consisted of three study-test phases with 144 shapes (16 sets of 9 exemplars). Each exemplar set alternated between presentation in the left and right visual field. Stimuli were projected onto a screen at the superior end of the scanner and were viewed through an angled mirror affixed to the head coil. Shapes were contained within a bounding square of 5.5º of visual angle in width, with the closest

edge offset 3º of visual angle from fixation during study. During the imaging portion of the experiment, each participant completed a single anatomic scan and three study-test runs. There was an approximately 7 min delay between the end of each study phase and the beginning of each test phase, during which an instruction reminder screen was presented. The test phase consisted of 96 shapes (16 sets of 2 studied exemplars, 2 related shapes, and 2 non-studied shapes). During the test phase, shapes were presented at fixation for 2.5 s followed by a confidence rating reminder screen for 1.4 s and a 0.1–8.1 s fixation period. For each shape, participants responded either old and on the "left," old and on the "right," or "new" with their left hand, followed by an "unsure"–"sure" response rating indicating their confidence of the preceding response. Participants were instructed to respond as quickly as possible without sacrificing accuracy.

*Experiment 2*

The details of Experiment 2 are identical to Experiment 1 unless otherwise stated. Participants completed a 1/4 full-length practice run followed by a full-length practice run. During the imaging portion of the experiment, each participant completed a single anatomic scan and six study-test runs. During the study phase of the full-length runs, 32 abstract shapes were presented in the left or right visual field. Between the study phase and the test phase, an instruction reminder screen was presented for 10 s. During the test-phase of the full-length runs, the 32 abstract shapes from the study phase and 16 new shapes were presented at fixation.

*Experiment 3*

In Experiment 3, participants completed a 1/4 full-length practice run followed by a full-length practice run. During the imaging portion of the experiments, participants completed seven to eight full-length study-test runs. Shapes spanned 6.7 º of visual angle with the closest edge offset 3.6 º of visual angle from fixation. During the study phase of the full-length runs, 32 abstract shapes were presented to the left or right visual field with random assignment so that no

more than 3 shapes were presented on either side sequentially. Between the study phase and the test phase, an instruction reminder screen was presented for 8 s. During the test phase of the full-length runs, each shape was presented at fixation for 3.0 s followed by a confidence rating reminder screen for 2.5 s and a 0.5–4.5 s fixation period. For each shape, participants responded either "left" or "right" with their left hand to indicate whether the shape was previously presented in the left or right visual field, followed by an "unsure"–"sure"–"very sure" confidence rating.

*Experiment 4*

The details of Experiment 4 are identical to Experiment 3 unless otherwise stated. Shapes spanned 3.8 º of visual angle in with the closest edge offset 2.1º of visual angle from fixation in the upper-left, lower-left, upper-right, or lower-right visual field quadrant. Participants responded either "upper-left", "lower-left", "upper-right", or "lower-right" with their left hand to indicate the quadrant in which the shape was previously presented.

*Image acquisition and analysis*

For Experiments 1 and 2, images were acquired using a 3-Tesla Siemens Allegra MRI scanner with a standard head coil. Anatomic data were acquired using a multiplanar rapidly acquired gradient echo (MPRAGE) sequence (TR = 30 m, TE = 3.3 m, 128 slices, 1 x 1 x 1.33 mm resolution) and functional data were acquired using a T2*-weighted echo planar imaging (EPI) sequence (TR = 2000 m, TE =30 m, 64 x 64 acquisition matrix, 26–30 slices in Experiment 1 and 30 slices in Experiment 2, 4.5 mm isotropic resolution). Images were slice-time corrected, motion corrected, temporal components below 2 cycles per run length were removed, and voxels were resampled at 3 $mm^3$. Anatomic and functional images were transformed into Talairach space. To maximize spatial resolution, spatial smoothing was not conducted. Image acquisition and pre-processing in Experiments 3 and 4 was identical to Experiments 1 and 2 except that images were acquired using a 3-Tesla Trio Scanner with a 32-channel head coil and functional

data were acquired with 33 slices and 4 mm isotropic resolution. For all experiments, images were acquired during both the study phase and the test phase.

A random-effect general linear model analysis was conducted. The general linear model included the following event types: encoding of items in the left visual field, encoding of items in the right visual field, accurate retrieval of items in the left visual field (left-hits), accurate retrieval of items in the right visual field (right-hits), inaccurate retrieval of items in the left visual field (left-misses), and inaccurate retrieval of items in the right visual field (right-misses; for Experiment 1, encoding events were not modeled as study runs and test runs were separate and only test images were included in the analysis). Confidence responses were collapsed across all analyses, unless otherwise specified. All contrasts were thresholded at $p < .001$, false discovery rate and cluster extend corrected to $p < .05$, unless otherwise specified. For cluster extent correction, we first computed the spatial autocorrelation for the contrast of female hits versus male hits in each experiment and employed the largest spatial autocorrelation value (3.72 mm) across experiments (this was a conservative estimate given that larger values could be attributed to spatial autocorrelation due to true activations rather than noise). 10,000 Monte Carlo simulations were conducted based on the acquisition volume parameters, computed spatial autocorrelation, and the desired individual voxel and familywise p-value (Slotnick, 2017a). Across all experiments, we selected the lowest cluster extent threshold (in an effort to estimate the noise distribution). This resulted in a cluster extent threshold of 10 voxels, which was applied to all contrasts, unless otherwise stated. For viewing purposes, a gray/white matter surface reconstruction was created from the anatomic data from one participant. Precise activation coordinates can be found in Table 1.

For the activation timecourse interaction analyses, event-related activity was extracted from a 10 mm cube centered on the most significant point of activity within each anatomic region. Each timecourse was baseline corrected from 1 to 0 s before stimulus onset. The magnitude of activity at 6 s after stimulus onset, the maximum amplitude of the mean activation

timecourse across all conditions in V1, was used for statistical analysis.

Within and between sex multi-voxel pattern correlation analyses were conducted within functional ROIs. Functional ROIs were defined as the union of activity produced from the group contrasts of female spatial memory hits > misses and male spatial memory hits > misses. For each contrast, a threshold of $p < .001$, uncorrected, was used to define the ROIs to reduce the number of task irrelevant voxels (analyses using more lenient thresholds of $p < .01$ and $p < .05$ were also conducted in the primary analysis to ensure the results were not specific to a particular threshold employed). For each pair of female and male participants, the magnitude of activity in all voxels within the ROIs were correlated with the same set of voxels (using a Pearson correlation). The independent correlation matrix values were used to compute within and between sex correlations (using a weighted ANVOA) and, for the primary analysis, to compare within-sex correlations to zero (using a one-tailed t-test, as only positive correlations were expected) and to compare between-sex correlations to zero (using a two-tailed t-test, as between-sex correlations could be positive or negative).

## Results

An analysis on all participants (40 females, 18 males) found no significant difference in spatial memory accuracy between females (74.75 ± 1.55%) and males (73.42 ± 1.22%, weighted $F(1, 56) < 1$; percentage of correct spatial location identification contingent on correct old item identification, chance = 50%). For the fMRI analysis, we selected 18 female participants with behavioral performance that most closely matched the male participants to even better match behavioral accuracy/variance and to ensure the statistical power of each group was similar (matched female performance = 74.25 ± 0.94%, $t(34) < 1$).

Accurate spatial memory was isolated by contrasting spatial memory hits ("left"/left, i.e., "left" response to items previously presented on the left side of the screen, or "right"/right) versus

spatial memory misses ("left"/right or "right"/left). As expected, for both females and males, accurate spatial memory produced activity in regions associated with visual long-term memory. For females this included the right lateral prefrontal cortex (right inferior frontal sulcus), bilateral sensorimotor cortex (right precentral gyrus, right central sulcus, left postcentral sulcus), bilateral parietal cortex (bilateral superior parietal lobule, bilateral intraparietal sulcus, left angular gyrus, left supramarginal gyrus), bilateral visual processing regions (bilateral middle occipital gyrus, right calcarine sulcus, bilateral inferior occipital gyrus, bilateral fusiform gyrus, left precuneus), bilateral putamen, and midline thalamus (Fig. 2A and Table 1, top). For males this included the right medial prefrontal cortex, bilateral sensorimotor cortex (bilateral postcentral sulcus, left postcentral gyrus), bilateral parietal cortex (bilateral intraparietal sulcus), bilateral visual processing regions (bilateral middle occipital gyrus, bilateral inferior occipital gyrus, bilateral fusiform gyrus, right collateral sulcus), bilateral temporal cortex (bilateral inferior temporal sulcus), right caudate, right putamen, and bilateral cerebellum (Fig. 2B and Table 1, middle). To assess the degree to which female and male activity overlapped, we conducted a conjunction analysis of the preceding contrasts. This conjunction identified one activation in left parietal cortex (intraparietal sulcus) and two activations in bilateral visual processing regions (right middle occipital gyrus, bilateral fusiform gyrus; Fig. 2C and Table 1, bottom).

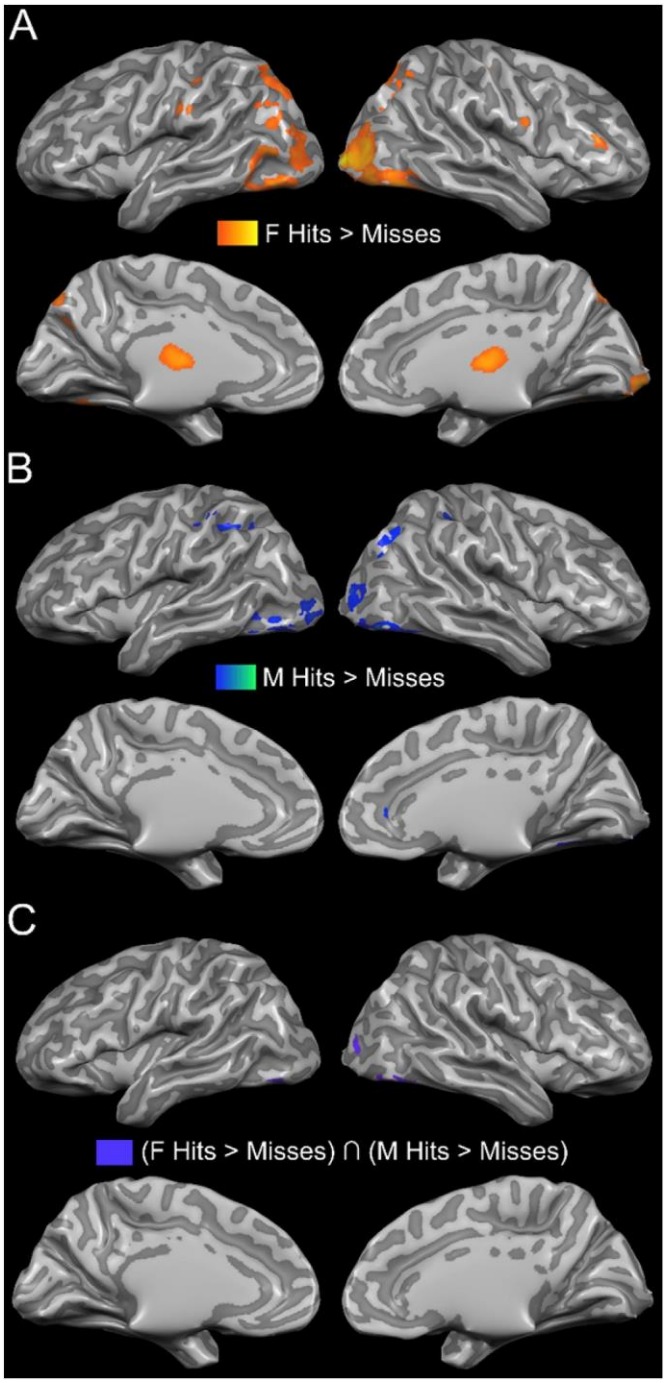


Fig. 2. Activity associated with spatial memory hits versus misses. (A) Activity associated with female hits versus misses (top, lateral views; bottom, medial views; key at the center). (B) Activity associated with male hits versus misses. (C) Overlapping activity of the preceding contrasts.

To determine whether the activations produced by the contrast of female hits versus misses (Fig. 2A) and male hits versus misses (Fig. 2B) were sex-specific (i.e., there was a sex by

accuracy interaction), activation timecourses were extracted from the center of activity within each unique brain region. It should be underscored that this was a conservative method of analysis (i.e., a high rate of type II error was expected), given the high between-subject variability associated with episodic memory (Miller et al., 2009). Still, nine activations were sex-specific (Fig. 3, selected regions, and Table 1, regions with asterisk). For females, there was sex-specific activity in the right superior parietal lobule. For males, there was sex-specific activity in the left middle occipital gyrus, right middle occipital gyrus, left inferior occipital gyrus, right collateral sulcus, left fusiform gyrus, right putamen, right caudate, and right cerebellum.

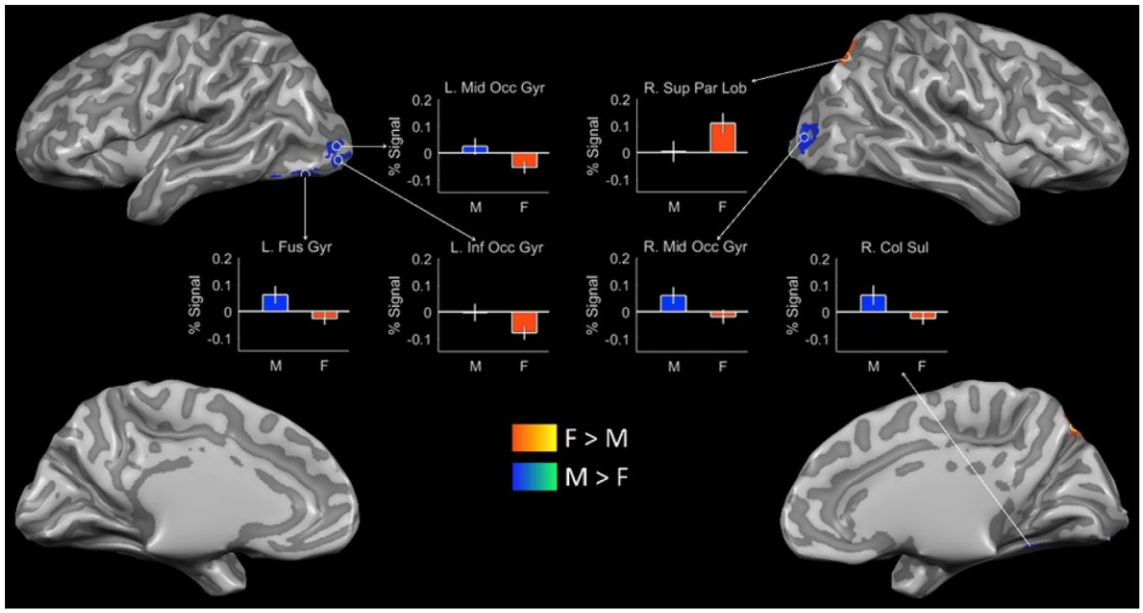


Fig. 3. Sex-specific activations (top, lateral views; bottom, medial views; key at the bottom center).

Our specific hypotheses were that males would produce greater activity than females in the hippocampus and females would produce greater activity than males in language processing regions. Although only females produced spatial memory activity in language processing cortex (left supramarginal gyrus), providing some support for one hypothesis, the interaction analysis did not show this activation to be sex-specific. In addition, males did not produce the predicted

spatial memory activity in the hippocampus. It is possible that there were sex-specific activations in these regions, but they were too small to survive the cluster extent threshold enforced, which is a known issue in small volume regions such as the hippocampus. As such, we conducted a targeted follow-up interaction analysis within these ROIs without enforcing the cluster extent threshold. Of importance, these results were still false discovery rate corrected for multiple comparison to $p < .05$. The male hit versus miss contrast produced one activation within the left hippocampus (coordinates: x = 23, y = 31, z = 5) that was sex-specific (Fig. 4, left) and no significant activity within language processing regions (Broca's area or Wernicke's area). The female hit versus miss contrast produced one additional activation within the left supramarginal gyrus (Wernicke's area, coordinates: x = 62, y = 34, z = 25) that was marginally sex-specific ($p$ = .083, Fig. 4, right) and no significant activity within the hippocampus.

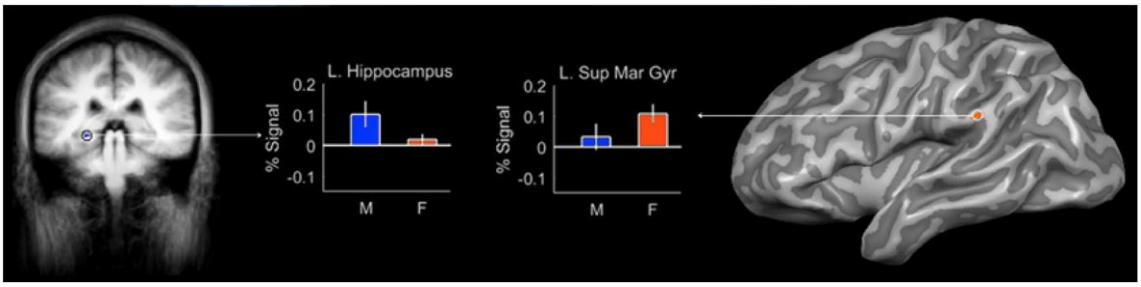


Fig. 4. Sex-specific activity within regions-of-interest (left, coronal view; right, lateral view).

To ensure the differences in spatial memory activation patterns were due to sex differences rather than other individual differences between the groups, we conducted a multi-voxel pattern correlation analysis on voxels within functional ROIs defined by the contrast of female hits versus misses or male hits versus misses (Fig. 5). If the observed differences in the group activation maps were due to other individual differences, rather than sex, there should be no difference in the within sex and between sex correlational values. However, for ROIs defined at a threshold of $p < .001$ (N = 3,096 voxels), the mean correlation within sex ($r = 0.022 \pm$

0.0046, which was significantly greater than zero, $t(305) = 4.83$, $p < 1 \times 10^{-5}$) was significantly higher than the mean correlation between sex ($r = 0.020 \pm 0.0049$, which was significantly less than zero, $t(323) = 3.94$, $p < 1 \times 10^{-4}$; $F(1, 628) = 37.87$, $p < 1 \times 10^{-8}$). There was similarly a significantly higher within than between sex correlation for functional ROIs defined at more lenient thresholds of $p < .01$ (N = 6,780 voxels, $F(1, 628) = 25.89$, $p < 1 \times 10^{-6}$) and $p < .05$ (N = 12,419 voxels, $F(1, 628) = 11.90$, $p < 1 \times 10^{-3}$). The fact that significance level decreased as a function of threshold suggests that more lenient thresholds selected a greater number of task irrelevant voxels; therefore, only the more stringent threshold was employed in subsequent analyses.

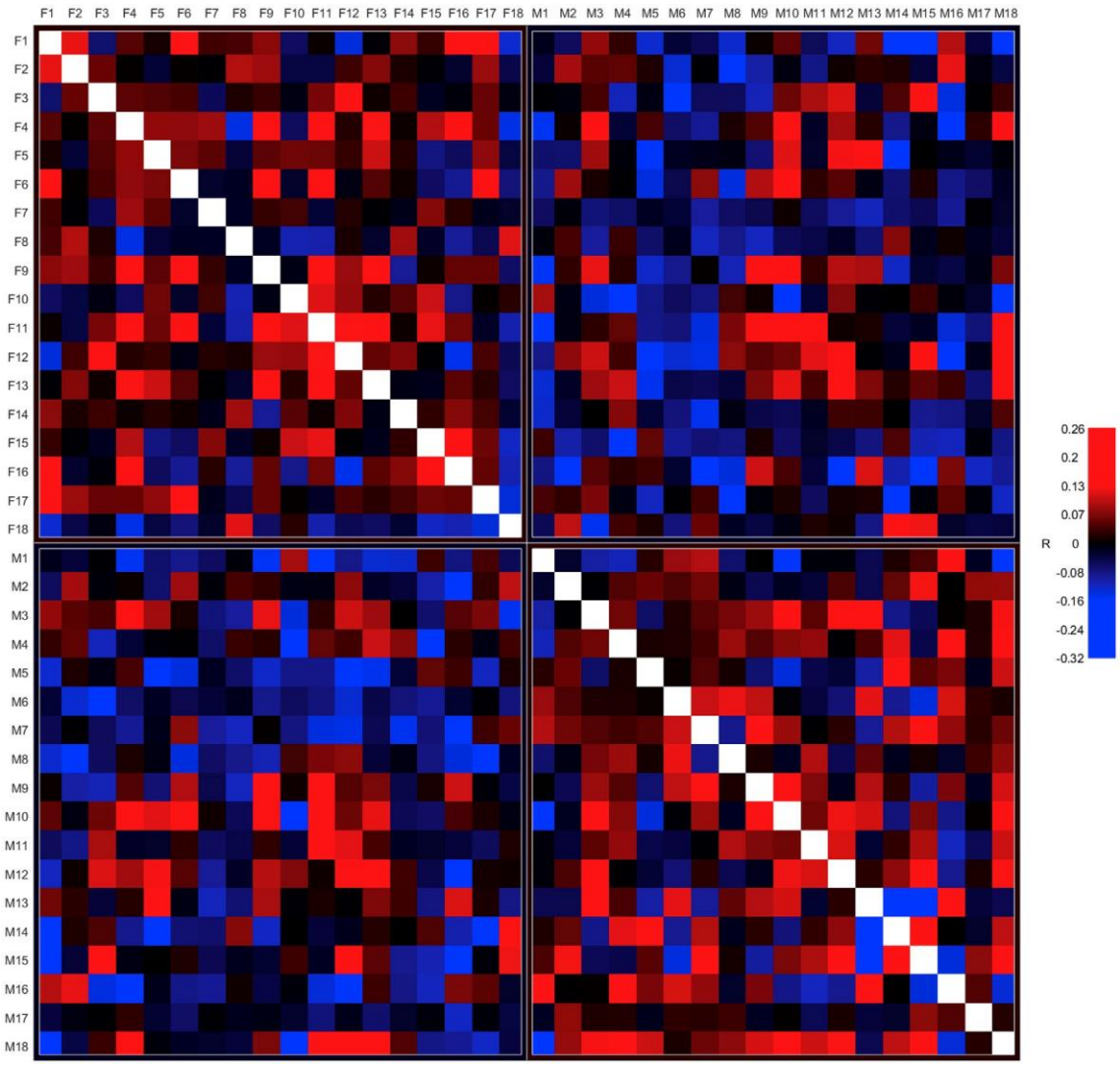


Fig. 5. Correlation matrix for the 18 selected female participants and the 18 male participants (mean activity within each quadrant shown within square border; key to the right).

To investigate whether a similar pattern of results would be observed for recollection (i.e., detailed retrieval, as opposed to non-detailed familiarity; cf., Slotnick, 2013), spatial memory hits with "sure" confidence judgments were contrasted with misses (Karanian and Slotnick, 2017, 2018; Santangelo and Macaluso, 2013; Santangelo et al., 2015). Overall, the patterns of activity associated with confident spatial memory for females and males (Fig. 6) were similar to the patterns of activity associated with spatial memory when collapsed over confidence (compare Fig. 2A to 6A and 2B to 6B). Although defined at a threshold of $p < .001$ (N = 5, 470

voxels), the mean correlation within sex was significantly higher than the mean correlation between sex ($F(1, 628) = 5.93$, $p < .05$), which shows the patterns of activity within sex were more similar to one another than the patterns of activity between sex.

To assess the degree to which task performance/difficulty might affect the pattern of results observed, an analysis was conducted (collapsed over confidence) for 18 females selected from the remaining 22—who were not included in the primary analysis—with the best behavioral performance (79.46 ± 2.24%). Spatial memory for these higher-performance females produced activity in the same brain regions as the matched-performance females including right lateral prefrontal cortex, bilateral sensorimotor cortex, bilateral parietal cortex, and bilateral visual processing regions (compare Fig. 7 and Fig. 2A), which were largely distinct from the pattern of spatial memory activity for males (Fig. 2B). However, these regions of activity had a greater spatial extent in the higher-performance females than the lower-performance females. A multi-voxel pattern correlation analysis showed that, for ROIs defined at a threshold of $p < .001$ (N = 12,009 voxels), the mean correlation within sex (for higher-performance females and males) was marginally significantly higher than the mean correlation between sex ($F(1, 628) = 3.64$, $p = .057$). Furthermore, the mean correlation between the two groups of females (higher-performance females, matched performance females) was significantly greater than the mean correlation between the higher-performance females and males ($t(323) = 1.69$, $p < .05$), which shows the two female groups were more similar than the higher-performance female group and the male group. It should be underscored that the extent of activity was greater and the within versus between sex correlation (for female and male groups) was less significant for the for the higher-performance females than the matched performance females. These findings suggest task performance affects the pattern of activity and thus behavioral accuracy and variance should be matched between groups.

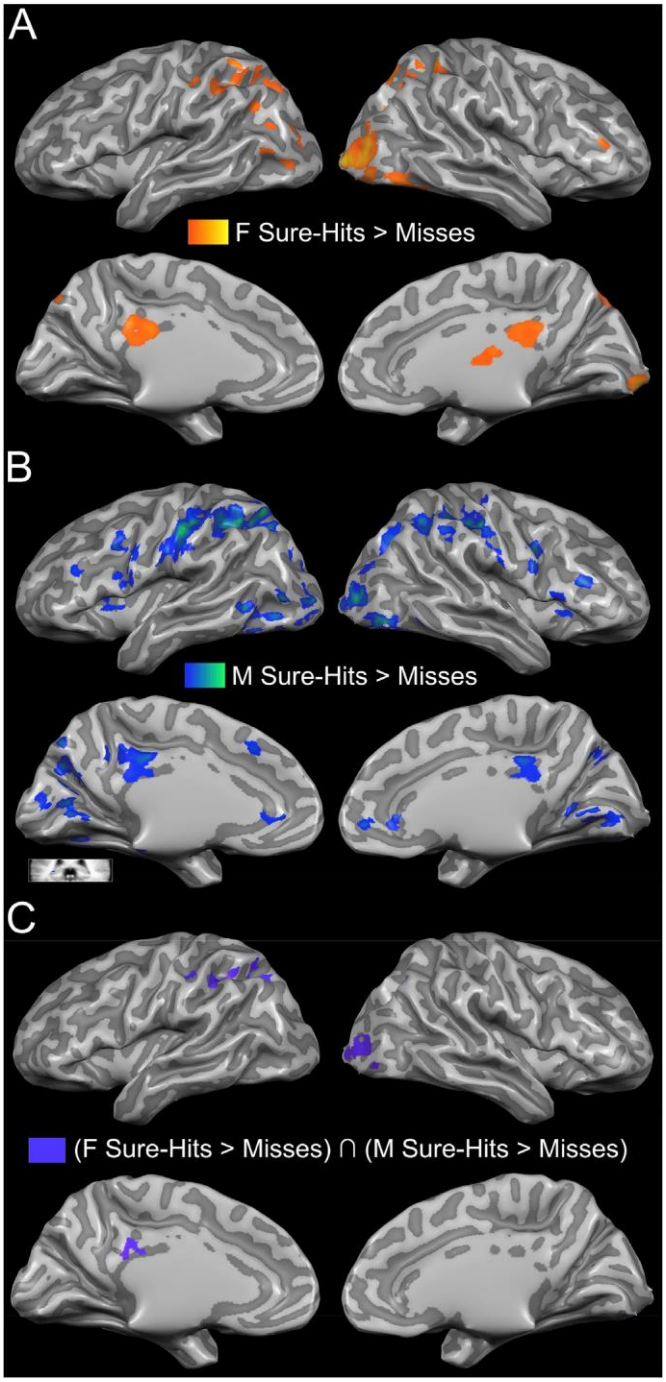


Fig. 6. Activity associated with confident spatial memory hits versus misses. (A) Activity associated with female confident hits versus misses (top, lateral views; bottom, medial views; key at the center). (B) Activity associated with male confident hits versus misses. (C) Overlapping activity of the preceding contrasts.

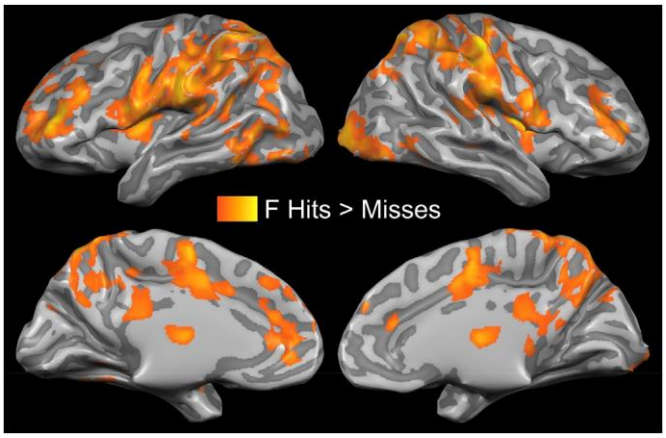


Fig. 7. Activity associated with spatial memory hits versus misses for a different group of 18 higher-performance females.

## Discussion

As expected, during spatial long-term memory, both females and males engaged regions associated with visual long-term including the prefrontal cortex, parietal cortex, and visual processing regions (Fig. 2A and B). However, females and males shared only three regions of common activity (Fig. 2C). Moreover, an interaction analysis revealed nine sex-specific regions including the right superior parietal lobule for females and bilateral visual processing regions (left middle occipital gyrus, right middle occipital gyrus, left inferior occipital gyrus, right collateral sulcus, left fusiform gyrus), the right putamen, the right caudate, and the right cerebellum for males. The current results suggest that spatial long-term memory is a more dissimilar than similar process in females and males.

As females are known to utilize a greater degree of verbal memory strategies and males are known to utilize a greater degree of spatial strategies during long-term memory tasks (Goldstein et al., 2001; Cahill, 2006; Frings et al., 2006; Herlitz and Rehnman, 2008; St. Jacques et al., 2011), we hypothesized that females would produce greater sex-specific activity within language processing regions whereas males would produce greater sex-specific activity within the hippocampus. A targeted ROI analysis identified a sex-specific activation for males within the left hippocampus and an additional activation for females within the left supramarginal gyrus

(i.e., Wernicke's area) that was marginally sex-specific. Although individual strategies were not assessed in the present study, these results support our hypotheses and suggest that during spatial long-term memory, females and males employ different retrieval strategies, even when behavioral accuracy is equated.

In the current study, the extent of activity in visual processing regions was larger for females than males (compare Fig. 2A and B). In one fMRI study that employed a picture naming task, which required semantic memory, the contrast of plants versus tools produced greater activity in females than males in left fusiform cortex (Garn et al., 2009). In a spatial working memory fMRI study, females produced greater activity than males in occipital and ventral visual processing regions (Zilles et al., 2016). An ERP study investigated sex differences during face perception and found that females had a higher amplitude N170 component (Sun et al., 2010), which has been linked to face perception. An ERP spatial attention study reported higher P1 and N1 amplitudes for females compared to males (Feng et al., 2011), indicating greater extrastriate attention effects in females. A greater extent of activity in visual processing regions in females may be due, in part, to their more vivid recollection of past events (Andreano and Cahill, 2009). Despite more distributed activity in visual processing regions for females, males produced a greater number of sex-specific activations within visual processing regions (Fig. 3, Table 1). Previous work has suggested that, compared to females, males utilize visuospatial processing strategies to a greater degree during spatial tasks (Andreano and Cahill, 2009; Clements-Stephens et al., 2009; Herlitz and Rehnman, 2008). One possibility is that, during the present task, males reconstructed a visual representation of the shape in space in order recall its precise location, which evoked activity in specific visual processing regions to a greater degree than females. This is a topic of future research.

Females produced only one sex-specific activation, within the superior parietal lobule. This region has previously been associated with shifts in spatial attention (Thakral and Slotnick, 2013; Yantis et al., 2002). One possibility is that during the current task, females did not bind the

shapes to their spatial context (i.e., left or right side of the screen) as well as males (which is suggested by the greater hippocampal activity in males), such that they may have shifted attention to the different spatial locations to determine the best match for that particular shape, and this process may have activated the superior parietal lobule. This is a topic of future investigation.

Some long-term memory and working memory studies that have investigated sex differences have reported null results. However, null results are always questionable as they can be due to factors such as low power (low trial number, low number of participants, or noisy data), poor choice of baseline, or an overly conservative analysis procedure. Some studies that have reported null results had a relatively low number of participants (Canli et al., 2002; Seurinck et al., 2004). One fMRI study investigating sex differences in brain regions associated with episodic and semantic autobiographical memory employed a control condition in which participants imagined a scene in a particular context (Compere et al., 2016). However, it is plausible that past events were retrieved during scene imagery. As such, when this baseline was subtracted from the other conditions, long-term memory processing may have been subtracted out, which could explain the null results. Finally, the null results of one working memory fMRI study can be attributed to a strict triple conjunction analysis (Haut and Barch, 2006). In light of the limitations of studies that have reported null results along with the numerous significant sex differences that have been observed in the present study and previous studies of long-term memory and working memory, the null hypothesis can be ruled out.

The large majority of studies that have investigated sex differences in the brain have employed fMRI, which has excellent spatial resolution but poor temporal resolution. As such, future studies that employ ERPs (event-related potentials) and EEG (electroencephalography), which have excellent temporal resolution, will greatly inform the field. There have been only a few studies that have employed ERPs or EEG to investigate sex differences during memory retrieval. One ERP study using an old-new face recognition task found significant old vs. new activity 400–800 m after stimulus onset over parietal electrodes (Guillem and Mograss, 2005),

which corresponds to the left-parietal old-new effect that has been associated with detailed memory/recollection and has been linked to the inferior parietal lobule in an fMRI-ERP study (Vilberg and Rugg, 2008). An EEG study compared females to males during elaboration of autobiographical memories and reported a decrease in alpha frequency power in parietal-occipital electrodes coupled with an increase in alpha frequency coherence in these electrodes starting 2 s after stimulus onset (Manns et al., 2018), which can be attributed to greater visual activity in females than males in the underlying cortical regions (Slotnick, 2017b). Long-term memory retrieval has been associated with three ERP components (the mid-frontal old-new effect, the left-parietal old-new effect, and the right-frontal old-new effect peaking within 300–500, 400–800, and 1000–1600 m after stimulus onset, respectively) and three EEG frequencies (theta, alpha, and gamma) (Slotnick, 2017b). Investigations of whether or not there are sex differences in each of these ERP components and EEG frequencies is a promising line of future research.

## Conclusion

The present results indicate that females and males use largely different brain regions during spatial long-term memory. These findings, and the many other significant sex differences that have been observed during long-term memory and working memory, indicate that females and males should not be assumed to rely on the same brain regions during a given cognitive process. As such, the widespread practice of collapsing across sex in cognitive neuroscience studies is questionable. More broadly, understanding that there are likely major sex differences in the brain is particularly important in studies that could ultimately inform diagnosis or treatment strategies for diseases that can affect long-term memory and differentially affect females and males such as depression and Alzheimer's Disease.

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## Table

Table 1. Contrasts and conjunction of female and male hits versus misses

| Region | BA | x | y | z |
|---|---|---|---|---|
| *Female hits > misses* | | | | |
| Right Inferior Frontal Sulcus | 46 | 41 | 37 | 14 |
| Right Precentral Gyrus | 4/6 | 51 | 1 | 25 |
| Right Central Sulcus | 3 | 34 | −21 | 44 |
| Left Postcentral Sulcus | 2/7/40 | −45 | −33 | 39 |
| Left Superior Parietal Lobule/Intraparietal Sulcus/Angular Gyrus/ Middle Occipital Gyrus/Inferior Occipital Gyrus/Fusiform Gyrus/ Precuneus | 7/18/19/37/39 | −18 | −71 | 40 |
| Right Superior Parietal Lobule*/Intraparietal Sulcus/ Superior Occipital Gyrus/Middle Occipital Gyrus/ Calcarine Sulcus/Inferior Occipital Gyrus/Fusiform Gyrus | 7/17/18/19/37 | 24 | −57 | 40 |
| Left Supramarginal Gyrus | 40 | −55 | −22 | 30 |
| Left Putamen | – | −27 | −2 | 1 |
| Right Putamen | – | 27 | −9 | 3 |
| Thalamus | – | −1 | −11 | 12 |
| | | | | |
| *Male hits > misses* | | | | |
| Right Medial Prefrontal Cortex | 32 | 12 | 34 | 5 |
| Right Postcentral Sulcus | 2/5/40 | 37 | −40 | 46 |
| Left Postcentral Sulcus/Postcentral Gyrus | 2/5 | −43 | −32 | 41 |
| Left Postcentral Sulcus/Intraparietal Sulcus | 5/7/40 | −35 | −52 | 39 |
| Right Intraparietal Sulcus | 19/39 | 28 | −61 | 34 |
| Left Middle Occipital Gyrus*/Inferior Occipital Gyrus* | 17/18 | −30 | −88 | 1 |
| Right Middle Occipital Gyrus* | 18 | 25 | −85 | 10 |
| Left Inferior Temporal Sulcus/Fusiform Gyrus | 19/37 | −44 | −68 | 0 |
| Right Inferior Temporal Sulcus/Fusiform Gyrus/Collateral Sulcus* | 19/37 | 34 | −71 | −11 |
| Left Fusiform Gyrus* | 19/37 | −31 | −64 | −14 |
| Right Caudate* | – | 10 | 7 | 5 |
| Right Putamen | – | 26 | 6 | 1 |
| Left Cerebellum* | – | −7 | −62 | −17 |
| Left Cerebellum | – | −21 | −54 | −18 |
| Right Cerebellum | – | 13 | −62 | −18 |
| Right Cerebellum* | – | 27 | −52 | −20 |
| | | | | |
| *(Female hits > misses) ∩ (male hits > misses)* | | | | |
| Left Intraparietal Sulcus | 7 | 25 | −58 | 40 |
| Right Middle Occipital Gyrus/Fusiform Gyrus | 18/19/37 | 33 | −72 | −10 |
| Left Fusiform Gyrus | 19/37 | −42 | −68 | −13 |

BA refers to Brodmann area and Talairach coordinate (x, y, z) refers to the center of each activation.
*Sex-specific region.

## CHAPTER 2

Similar patterns of cortical activity in females and males during item memory.
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Published in *Brain and Cognition*
DOI: 10.1016/j.bandc.2019.103581

Anatomic and molecular sex differences exist in the brain, which suggests there may be functional differences. The present functional magnetic resonance imaging (fMRI) investigation aimed to identify the similarities and differences in brain activity between females and males during item memory. During encoding, abstract shapes were presented to the left or right of fixation. During retrieval, old and new shapes were presented at fixation and participants made "old-left", "old-right", or "new" judgments. Item memory was isolated by contrasting correct "old" responses to old items (with incorrect spatial memory responses; item memory hits) and "new" responses to old items (item memory misses). For both sexes, item memory produced activity in regions associated with visual long-term memory including the prefrontal cortex, parietal cortex, and visual processing regions. A sex by accuracy interaction analysis within each sub-region of activity produced largely null results, supporting common patterns of brain activity. However, there was sex-specific (male > female) activity within default network regions, which suggests males may have been less engaged in the task, and there was evidence for greater activity for females than males in language processing cortex. The present findings indicate that females and males employ similar patterns of brain activity during item memory.

There are many anatomical and neurochemical sex differences in the brain, including in regions associated with long-term memory (Andreano and Cahill, 2009, Goldstein et al., 2001, Slotnick, 2017a). These anatomical and neurochemical sex differences in the brain may explain, in part, the differential behavioral performance often observed during long-term memory tasks (Cahill, 2006). Females typically perform better than males in tasks where a verbalization strategy is helpful (e.g., associative memory, autobiographical memory), while males typically perform better than females in visuospatial processing tasks (e.g., mental rotation, navigation; Herlitz and Rehnman, 2008, Andreano and Cahill, 2009). Such anatomic, neurochemical, and behavioral sex differences indicate that there should also be functional differences in brain activity.

Some functional magnetic resonance imaging (fMRI) studies have reported sex differences in core long-term memory regions, including the dorsolateral prefrontal cortex, the parietal cortex, and the medial temporal lobe (for a review, see Slotnick, 2017a). For instance, during an autobiographical memory task, when given pictorial cues versus verbal cues, females produced activity in the occipital cortex whereas males produced activity in the inferior parietal cortex, the hippocampus, and the retrosplenial cortex (St Jacques, Conway, & Cabeza, 2011). However, previous fMRI studies that have investigated sex differences during long-term memory are limited in that they utilized blocked designs (Banks et al., 2012, Bell et al., 2006, Frings et al., 2006, Grön et al., 2000, St Jacques et al., 2011) and thus have a possible vigilance confound, they did not equate behavioral performance (Goldstein et al., 2001, Guillem and Mograss, 2005, Speck et al., 2000) and thus have a possible task difficulty confound, or they did not isolate one cognitive process (cf., Cahill, 2006, Slotnick, 2017a).

The aim of the present fMRI investigation was to identify the differences and similarities in brain activity between females and males during item memory. Data was reanalyzed from two previous long-term memory experiments that had very similar stimulus and acquisition protocols (Slotnick and Schacter, 2004, Slotnick and Schacter, 2006). During each study phase, abstract

shapes were presented to the left or right of fixation (Fig. 1, left). During each test phase, old shapes from the study phase and new shapes were presented at fixation and participants made "left", "right", or "new" judgments. Item memory was isolated by contrasting "old" responses to old items (with incorrect spatial memory responses, to isolate the process of item memory from spatial memory; item memory hits) and "new" responses to old items (item memory misses; Fig. 1, right) (see Davachi, Mitchell, & Wagner, 2003). Across the two experiments there were fifteen females and eleven males. Eleven female participants were selected to equate statistical power and ensure that behavioral accuracy and variance was closely matched between the sexes. By selecting participants with matched behavioral performance and employing an event-related design, we were able to isolate the cognitive process of item memory.

Based on previous findings (Frings et al., 2006, Herlitz and Rehnman, 2008, Andreano and Cahill, 2009), we predicted that females would produce greater activity than males in language processing regions. Moreover, we hypothesized that females would produce more bilateral activity than males, as the female structural connectome is known to have more bilateral connections compared to the male connectome (Ingalhalikar et al., 2014, Volf and Razumnikova, 1999). As this is the first event-related fMRI study that has investigated sex differences during item memory, it is difficult to predict whether the overall patterns of brain activity in females and males would be more similar or different. To anticipate the results, females and males produced similar patterns of activity, although there were some differences.

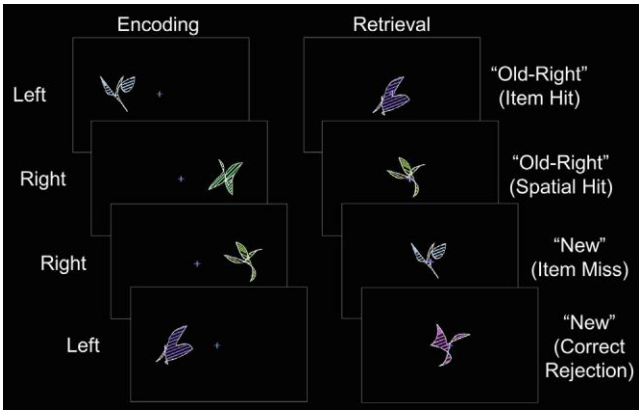


Fig. 1. Stimulus and response protocol. During the study phase, abstract shapes were presented to the left or right of fixation (labeled to the left). During the test phase, old and new shapes were presented at fixation and participants indicated whether the shapes were previously on the "left", "right", or "new". Example responses are shown to the right (corresponding response types are shown in parentheses).

## Methods

*Participants*

We reanalyzed data from two long-term memory experiments that were conducted in one of our previous studies (Slotnick and Schacter, 2004, Jeye et al., 2018). All of the participants were from the Harvard University community, with 12 included in the analysis of Experiment 1 (7 females, age range 18–22 years; 2 out of 14 participants were excluded) and 14 included in the analysis of Experiment 2 (8 females, age range 18–25 years; in the original study, 4 out of 16 participants were excluded, but 2 participants were added to the present study based on more lenient inclusion criteria). For the current study, eleven females were selected from all the female participants that best matched the item memory accuracy of the 11 male participants (an iterative matching procedure was used; see the Experimental design section below). All participants had normal or corrected-to-normal vision. Both experiments were approved by the Harvard University Institutional Review Board (for the training protocol) and the Massachusetts General Hospital Institutional Review Board (for the imaging protocol). Participants received $10 for the

training session and $25 per hour for the fMRI session. Informed consent was obtained prior to each session.

*Stimulus protocol and task*

In both Experiments 1 and 2, participants completed a training session to familiarize them with the task. During the scanning session, each participant completed a single anatomic scan and three study-test runs in Experiment 1 and six study-test runs in Experiment 2. During the study phase, abstract shapes were presented in the left or right visual field (Fig. 1, left). In Experiment 1, the study phase consisted of 144 shapes (16 sets of 9 similar shapes) and in Experiment 2, the study phase consisted of 32 abstract shapes. In both experiments, during each study phase, shapes were contained within a bounding square of 5.5° of visual angle in width, with the closest edge 3° of visual angle from fixation. During each test phase, shapes were presented at the center of the screen for 2.5 s with a 4 to 12 s inter-trial-interval. In Experiment 1, the test phase consisted of 96 shapes (32 shapes from the study phase, 32 related shapes, and 32 new shapes) and in Experiment 2, the test phase consisted of 48 shapes (32 shapes from the study phase and 16 new shapes). For both experiments, participants were instructed to remember each shape and its spatial location while maintaining fixation. During the test phase of both experiments, for each shape, participants responded either "old-left," "old-right," or "new" followed by an "unsure" or "sure" confidence rating with their left hand (Fig. 1, right). Shape sets were randomized such that no more than 3 shapes of a given type were presented during the study phase or test phase. Shape sets were counterbalanced across participants using a Latin Square design and shapes were never repeated across runs.

*Experimental design*

Item memory accuracy was the weighted percentage of correctly identified old and new shapes: p(old) × old-hit rate + p(new) × new-correct rejection rate (Macmillian & Creelman,

2004). Within each experiment, a subset of female participants was selected (there were a greater number of female participants than male participants) such that their average item memory accuracy and variance best matched the average item memory accuracy and variance of the male participants. In Experiment 1, we selected 5 females from the original 7 to best match the item memory accuracy of the 5 males. We selected these females on an individual basis such that the item memory accuracy of each selected female was closely matched to the item memory accuracy of a single male participant (i.e., a matched-pair procedure was employed). In Experiment 2, 6 females were selected from 8 to match the 6 males using the same matched-pair procedure. For each experiment, following selection, we ran independent samples t-tests to determine whether there were any significant differences in item memory accuracy between the groups. Using an iterative procedure, if the average accuracy of one group was marginally higher than the other or the variances deviated from one another, we selected alternative female participants until we obtained a combination of female and male participants that were best matched on both item memory accuracy and variance.

*Image acquisition and analysis*

In both experiments, images were acquired using a 3-Tesla Siemens Allegra MRI scanner. Anatomic data were acquired using a multiplanar rapidly acquired gradient echo (MPRAGE) sequence (TR = 30 ms, TE = 3.3 ms, 128 slices, 1 × 1 × 1.33 mm resolution) and functional data were acquired using a T2*-weighted echo planar imaging (EPI) sequence (TR = 2,000 ms, TE = 30 ms, 64x64 acquisition matrix, 26 to 30 slices in Experiment 1 and 30 slices in Experiment 2). BrainVoyager QX (Brain Innovation B.V., Maastricht, the Netherlands) was used to conduct the analysis. Images were slice-time corrected, motion correction, temporal components below 2 cycles per run length were removed, and voxels were resampled at 3 $mm^3$. To maximize spatial resolution, spatial smoothing was not conducted. Anatomic and functional images were transformed into Talairach space.

A random-effect general linear model analysis was conducted. The general linear model included the following event types: encoding of items in the left visual field, encoding of items in the right visual field, accurate retrieval of item and spatial location in the left visual field, accurate retrieval of item and spatial location in the right visual field, accurate retrieval of item and inaccurate retrieval of spatial location in the left visual field, accurate retrieval of item and inaccurate retrieval of spatial location in the right visual field, misses in the left visual field, misses in the right visual field, and correct rejections. Item memory was isolated by contrasting accurate item recognition with inaccurate retrieval of spatial location (i.e., "right"/left responses, "right" responses to items previously presented in the left visual field, or "left"/right responses) and item misses (i.e., "new"/left or "new"/right). To maximize power, confidence responses were collapsed for all analyses. All contrasts were thresholded at $p = 0.001$, which was false discovery rate corrected to $p < 0.05$, and also cluster-extent threshold corrected to $p < 0.05$. To determine the minimum cluster extent, we first computed the spatial autocorrelation for the contrast of female hits versus male hits in each experiment and employed the highest spatial autocorrelation value across the two experiments (3.31 mm). For each experiment, ten thousand Monte Carlo simulations were conducted based on the acquisition volume parameters, the computed spatial autocorrelation, the individual voxel p-value (0.001), and desired familywise $p < 0.05$ (Slotnick, 2017b). The largest cluster extent for the two experiments (14 voxels) was enforced for all contrasts, unless otherwise stated. For viewing purposes, a gray/white matter surface reconstruction was created from the anatomic data from one representative participant. Precise activation coordinates can be found in Table 2.

For the activation timecourse analysis, event-related activity −1 to 6 s after stimulus onset (baseline corrected from −1 to 0 s) was extracted from voxels within a 10 mm cube at the center of each anatomic region with significant activity. The magnitude of activity at 8 s after stimulus onset, the maximum amplitude of the mean activation timecourse across all conditions in V1, was used for statistical analysis.

To determine if differences in the patterns of activity were due to sex rather than individual differences, we ran Monte Carlo Simulations. The number of females and males in each group was varied from 6 females and 5 males (baseline mixture of males and females) to 11 females and 0 males (only one sex in the group), randomly selecting the participants without replacement. A random-effect analysis was conducted using the item hit versus miss contrast images for the participants in each group, and the number of significant clusters of activity were computed (using the same thresholding procedures described above). Ten thousand simulations were run for each group and the mean number of significant clusters was used to assess whether there was a significant increase as a function of sex.

## Results

Across all participants (15 females, 11 males), there was no significant difference in item memory accuracy between females (68.32 ± 1.29%, mean ± standard error, chance = 50%) and males (66.59 ± 1.79, weighted $F(1,24) < 1$). For the fMRI analysis, we selected 11 female participants such that behavioral accuracy and variance was even better matched (female performance = 66.86 ± 1.41, $t(20) < 1$). For item hits and item misses, the two event types of interest, there were no significant differences between females and males in response rate, reaction time, or percentage of confident responses (Table 1). Although there was a significant difference in reaction time for source hits, this event type was not included in the fMRI analysis.

Item memory was isolated by contrasting item memory hits and item memory misses. As expected, for both females and males, accurate item memory produced activity in regions associated with visual long-term memory. For females this included anterior prefrontal cortex, ventrolateral and dorsolateral prefrontal cortex (inferior frontal gyrus, inferior frontal sulcus, middle frontal gyrus, and superior frontal sulcus), medial prefrontal cortex, sensorimotor processing regions (precentral sulcus and precentral gyrus), parietal cortex (angular gyrus, supramarginal gyrus, intraparietal sulcus, superior parietal lobule, and precuenus), visual

processing regions (superior occipital gyrus, cuneus, and parietooccipital sulcus), the insula, and the caudate (Fig. 2A and Table 2, top). For males this included anterior prefrontal cortex, ventrolateral and dorsolateral prefrontal cortex (inferior frontal gyrus, inferior frontal sulcus, middle frontal gyrus, superior frontal sulcus, and superior frontal gyrus), medial prefrontal cortex, sensorimotor processing regions (precentral sulcus), anterior cingulate cortex, parietal cortex (angular gyrus, supramarginal gyrus, intraparietal sulcus, superior parietal lobule, and precuneus), the insula, and the caudate (Fig. 2B and Table 2, middle).

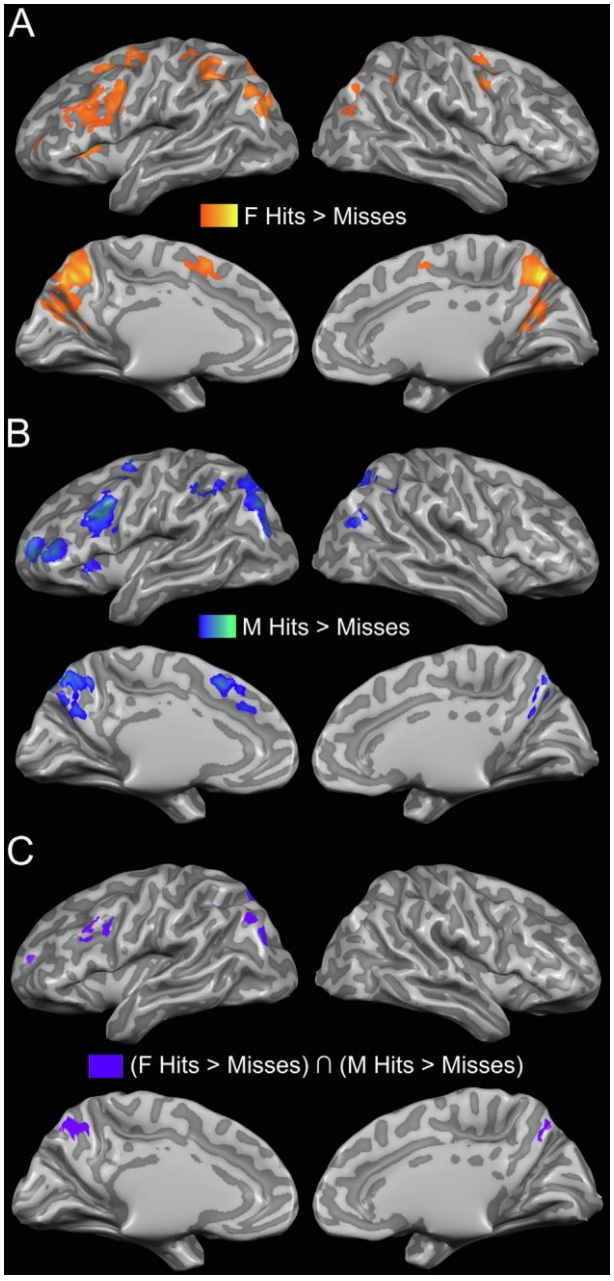


Fig. 2. Activity associated with item memory hits versus misses. (A) Activity associated with female hits versus misses (top, lateral views; bottom, medial views; key at the center). (B) Activity associated with male hits versus misses. (C) Conjunction of the preceding contrasts.

To assess the degree to which female and male activity during item memory overlapped, we conducted a conjunction of the female hits versus misses contrast and the male hits versus misses contrast. This conjunction produced activations in anterior prefrontal cortex, ventrolateral and dorsolateral prefrontal cortex (inferior frontal sulcus, and middle frontal gyrus), sensorimotor

processing regions (precentral sulcus), parietal cortex (angular gyrus, intraparietal sulcus, superior parietal lobule, and precuneus), and the caudate (Fig. 2C and Table 2, bottom).

To investigate whether the activations produced by females and males during accurate item memory were sex-specific, we extracted the activation timecourses from the center of activity within each unique brain region and assessed whether there was a sex by accuracy interaction. Notably, this was a conservative method of analysis given the high between-subject variability exhibited in episodic memory (Miller et al., 2009). Seven activated regions were found to be sex-specific (Fig. 3 and Table 2, regions with an asterisk). For females, this included one activation in the precentral gyrus. For males, this included ventrolateral prefrontal cortex (inferior frontal sulcus and inferior frontal gyrus), medial prefrontal cortex, and parietal cortex (angular gyrus).

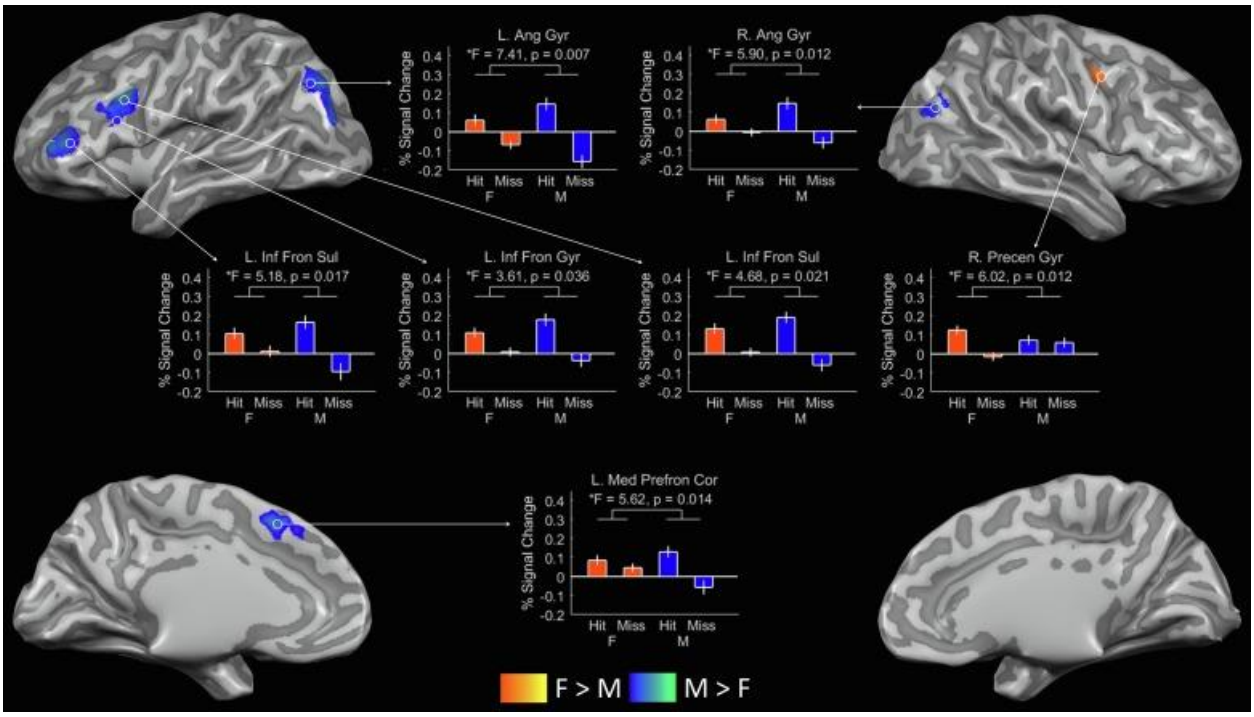


Fig. 3. Sex-specific activations (top, lateral views; bottom, medial views; key at the bottom center).

Given our specific hypothesis that females would produce greater activity than males in language processes regions, we conducted a targeted region-of-interest (ROI) analysis in language processing cortex (i.e., Wernicke's area and Broca's area) without enforcing the cluster extent threshold (results were still false discovery rate corrected to $p < 0.05$). The female hit versus miss contrast produced two activations within our ROIs: one within left supramarginal gyrus (Wernicke's area; coordinates: x = −52, y = −32, z = 39) and one within left inferior frontal gyrus (Broca's area; coordinates: x = −54, y = 10, z = 25). A sex by accuracy interaction analysis show that the activity within the left supramarginal gyrus was marginally sex-specific ($p = 0.051$, Fig. 4), while activity in the left inferior frontal gyrus was not sex-specific ($p > 0.20$). There were no activations identified in language processing cortex for males.

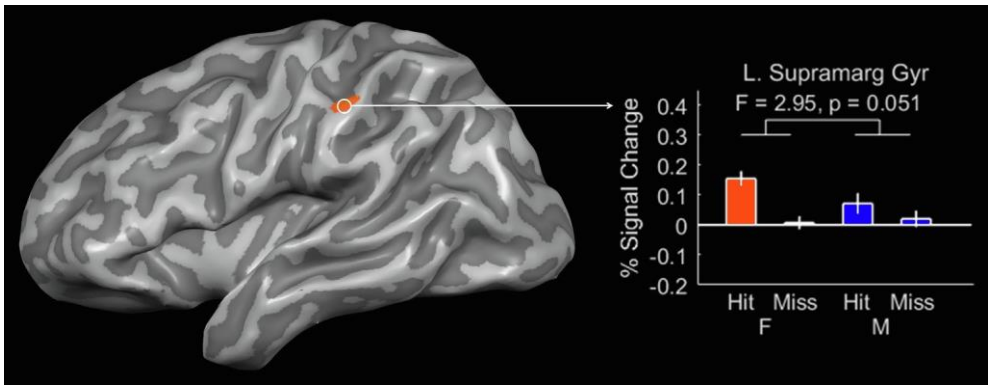


Fig. 4. Sex-specific activity within one region of interest (lateral view).

To ensure that the differences observed were sex-specific and not due to individual differences between groups, we ran Monte Carlo simulations (10,000 per group) by parametrically varying the number of females and males included in the contrast of item memory hits versus item memory misses. If the differences observed in the female and male contrasts of item memory were due to individual differences between the groups, rather than sex differences, there should be no significant increase in the number of significant thresholded clusters of activity as a function of the number of females/males per group. However, there was a significant

correlation (monotonic increase) between the number of females/males in each group and the probability of significant activity ($R_s^2 = 1$, $p < 0.01$, Spearman correlation; Fig. 5).

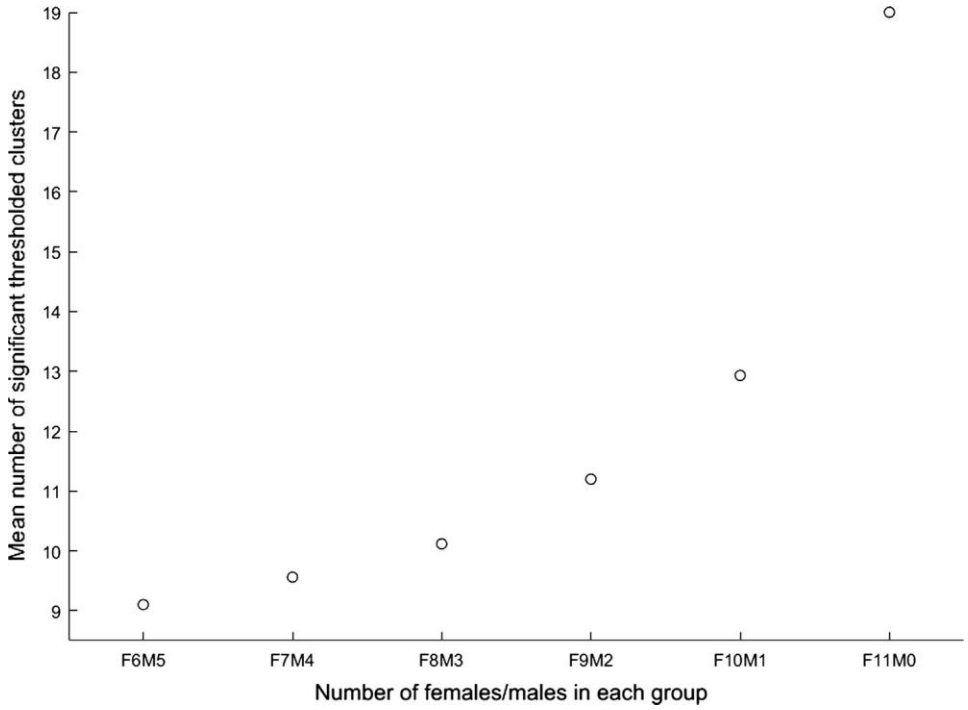


Fig. 5. Mean number of significant thresholded clusters associated with the female hit versus miss contrast as a function of number of females/males in each group.

## Discussion

For both females and males, item memory (isolated by contrasting item hits and misses) was associated with activity in brain regions associated with visual long-term memory including the prefrontal cortex, parietal cortex, and visual processing regions (Table 2). A conjunction analysis showed that females and males recruited many of the same regions of the prefrontal cortex and parietal cortex (Fig. 2C, Table 2, bottom). By comparison, of the fifty-seven regions that were associated with either female item memory or male item memory, an interaction analysis revealed that only seven regions were sex-specific. These results indicate that females and males employ similar brain regions during item memory.

Despite the general similarity in brain regions associated with item memory for females and males, there were some differences. The brain regions that had greater activation for males than females were within the default network, which includes the dorsolateral prefrontal cortex, the medial prefrontal cortex, the inferior parietal cortex, and the medial parietal cortex (Buckner, Andrews-Hanna, & Schacter, 2008). Although the behavioral performance between females and males was not significantly different for item memory hits and item memory misses, across all event types, males were consistently faster at responding ($F(1,100) = 10.67$, $p < 0.01$) and more confident ($F(1,100) = 2.82$, $p = 0.096$) than females (Table 1), which may reflect that males were less engaged in the task than females. This is a topic for future research. Females produced a sex-specific activation in the right precentral sulcus/gyrus (BA4/6)—the primary motor and premotor cortex. This may have been due to females having consistently slower response times than males (which reached significance for source hits and was significant across all event types), where longer response preparation could have produced greater activity in motor processing cortex.

It is notable that females produced item memory activity in early visual regions (BA17/18/19), while males did not (although there was no significant sex × accuracy interaction at the coordinates tested). This may reflect more vivid visualization of remembered items for females, which is consistent with previous findings of greater activity for females than males in visual processing regions (Feng et al., 2011, Garn et al., 2009, Sun et al., 2010, Zilles et al., 2016). This is also consistent with behavioral findings, as females have reported more vivid recollection of past events than males (Andreano & Cahill, 2009).

Females also produced more bilateral activity than males, which supports greater bilateral connections for females than males that has been reported in connectome studies (Ingalhalikar et al., 2014, Volf and Razumnikova, 1999). The interaction analysis revealed a marginally significant sex-specific activation for females in the left supramarginal gyrus (i.e., Wernicke's area; Fig. 4), and although the interaction analysis did not reveal female-specific activity in the left inferior ventrolateral prefrontal cortex (Broca's area, BA44), the extent of activity in and

around this region was greater for females than males (compare Fig. 2A to B). These findings lend some support to the hypothesis that females relied more on language strategies during item memory.

## Conclusion

The brain regions associated with item memory in females and males were largely similar. However, there were some differences including greater activity in default network regions in males and greater activity in language processing regions in females. It is notable that we employed abstract shapes in the present study. It is possible that different types of stimuli, such as objects, may produce greater sex differences during item memory. This is an important line of future research.

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## Tables

Table 1
Behavioral Results.

| | % Response | | | Reaction Time (ms) | | | % Confident | | |
|---|---|---|---|---|---|---|---|---|---|
| | F | M | *p* | F | M | *p* | F | M | *p* |
| Source Hit | 48.60 | 45.97 | 0.559 | 2350.6 | 2001.7 | 0.027* | 49.24 | 54.89 | 0.569 |
| Item Hit | 22.46 | 17.44 | 0.113 | 2528.5 | 2347.6 | 0.376 | 28.50 | 34.75 | 0.514 |
| Item Miss | 28.94 | 36.59 | 0.189 | 2215.6 | 2002.9 | 0.273 | 28.65 | 38.49 | 0.352 |
| Item FA | 44.12 | 30.67 | 0.034* | 2488.0 | 2203.9 | 0.182 | 19.24 | 28.81 | 0.343 |
| Item CR | 55.88 | 69.32 | 0.034* | 2252.3 | 2079.7 | 0.308 | 41.65 | 47.49 | 0.601 |

FA refers to false alarm and CR refers to correct rejection.
* Significant difference between females and males.

Table 2. Contrasts and conjunction of female and male hits versus misses

| Region | BA | x | y | z |
|---|---|---|---|---|
| *Female hits > misses* | | | | |
| Left Anterior Prefrontal Cortex | 10 | −28 | 48 | 12 |
| Left Inferior Frontal Gyrus/Inferior Frontal Sulcus/ Middle Frontal Gyrus/Superior Frontal Sulcus/ Precentral Sulcus/Precentral Gyrus* | 4/6/8/9/44/46 | −24 | 4 | 46 |
| Right Middle Frontal Gyrus/Superior Frontal Sulcus/ Precentral Sulcus/Precentral Gyrus | 4/6/8/9 | 27 | 5 | 46 |
| Left Medial Prefrontal Cortex | 6/8 | −5 | 6 | 48 |
| Right Medial Prefrontal Cortex | 6 | 3 | 7 | 47 |
| Right Angular Gyrus/Superior Occipital Gyrus | 19/39 | 35 | −71 | 27 |
| Right Supramarginal Gyrus/Intraparietal Sulcus | 7/40 | 40 | −45 | 43 |
| Left Intraparietal Sulcus/Superior Parietal Lobule/ Postcentral Gyrus | 1/2/3/5/7/40 | −35 | −47 | 38 |
| Left Angular Gyrus/Superior Occipital Gyrus/ Parietooccipital Sulcus/Precuneus/Cuneus | 7/17/18/19/31/39 | −4 | −61 | 44 |
| Right Parietooccipital Sulcus/Precuneus/Cuneus | 7/17/18/19/31 | 2 | −62 | 43 |
| Left Insula | – | −30 | 21 | 8 |
| Left Caudate Nucleus | – | −9 | 10 | 7 |
| Right Caudate Nucleus | – | 7 | 3 | 5 |
| *Male hits > misses* | | | | |
| Left Inferior Frontal Sulcus*/Anterior Prefrontal Cortex | 10/46 | −32 | 45 | 10 |
| Left Inferior Frontal Gyrus | 44 | −40 | 11 | 9 |
| Left Inferior Frontal Gyrus*/Inferior Frontal Sulcus*/ Middle Frontal Gyrus | 6/8/9/44 | −44 | 12 | 29 |
| Left Middle Frontal Gyrus/Superior Frontal Sulcus/ Superior Frontal Gyrus/Precentral Gyrus | 6/8 | −26 | 0 | 53 |
| Left Medial Prefrontal Cortex*/Anterior Cingulate Cortex | 8/24/32 | −6 | 18 | 43 |
| Left Angular Gyrus*/Supramarginal Gyrus/Intraparietal Sulcus/ Superior Parietal Lobule/Precuneus | 7/39/40 | −32 | −71 | 38 |
| Right Supramarginal Gyrus | 40 | 35 | −46 | 36 |
| Right Angular Gyrus* | 39 | 39 | −68 | 27 |
| Right Superior Parietal Lobule/Precuneus | 7 | 16 | −63 | 49 |
| Left Insula | – | −29 | 21 | 2 |
| Left Caudate | – | −10 | 8 | 8 |
| *(Female hits > misses) ∩ (male hits > misses)* | | | | |
| Left Anterior Prefrontal Cortex | 10 | −27 | 48 | 10 |
| Left Inferior Frontal Sulcus/Middle Frontal Gyrus/Precentral Sulcus | 6/9/46 | −41 | 6 | 29 |
| Left Superior Parietal Lobule | 7 | −16 | −72 | 44 |
| Left Angular Gyrus | 39 | −33 | −72 | 36 |
| Left Intraparietal Sulcus | 7/40 | −33 | −48 | 36 |
| Left Precuneus | 7 | −3 | −61 | 44 |

| | | | | |
|---|---|---|---|---|
| Right Precuneus | 7 | 9 | −67 | 44 |
| Left Caudate | – | −10 | 6 | 10 |

BA refers to Brodmann area and Talairach coordinate (x, y, z) refers to the center of each activation.
* Sex-specific region.

## CHAPTER 3

High confidence spatial long-term memories produce greater cortical activity in males than females.

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In press at *Cognitive Neuroscience*
DOI: 10.1080/17588928.2020.1807924

Many functional resonance imaging (fMRI) studies have reported sex differences during long-term memory. The present fMRI investigation aimed to identify whether sex differences exist during high- versus low-confidence accurate spatial memories. During the study phase, abstract shapes were presented to the left or right of fixation. During the test phase, each shape was presented at fixation and participants made an old-"left" or old-"right" judgment followed by an "unsure" or "sure" response. The conjunction of female high- versus low-confidence spatial memory and male high- versus low-confidence spatial memory identified common activity in visual processing regions and parietal cortex, which suggests amplification of activity in some of the regions commonly associated with long-term memory yields high confidence. The contrast of female high- versus low-confidence spatial memory and male high- versus low-confidence spatial memory did not produce any significant activity. However, the reverse contrast produced greater male than female activity in the lateral prefrontal cortex, parietal cortex, sensorimotor cortex, and visual processing regions. An independent region-of-interest (ROI) analysis (ROIs were identified by contrasting hits versus misses) produced complementary results in the lateral prefrontal cortex. Greater lateral prefrontal cortex activity suggests a higher degree of subjective confidence in males than females, greater parietal cortex and visual processing activity suggests more vivid visualization in males than females, and greater activity in sensorimotor cortex indicates that males have a more reactive processing style than females. More broadly, the present and previous functional sex differences argue against the practice of collapsing across sex in cognitive neuroscience studies.

Sex differences exist in the brain at both the neurochemical and anatomic levels (Andreano & Cahill, 2009). Females, for example, have larger volumes of the lateral prefrontal cortex (PFC) relative to overall brain size (Andreano & Cahill, 2009; Goldstein et al., 2001; lateral PFC includes the dorsolateral PFC and the ventrolateral PFC). Differences in brain connectivity have also been reported, with females exhibiting greater inter-hemispheric connectivity than males and males exhibiting greater intra-hemispheric connectivity than females (Ingalhalikar et al., 2014). Functional differences have been reported across many different cognitive domains, including long-term memory (Frings et al., 2006; Ino et al., 2010; Sneider et al., 2011; Spets et al., 2019; Spets & Slotnick, 2019; St. Jacques et al., 2011).

Activity in the lateral PFC has previously been associated with long-term memory confidence. One study found that the right and left lateral PFC were associated with subsequent high-confidence judgments of accurate memories, while the left lateral PFC was associated with subsequent high-confidence judgments of both accurate and inaccurate memories (Chua et al., 2004). Another study similarly found that high-confidence during long-term memory encoding (predicted subsequent remembering) produced activity in the right lateral PFC (Kao et al., 2005). The lateral PFC has also been associated with low-confidence versus high-confidence judgments in a number of long-term memory studies (Chua et al., 2009; Hayes et al., 2011; Henson et al., 2000; Kim & Cabeza, 2009). While some studies have linked the lateral PFC to high- versus low-confidence responses and other studies have linked the lateral PFC to low- versus high-confidence, this is a large cortical region and different sub-regions may mediate disparate functions.

Greater activity in visual processing regions has also been associated with memory confidence. High- versus low-confidence long-term memory activity has been reported in the fusiform cortex (Chua et al., 2004; Kuchinke et al., 2013) and the cuneus (Hayes et al., 2011; Kuchinke et al., 2013; Moritz et al., 2006). To our knowledge, only one study has reported visual

processing activity (in the fusiform cortex) for low- versus high-confidence memories (Hayes et al., 2011).

The current fMRI investigation sought to determine whether there are sex differences in the brain associated with high- versus low-confidence accurate spatial long-term memories. During the study phase of the present paradigm, abstract shapes were presented to the left or right of fixation (Figure 1). During the test phase, each shape was presented at fixation and participants made an old-"left" or old-"right" judgment followed by an "unsure" (low-confidence) or "sure" (high-confidence) response. Although behavioral sex differences exist in certain spatial tasks (e.g., mental rotation, navigation; Andreano & Cahill, 2009; Herlitz & Rehnman, 2008), such differences have not been observed during spatial long-term memory for shapes (Rahman et al., 2011). As detailed above, greater activity in the lateral PFC and visual processing regions has previously been associated with high confidence judgments. As males have been shown to produce a relatively higher proportion of confident responses than females during long-term memory (Spets & Slotnick, 2019), we hypothesized that males would produce greater activity in these regions during high-confidence accurate memories. To anticipate the results, sex differences were observed during high- versus low-confidence spatial memory as males produced greater activity than females in the lateral PFC, sensorimotor cortex, parietal cortex, and visual processing regions.

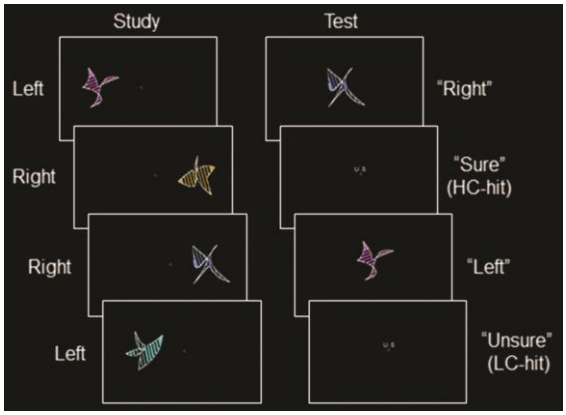


Figure 1. Stimulus and response protocol. During the study phase, abstract shapes were presented to the left or right of fixation. During the test phase, old shapes were presented at fixation followed by a confidence reminder screen. Participants indicated whether each shape was previously on the "left" or "right" followed by an "unsure"–"sure" confidence rating.

## Methods

The present study reanalyzed data from two spatial long-term memory studies (Jeye et al., 2018; Slotnick & Schacter, 2004), which were each comprised of two experiments. Only essential methodological details are provided here (full details can be found in Spets et al., 2019).

### *Participants*

Across the two studies there were 40 female and 18 male participants. Eighteen females were selected from the 40 female participants to best match the spatial memory accuracy and variance of the 18 male participants.

### *Stimulus protocol and task*

Each participant completed a behavioral training session prior to the scanning session, a single anatomic scan, and three to eight study-test runs. During each study phase, abstract shapes were presented in randomized order to the left or right of a fixation cross (shape construction details can be found in Slotnick & Schacter, 2004). Participants were instructed to remember each

shape and its spatial location while maintaining fixation. The delay between the end of each study phase and the beginning of the subsequent test phase was approximately 7 min and 10 sec, respectively, for Experiments 1 and 2 (Slotnick & Schacter, 2004) and 8 sec for Experiments 3 and 4 (Jeye et al., 2018). For each shape presented during the test phase, participants made an old-"left" or old-"right" judgment followed by an "unsure" or "sure" judgment with their left hand (Figure 1). Spatial location accuracy was computed as the percentage of correct spatial location identification contingent on correct old item identification (chance = 50%). Shape sets were counterbalanced across participants using a Latin Square design.

*Image analysis*

A random-effect general linear model analysis was conducted in SPM12 (Wellcome Center for Human Neuroimaging, London, UK). Functional image pre-processing included slice-time correction, motion correction to the first volume of each run, and spatial normalization to the Montreal Neurological Institute (MNI) template, which included resampling at 2 $mm^3$. Anatomic images were normalized to MNI space with 1 $mm^3$ resolution and then averaged across participants. As mentioned previously, females have larger volumes of the lateral PFC than males, relative to overall brain size (Andreano & Cahill, 2009; Goldstein et al., 2001). Of importance, the normalization procedure should eliminate such anatomic sex differences (even if structural differences existed between the sexes, they would not be expected to produce differences in functional activation). The event types entered into the general linear model included accurate or inaccurate spatial memory in the left or right visual field with low or high confidence (i.e., unsure-old-left-hits, sure-old-left-hits, unsure-old-left-misses, sure-old-left-misses, unsure-old-right-hits, sure-old-right-hits, unsure-old-right-misses, and sure-old-right-misses). For each participant, activity associated with high confidence hits (HC-hits) was isolated with a weighted contrast of HC-hits (i.e., left-sure-hits or right-sure-hits) versus low-confidence hits (LC-hits; i.e., left-unsure-hits or right-unsure-hits). A random-effect analysis was conducted

to directly compare HC-hits and LC-hits between females and males using an independent-samples t-test. The ImCalc function was used to create the conjunction of activity associated with HC-hits versus LC-hits for females and HC-hits versus LC-hits for males.

All contrasts were thresholded at $p < .01$, cluster extent corrected to $p < .05$. To compute the cluster extent threshold, we first computed the spatial autocorrelation for the contrast of male versus female HC-hits versus LC-hits in each experiment and employed the smallest spatial autocorrelation value (3 mm) across experiments (as larger spatial autocorrelations can be assumed to be due to activations rather than noise). Ten thousand Monte Carlo simulations were conducted based on the acquisition volume parameters, computed spatial autocorrelation, and the desired individual voxel and familywise p-value (Slotnick, 2017a). Across all experiments, we selected the lowest cluster extent threshold. This resulted in a cluster extent threshold of 24 voxels, which was applied to all contrasts. Images were imported into MRIcroGL (www.nitrc.org) and overlaid on the average anatomic for viewing purposes. Precise activation coordinates can be found in Table 2.

In addition to the standard general linear model analysis described above, a region-of-interest (ROI) analysis was conducted to assess whether there was a positive relationship between the magnitude of lateral PFC activity and confidence ratings (the same analysis was conducted in visual processing regions and the hippocampus). Functional ROIs were identified by contrasting hits and misses (collapsed across confidence) across all participants. The most significant activation within each region (e.g., within the lateral PFC) served as a single ROI for further evaluation, to minimize issues associated with multiple comparisons. For each ROI, beta-weights were extracted for each participant using custom scripts written in MATLAB (MathWorks, Natick, MA). For each participant of a given sex, the percentage of HC-hit responses (i.e., the number of HC-hits divided by the number of HC-hits and LC-hits) was plotted as a function of HC-hit beta-weight value in the ROI, and then a Pearson correlation was conducted.

## Results

There was no difference in the spatial memory accuracy of the 18 female participants (74.25 ± 0.94%, mean ± 1 SE) and 18 male participants (73.42 ± 1.22%, $t(34) < 1$). There were no significant sex differences for either the percentage of high-confidence responses or reaction time for HC-hits, LC-hits, HC-misses, or LC-misses (Table 1). It is notable that percentage of high-confidence responses for HC-hits was numerically higher for males (63.99 ± 5.58%) than females (60.63 ± 4.81%) and the reaction time for HC-hits was numerically faster for males (1762 ± 41 ms) than females (1851 ± 93 ms).

The brain regions commonly associated with high-confidence accurate spatial memory for females and males were isolated using the conjunction of female HC-hits versus LC-hits and male HC-hits versus LC-hits. This produced activity in right sensorimotor cortex (right precentral sulcus, right central sulcus, and right postcentral sulcus), bilateral parietal cortex (bilateral intraparietal sulcus and precuneus), bilateral visual processing regions (left parieto-occipital sulcus and right middle occipital gyrus), bilateral caudate, right thalamus, and left cerebellum (Figure 2, green and Table 2, top).

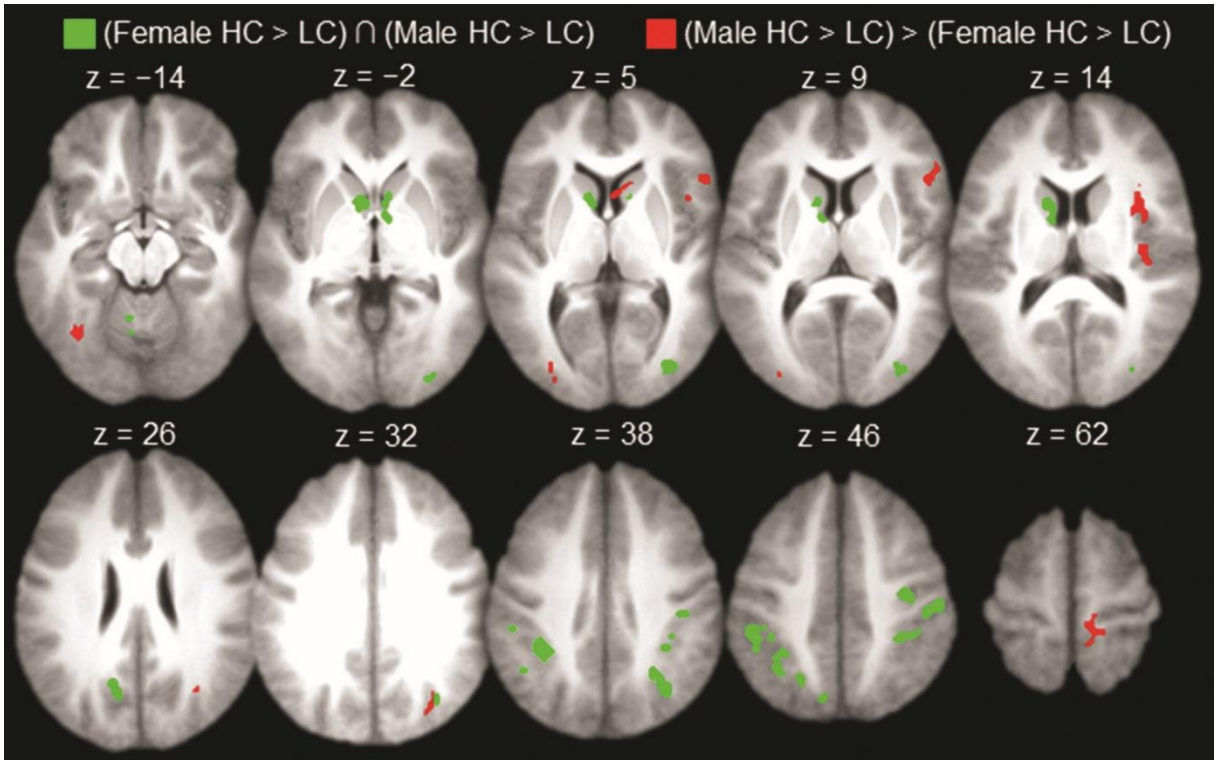


Figure 2. Common (green) and differential (red) activity between females and males for the contrast of HC-hits and LC-hits (axial slices with z-coordinates, key at the top).

Sex differences in the brain during high- versus low-confidence accurate spatial memories were isolated using the contrast of (female HC-hits versus LC-hits) and (male HC-hits versus LC-hits). The female versus male HC-hits versus LC-hits contrast produced no significant activations. However, the male versus female HC-hits versus LC-hits contrast produced activity in the right lateral PFC (right inferior frontal gyrus), right sensorimotor cortex (right central sulcus, right postcentral gyrus, and right postcentral sulcus), right parietal cortex (right intraparietal sulcus), left visual processing regions (left fusiform gyrus and left middle occipital gyrus), right insula, and right caudate (Figure 2, red and Table 2, bottom).

It is notable that the contrast of female HC-hits versus LC-hits produced activity in bilateral hippocampus (Figure 3), a region that has been associated with spatial memory (activation 1, x = 30, y = −10, z = −19; activation 2, x = −30, y = −10, z = −20; activation 3, x

= −30, y = −31, z = −8; activation 4, x = −21, y = −36, z = 0; activation 5, x = 28, y = −36, z = 0). However, the contrast of male HC-hits and LC-hits did not produce significant activity in the hippocampus and the female versus male HC-hits versus LC-hits comparison did not produce significant activity in this region.

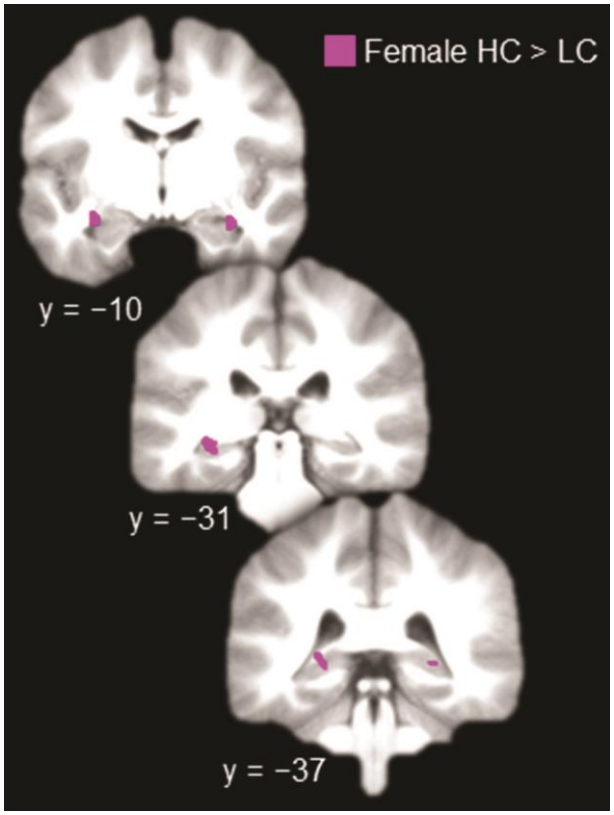


Figure 3. Hippocampal activity produced by the contrast of female HC-hits and LC-hits (coronal slices with y coordinates, key at the top right).

For the ROI analysis, the contrast of hits versus misses (collapsed over confidence) produced one significant activation in the right lateral PFC ($x = 53$, $y = 9$, $z = 31$, k = 33; inferior frontal sulcus/gyrus, BA 6/9/44). In this ROI (Figure 4, left), the correlation between the magnitude HC-hit beta-weight activity and the percentage of HC-hit responses and was positive for males ($r = 0.30$, $p > .20$) and negative for females ($r = −0.65$, $p < .005$) and, critically, the difference between these correlations was statistically significant ($p < .005$; Figure 4, right). In

visual processing regions and the hippocampus, a stricter individual voxel threshold ($p < .001$, uncorrected) was employed to ensure each activation was restricted to one region. The hits versus misses contrast produced many significant activations in visual processing regions, the most significant of which was located in V1 ($x = 12$, $y = -90$, $z = 4$, k = 23). This contrast produced only one activation in the hippocampus ($x = -24$, $y = -36$, $z = -4$, k = 7). Unlike the lateral PFC ROI results, there were no significant sex differences in either of these ROIs (both p-values > .20).

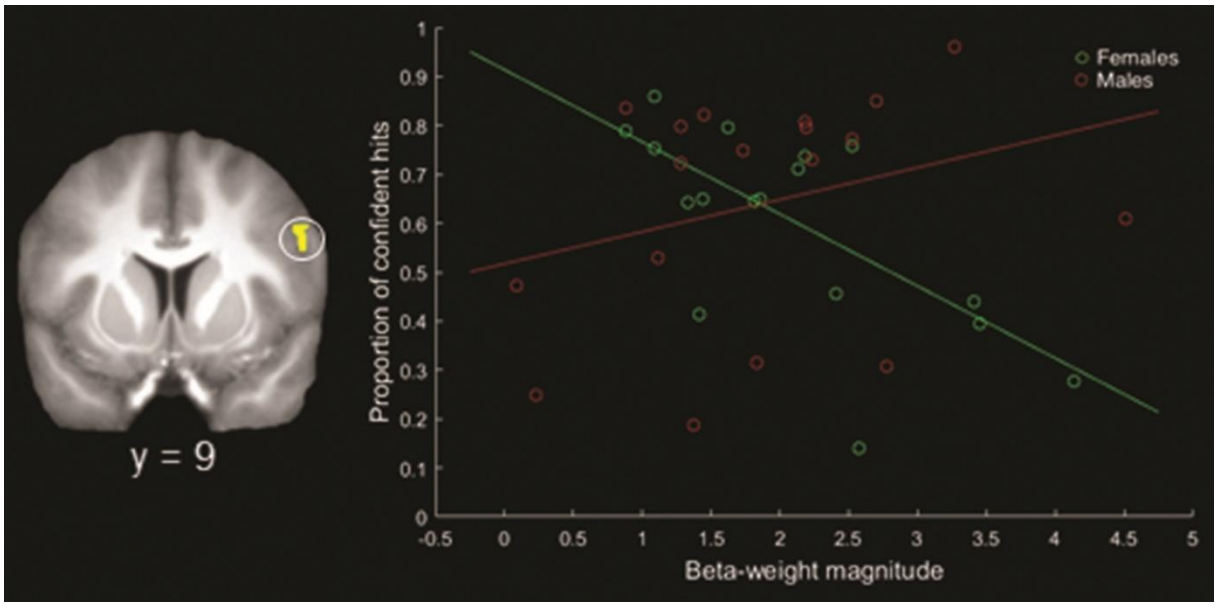


Figure 4. Left, right lateral PFC ROI identified by contrasting hits versus misses (in yellow). Right, correlation between the HC-hit beta-weight values and the proportion of confident hits for females (in green) and males (in red; key to upper right).

## Discussion

There were many areas commonly activated for females and males during successful retrieval of high- versus low-confidence memories including parietal and visual regions, which have been associated with long-term memory retrieval (Slotnick, 2017b). These findings suggest either that high confidence responses amplified the same regions associated with long-term

memory retrieval or that greater activity in regions associated with long-term memory retrieval produced higher confidence ratings (both possibilities are viable given that the present study was not designed to assess causality).

The comparison of female versus male HC-hits versus LC-hits produced no significant activity. That is, there were no brain regions recruited to a greater extent in females compared to males for high- versus low-confidence memories. The comparison of male versus female HC-hits versus LC-hits, however, produced greater activity in the lateral PFC, sensorimotor cortex, parietal cortex, and visual processing regions. The independent ROI analysis produced complementary results in the lateral PFC. As activity in the lateral PFC has been reported in instances of both accurate and inaccurate high-confidence memory, the lateral PFC has been postulated to be involved in the subjective feeling of confidence rather than accuracy (Bona & Silvanto, 2014; Chua et al., 2004). To determine if this was also true of the right lateral PFC activity in the current investigation, we collapsed across accuracy and contrasted male versus female HC-(hits and misses) versus LC-(hits and misses). Males produced significantly greater activity in the right lateral PFC, even after collapsing over accuracy (activation coordinate, x = 50, y = 20, z = 8; BA = 44). These results support the hypothesis that the lateral PFC is involved in the subjective feeling of confidence.

The lateral PFC has also been associated with post-retrieval monitoring during long-term memory (Slotnick, 2017b). Thus, it might also be possible that activity in the lateral PFC during high-confidence memories is related to memory monitoring processes rather than subjective confidence. The post-retrieval monitoring hypothesis would predict longer reaction times for males compared to females. Although there were no significant differences in reaction time between female or male participants during HC-hits (female reaction time = 1851.3 ± 93 ms; male reaction time = 1761.6 ± 41 ms, $t(34) < 1$) or LC-hits (female reaction time = 2365.1 ± 82 ms; male reaction time = 2207.5 ± 84, $t(34) < 1$), the reaction times for males were numerically faster than females in both conditions. These reaction time results are in direct opposition to the post-retrieval

monitoring hypothesis and support the hypothesis that the lateral PFC is associated with higher subjective confidence in males than females.

Males also showed greater activity in visual processing regions including the middle occipital gyrus and fusiform gyrus. Greater activity in visual processing regions has previously been associated with successful retrieval of high-confidence memories (Chua et al., 2004; Hayes et al., 2011; Kuchinke et al., 2013; Moritz et al., 2006). Moreover, behavioral evidence suggests that the subjective experience of memory (including one's confidence in a memory) is related to the vividness of memory contents (Robinson et al., 2000). This behavioral result suggests that greater activity in visual processing regions for high-confidence versus low-confidence memories in the current study reflects more vivid visualization in males.

Males also produced greater activity than females in the intraparietal sulcus. Greater activity in the parietal cortex has previously been associated with high-confidence long-term memory (Hayes et al., 2011; Kuchinke et al., 2013; Moritz et al., 2006). As the parietal cortex has previously been associated with the recollection of vivid and specific memory details (i.e., "remembering"; Wheeler & Buckner, 2004), it may be that greater recruitment of the parietal cortex during high-confidence memories in males also supports more vivid memories.

Faster reaction times for males than females have been reported across different age groups and tasks (cf., Dykiert et al., 2012). A recent event-related potential study suggests that this differential reaction time may be due to processing differences between females and males, where females engage in more proactive and cautious processing and males engage in more reactive and fast processing (Bionco et al., 2020). Pre- and post-stimulus responses were compared between females and males across prefrontal and occipital electrodes. Pre-stimulus, males produced smaller prefrontal and visual components, suggesting less preparation/attentional allocation. This, along with a decrease in reaction time and accuracy, suggests that processing in males is faster and more reactive than females. These results align with the findings in the current study in terms of increased activity in motor processing regions for males during high-confidence memories. It may be that

males recruit motor processing regions to a greater extent during high-confidence memories to support their fast and reactive processing style.

Although the sex difference was not significant, the contrast of female HC-hits versus LC-hits produced bilateral hippocampal activity. Notably, in a previous study, we found that successful spatial memory retrieval (i.e., spatial memory hits versus misses) did not produce activity in the hippocampus for females (Spets et al., 2019). Moreover, in that study, males produced significantly greater activity than females in this region. In light of these two findings, it might be that hippocampal activity in females is specific to high-confidence accurate memories. These results argue against the hypothesis that the hippocampus is only associated with the objective binding of context and item information rather than subjective remembering (Slotnick, 2010). If the hippocampus is only associated with subjective experience/high confidence in females, it may be that the phenomenon is unobservable when participants are collapsed across sex.

The present results suggest that, although similarities exist in the parietal cortex and visual processing regions, the neural mechanisms underlying high-confidence memory retrieval differs between females and males. Greater right lateral PFC activity for males suggests a greater sense of subjective confidence, compared to females. Faster reaction times in males compared to females suggests that this right lateral PFC activity supports a subjective sense of high confidence rather than post-retrieval monitoring processes. Moreover, greater activity in sensorimotor cortex supports males' faster and more reactive processing style. Greater activity in visual processing and parietal cortex suggests more vivid retrieval of high-confidence memories. More broadly, the present functional sex differences and previous functional sex differences argue against the practice of collapsing across sex in cognitive neuroscience studies.

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# Tables

Table 1. Behavioral results

| | Percent HC responses | | | Reaction time (ms) | | |
|---|---|---|---|---|---|---|
| | Female | Male | *p* | Female | Male | *p* |
| HC-hits | 60.63 | 63.99 | 0.325 | 1851 | 1762 | 0.192 |
| LC-hits | 39.37 | 36.01 | 0.325 | 2365 | 2208 | 0.119 |
| HC-misses | 35.02 | 41.92 | 0.155 | 2171 | 2124 | 0.355 |
| LC-misses | 64.98 | 58.08 | 0.155 | 2312 | 2351 | 0.615 |

HC = high confidence, LC = low confidence. Percent HC responses = number of high-confidence ("sure") responses/total ("unsure" + "sure") responses. P-values (*p*) compare behavioral performance between the sexes.

Table 2. Conjunction and contrasts of male and female high-confidence hits (HC) versus low-confidence hits (LC)

| Region | BA | x | y | z | *k* |
|---|---|---|---|---|---|
| *Female (HC > LC) ∩ Male (HC > LC)* | | | | | |
| Right Precentral Gyrus/Central Sulcus | 3/4 | 39 | −17 | 50 | 74 |
| Right Post Central Sulcus | 2 | 50 | −23 | 44 | 64 |
| Left Intraparietal Sulcus | 7/40 | −45 | −36 | 44 | 135 |
| Right Intraparietal Sulcus | 7 | 37 | −36 | 42 | 51 |
| Left Intraparietal Sulcus | 7 | −34 | −59 | 51 | 42 |
| Left Intraparietal Sulcus | 7 | −15 | −64 | 51 | 24 |
| Right Intraparietal Sulcus | 7 | 33 | −64 | 38 | 48 |
| Left Precuneus | 7 | −12 | −72 | 43 | 25 |
| Left Parieto-occipital Sulcus | 31 | −11 | −65 | 26 | 25 |
| Right Middle Occipital Gyrus | 19 | 33 | −81 | 6 | 50 |
| Left Caudate | – | −7 | 6 | 0 | 121 |
| Right Caudate/Thalamus | – | 7 | 6 | 0 | 26 |
| Left Cerebellum | – | −7 | −53 | −17 | 25 |
| Left Cerebellum | – | −1 | −65 | −17 | 27 |
| | | | | | |
| *Female (HC > LC) > Male (HC > LC)* | | | | | |
| No activations | | | | | |
| | | | | | |
| *Male (HC > LC) > Female (HC > LC)* | | | | | |
| Right Inferior Frontal Gyrus | 44/45 | 50 | 21 | 8 | 96 |
| Right Central Sulcus/Postcentral Gyrus/Postcentral Sulcus | 1/2/3/5 | 12 | −36 | 62 | 58 |
| Right Intraparietal Sulcus | 19/39 | 32 | −67 | 31 | 25 |
| Left Fusiform Gyrus | 37 | −34 | −62 | −14 | 26 |
| Left Middle Occipital Gyrus | 19 | −31 | −85 | 7 | 24 |
| Right Insula | – | 36 | 6 | 14 | 95 |
| Right Insula | – | 40 | −21 | 16 | 53 |
| Right Caudate | – | 4 | 12 | 4 | 31 |

BA refers to Brodmann area, k refers to the cluster size, and MNI coordinate (x, y, z) refers to the center of each activation.

## CHAPTER 4

False memories activate distinct brain regions in females and males.
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Under review

The constructive process of memory is generally successful; however, it can also lead to memory failures such as false memories. Although true memories and false memories rely on some of the same brain regions, these memory types are also mediated by distinct neural substrates. Of relevance, there is a growing body of evidence that there are sex differences in the brain during true memories. However, no studies have investigated whether there are neural sex differences during false memories. In the current fMRI study, across all subjects, false memories produced activity in the precentral sulcus and superior parietal lobule, replicating previous findings. Males produced greater activity than females in the precuneus, posterior cingulate cortex, parietooccipital sulcus, and fusiform gyrus. Females produced greater activity than males in the medial prefrontal cortex, anterior cingulate cortex, paracentral lobule, supramarginal gyrus, lateral sulcus, cingulate sulcus, the putamen, and V1. An interaction analysis revealed a significant interaction between sex and region with a higher magnitude of activity in the hippocampus for males than females and a higher magnitude of activity in V1 for females than males. The current results suggest that false memories are supported by distinct brain regions and cognitive processes in females and males.

Long-term memory is a constructive process in which individual details of a memory are discretely encoded and recombined at retrieval (Schacter, 2012a). While this type of memory system is generally successful, it can also lead to memory failures through the erroneous combination of previously encoded details (Schacter, 2012b). As the formation of true and false memories rely on the same constructive process as true memories, it is not surprising that true and false memories rely on some of the same brain regions including the prefrontal cortex, parietal cortex, late visual processing regions, and the hippocampus (Cabeza et al., 2001; Okado & Stark, 2003; Slotnick & Schacter, 2004a; Kim & Cabeza, 2007; Dennis et al., 2012; Gutchess & Schacter, 2012; Slotnick, 2017a; Karanian et al., 2020; for a review, see Schacter & Slotnick, 2004b).

However, the brain regions mediating true and false memories are not completely overlapping. False memories, for example, have been shown to produce greater activity in subregions of the prefrontal cortex including the lateral and anterior prefrontal cortex (e.g., Schacter & Slotnick, 2004a, 2004b, 2007), language processing cortex (e.g., Garoff-Eaton et al., 2006; Karanian & Slotnick, 2014), inferior parietal cortex (e.g., Kim & Cabeza, 2007; Dennis et al., 2014), and anterior cingulate cortex (e.g., Slotnick & Schacter, 2004a; Dennis et al., 2014; for a meta-analysis, see Kurkela & Dennis, 2016). True memories have also been shown to produce activity in early visual processing regions (i.e., Brodmann area (BA)17 and BA18), whereas both true and false memories produce activity in later visual processing regions (i.e., BA19 and BA37; Slotnick & Schacter, 2004a; Kim & Cabeza, 2007; Dennis et al., 2012; Karanian & Slotnick, 2014). Some studies, however, have since identified activity in BA17 (c.f. Karanian & Slotnick, 2018) and BA18 (Kurkela & Dennis, 2016) during false memories. Thus, the involvement of early visual regions, specifically V1 (BA17), in false memory formation may depend on certain features of the task or the type of stimuli employed.

Mounting evidence suggests that sex differences exist in the brain during long-term memory (for a review, see Spets & Slotnick, 2020). In a previous spatial long-term memory

functional magnetic resonance imaging (fMRI) study, we found that males had greater activity in visual processing regions and hippocampus than females, while females had greater activity in language processing cortex than males (Spets et al., 2019). Greater activity for males in the hippocampus has been identified across a variety of long-term memory tasks including spatial long-term memory, autobiographical memory, and virtual maze navigation (St. Jacques et al., 2011; Young et al., 2013; Spets et al., 2019). In a recent fMRI meta-analysis investigating sex differences in the brain during long-term memory, we identified greater activity for males than females in the prefrontal cortex, early/late visual processing regions, and parahippocampal cortex (Spets & Slotnick, 2020). Accordingly, we hypothesized that sex differences may also exist for false memories given that the above-mentioned regions, which display sex differences during true memories, have also been associated with false memories.

In the current investigation, abstract shapes were presented to the left and right of fixation during the study phase. During the test phase, shapes were presented at fixation and participants made an "old-left" or "old-right" judgment followed by a confidence ("unsure" or "sure") judgment. False memory was isolated using two contrasts: false memories versus misses (masked exclusively by the contrast of high confidence versus low confidence true memories, to eliminate regions generally associated with high- versus low-confidence) and false memories versus true memories. Based on previous findings in sex differences studies of true memories, we predicted that males would produce greater activity in late visual processing regions as well as the hippocampus (St. Jacques et al., 2011; Young et al., 2013; Spets et al., 2019, Spets & Slotnick, 2020), whereas females would produce greater activity in language processing cortex (Cahill, 2006; Spets et al., 2019; Spets & Slotnick, 2019). Based on the results of Karanian and Slotnick (2018), we were also interested in whether false memories would produce activity in the earliest of visual processing regions (i.e., V1; BA17), and whether activity in V1 may be sex-specific.

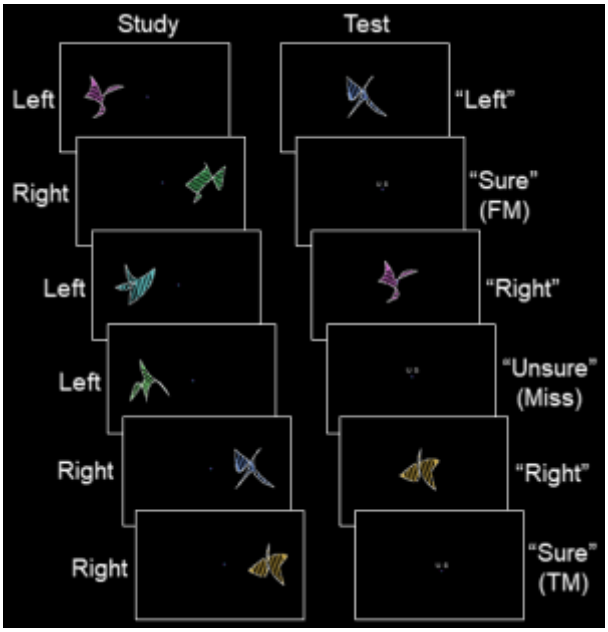


Figure 1. Stimulus and response protocol. During the study phase, abstract shapes were presented to the left or right of fixation. During the test phase, old shapes were presented at fixation followed by a confidence reminder screen. Participants indicated whether each shape was previously on the "left" or "right" followed by an "unsure"–"sure" confidence rating.

## Methods

The current study reanalyzed data from two spatial long-term memories studies (Jeye et al., 2018; Slotnick & Schacter, 2004a). Each study was comprised of two experiments. The experiments in Slotnick and Schacter (2004a) will be referred to as Experiments 1 and 2 and the experiments in Jeye et al. (2018) will be referred to as Experiments 3 and 4. Essential methodological details are provided here (for full methodological details see Spets et al., 2019).

### *Participants*

Across the four experiments, there were 40 female and 18 male participants. The false memory rate was computed for each participant (this calculation is delineated below in Methods section 2.2). Across the four experiments, there were one female and two male participants that had no false memories and thus were excluded from the analysis, leaving 39 female participants and 16 male participants. Sixteen female participants were selected to best match the false

memory rate, variance, and number of false memory event types of the male participants. The matching procedure was repeated for each experiment such that within each experiment, each male participant was matched with a female participant whose false memory rate and number of false memory event types most closely matched that of the male participant (i.e., a matched-pair procedure was employed). In the first experiment, four females were selected from seven to match the four males. In the second experiment, five females were selected from seven to match the five males. In the third experiment, four females were selected from 12 to match the four males. In the fourth experiment, three females were selected from 13 to match the three males. For each experiment, following selection of the females, we ran independent sample t-tests to determine whether there were any significant differences in the false memory rate or number of false memory event types between the groups. Using an iterative procedure, we selected alternative female participants and ran subsequent t-tests until the combination of female and male participants were best matched on both the rate and number of false memories. Independent samples t-test were then run to compare the sixteen matched female and male participants to ensure the groups did not statistically differ in the to-be-equated behavioral measures.

*Stimulus protocol and task*

All participants completed a behavioral training session prior to the scanning session. During the scanning session, participants completed a single anatomic scan and a variable number of study-test runs (six runs in Experiment 1, three runs in Experiment 2, and seven to eight runs in Experiments 3 and 4). During the study phase of each experiment, abstract shapes were presented to the left or right of fixation for 2.5 s in pseudorandomized order such that no more than three shapes were sequentially presented to the same side (shape construction details can be found in Slotnick & Schacter, 2004a). Participants were instructed to remember each shape and its spatial location while maintaining fixation. During the test phase, shapes were presented at fixation for 2.5–3.0 s (a constant duration for each experiment) and participants made an old-“left” or old-

"right" judgment followed by a confidence reminder screen for 1.4–2.5 s (a constant duration for each experiment) at which point participants made a confidence judgment with their left hand. In Experiments 1 and 2, the confidence judgment consisted of either a "unsure" or "sure" response. In Experiments 3 and 4, the confidence judgment consisted of either an "unsure", "sure", or "very sure" response. Confidence judgments of "sure" and "very sure" were collapsed for Experiments 3 and 4 and will hereafter be considered together as "sure" judgments. False memory rate was calculated as the percentage of incorrect spatial location identification assigned a high confidence ("sure") response across all incorrect spatial location identifications. True memory rate was calculated as the percentage of correct spatial location identification, regardless of confidence, across all spatial location identifications. A Latin Square design was used to counterbalance shape sets across participants.

*Image acquisition and analysis*

In Experiments 1 and 2, images were acquired using a 3-Tesla Siemens Allegra MRI scanner (Siemens, Erlagen, Germany) with a standard head coil. Anatomic data were acquired using a multiplanar rapidly acquired gradient echo (MPRAGE) sequence (TR = 30 m, TE = 3.3 m, 128 slices, 1 x 1 x 1.33 mm resolution). Functional data were acquired using a T2*-weighted EPI sequence (TR = 2000 m, TE = 3.3 m, 64 x 64 acquisition matrix, 26-30 slices in Experiment 1 and 30 slices in Experiment 2, 4.5 mm isotropic resolution). In Experiments 3 and 4, image acquisition parameters were identical to Experiments 1 and 2 except that a 3-Tesla Trio Scanner (Siemens, Erlagen Germany) was used with a 32-channel head coil and that 33 slices and a 4mm isotropic resolution was used to acquire the functional data.

A random effect-general linear model (GLM) analysis was conducted in SPM12 (Wellcome Trust Centre for Neuroimaging, London, UK; https://www.fil.ion.ucl.ac.uk/spm/software/spm12/). Functional image pre-processing included slice-time correction, motion correction to the first volume of each run, and spatial normalization

to the Montreal Neurological (MNI) template, which included resampling at 2 $mm^3$. Anatomic images were normalized to MNI space with 1 $mm^3$ resolution and then averaged across participants. The following event types were entered into the general linear model: encoding of items in the left visual field, encoding of items in the right visual field, and inaccurate or accurate spatial memory in the left or right visual field with low or high confidence. False memories were defined as high-confidence incorrect spatial location identification (e.g., "sure–right" responses to an items previously presented on the left), misses were defined as low-confidence incorrect spatial location identification (e.g., "unsure–right" responses to an items previously presented on the left), and true memories were defined as high-confidence correct spatial location identification (e.g., "sure-left" responses to items previously presented on the left).

For each participant, activity associated with false memories was isolated using two weighted contrasts: false memories versus misses masked exclusively by the contrast of high confidence versus low confidence true memories (to eliminate regions generally associated with high- versus low-confidence) and false memories versus true memories (these two contrasts were utilized as both have previously been shown to successfully capture false memory activity; e.g. Karanian & Slotnick, 2014, 2018). Second level models were created for both of these contrasts for all participants, female participants, and male participants. For all contrasts of false memories versus misses (i.e., group, female, male, and between-sex direct comparisons), an exclusive mask of the corresponding high confidence true memory contrast (i.e., sure-old-left-hits and sure-old-right-hits versus sure-old-left-misses and sure-old-right-misses) was employed to ensure that any activations resulting from the contrast of false memories versus misses were not confounded by confidence. Direct comparisons between females and males were conducted using independent sample t-tests while computing the second level models of the aforementioned contrasts as well as the direct comparison of female false memories versus male false memories (and vice-versa).

All contrasts were thresholded at $p < .01$, cluster extent corrected to $p < .05$. To compute the cluster extent threshold, we first computed the spatial autocorrelation for the contrast of

female false memories versus male false memories which produced a spatial autocorrelation value of 3 mm. Ten thousand Monte Carlo simulations were conducted based on the acquisition volume parameters, computed spatial autocorrelation, as well as the desired individual voxel and familywise p-value for each experiment (Slotnick, 2017). We then selected the lowest cluster extent threshold across all experiments. This resulted in a cluster extent threshold of 24 voxels, which was applied to all contrasts. Images were imported into MRIcroGL (www.nitrc.org) and overlaid on an anatomic average for viewing purposes.

A region-of-interest (ROI) analysis was conducted by extracting beta-weights for each participant using custom scripts in MATLAB (MathWorks, Natick, MA). For each participant, the average beta-weight was recorded for false memory event types in two ROIs: the hippocampus and V1 (see Results). One-tailed independent sample t-tests were conducted to determine if the magnitude of activity in the ROIs was significantly higher for males or females. A 2 x 2 (sex x ROI) ANOVA was conducted to determine if there was a significant sex x region interaction.

## Results

An analysis on all participants (40 females, 18 males) found no significant difference in the false memory rate between females (0.33 ± 0.027, mean ± 1 SE) and males (0.41 ± 0.055, weighted $F(1, 56) = 1.94$, $p = 0.17$). There was also no significant difference in the number of false memory events between females (17.70 ± 2.56) and males (17.28 ± 3.04, weighted $F(1,56) < 1$). Moreover, there was no significant difference in true memory rate between all females (74.95 ± 1.50) and males (73.81 ± 1.30, weighted $F(1, 56) < 1$).

As expected, due to the female–male matching procedure described in section 2.1, there was no significant difference in the false memory rate between the sixteen matched females (39.25 ± 3.64) and sixteen matched males (45.79 ± 4.78, $t(30) = 1.09$, $p = 0.28$). There were also no significant difference in the number of false memory events between females (18.23 ± 3.12)

and males (19.44 ± 3.00, $t(30) < 1$). Moreover, there was no significant difference in true memory rate for the matched females (70.02 ± 2.27) and males (74.55 ± 1.28, $t(30) = 1.74$, $p = 0.092$).

The group comparison of false memories versus misses produced two activations, one in the prefrontal cortex (left precentral sulcus) and one in the parietal cortex (right superior parietal lobule) (Table 1 and Fig. 2). There were no significant activations produced by the comparison of false memories versus true memories (Table 1).

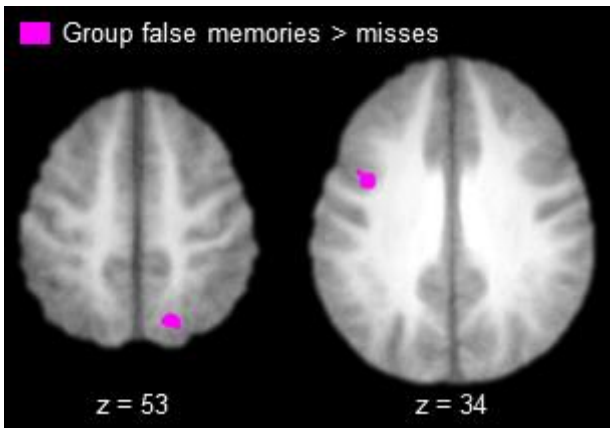


Figure 2. Activity associated with the group contrast of false memories versus misses (axial slices with z-coordinates, key at top).

The comparison of false memories versus misses in males produced activations in the parietal cortex (left intraparietal sulcus) and visual processing regions (bilateral parietooccipital sulcus and left fusiform gyrus) (Table 2 and Fig. 3). There were no significant activations produced by the comparisons of false memories versus true memories in males, false memories versus misses in females, or false memories versus true memories in females (Table 2).


Figure 3. Activity associated with the male contrast of false memories versus misses (axial slices with z-coordinates, key at top).

The comparison of (male false memories versus misses) versus (female false memories versus misses) produced activations in the parietal cortex (bilateral precuneus), cingulate cortex (bilateral posterior cingulate cortex), and visual processing regions (bilateral parieto-occipital cortex and left fusiform cortex) (Table 3 and Fig. 4, cyan). There were no significant activations produced in the comparisons of (male false memories versus misses) versus (female false memories versus misses), male false memories versus female false memories, or (female false memories versus misses) versus (male false memories versus misses) (Table 3). There were, however, many significant activations produced by the comparison of (female false memories versus true memories) versus (male false memories versus true memories), including in the prefrontal cortex (bilateral medial prefrontal cortex), motor cortex (bilateral paracentral lobule), cingulate cortex (bilateral anterior cingulate cortex and cingulate sulcus), and the right putamen (Table 3 and Fig. 4, yellow). The comparison of female false memories versus male false memories produced activations in the parietal cortex (left supramarginal gyrus), bilateral lateral sulcus, and primary visual cortex (left calcarine sulcus/V1) (Table 3 and Fig. 4, red).

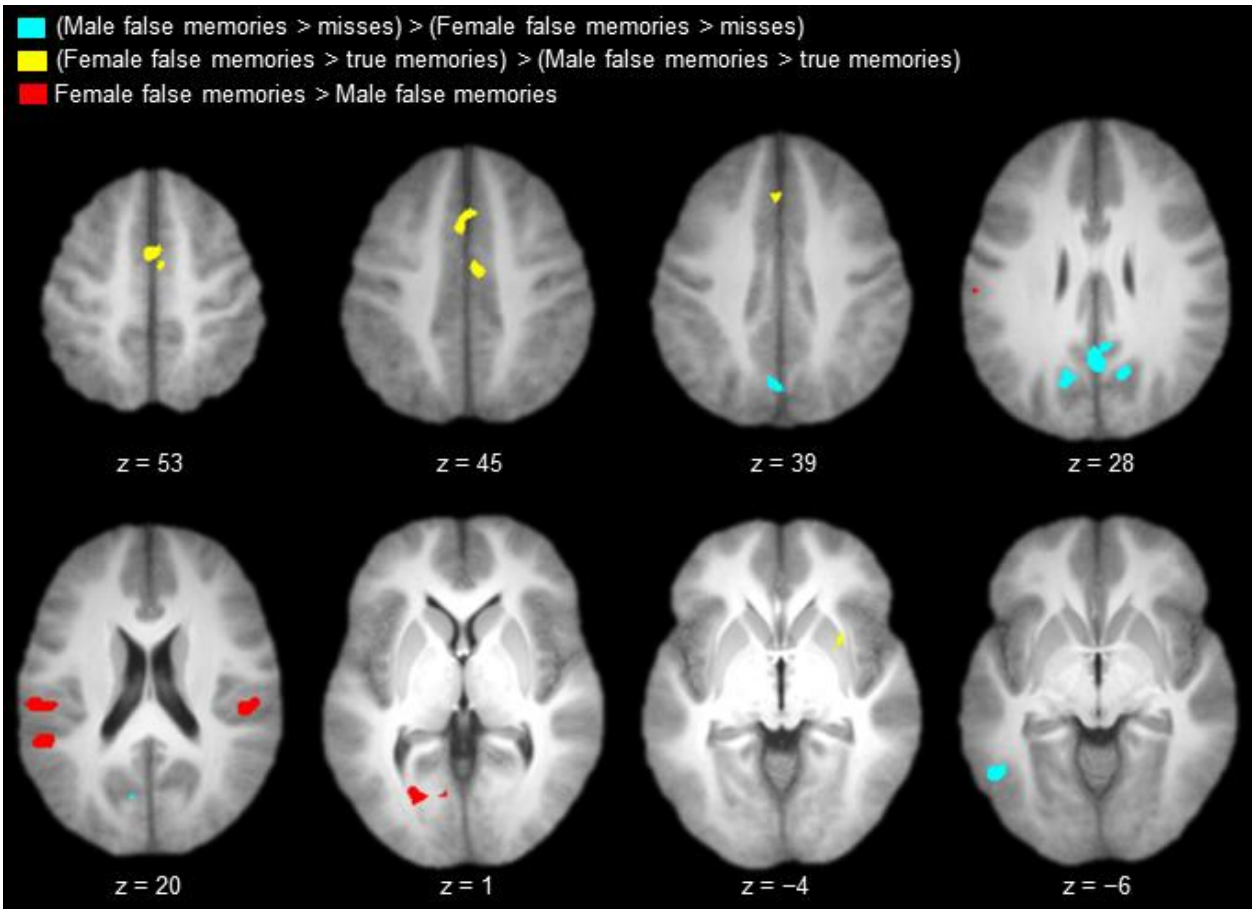


Figure 4. Differential activity for females and males for the contrasts of false memories versus misses (male versus female in cyan), false memories versus true memories (female versus male in yellow), and false memories alone (female versus male in red; axial slices with z-coordinates, key at top).

To test our a priori hypothesis that hippocampal activity would be greater for males than females during false memories, we removed the cluster extent threshold from the group contrast of false memories versus misses. This revealed one hippocampal activation (x = −32, y = 36, z = −4, k = 6) that was used as an ROI for the subsequent beta-weight analysis (Fig. 5a). There was a marginally significant difference in the hypothesized direction between the mean false memory beta-weight in this ROI for males (0.306 ± 0.16) and females (−0.086 ± 0.19; one-tailed $t(30)$ = 1.56, $p$ = .065). We ran the same beta-weight analysis on the single V1 activation (x = −22, y = −68, z = 1) produced by the comparison of female false memories versus male false memories (Table 3). There was a marginally significant difference between the mean false memory beta-

weight in V1 for females (0.92 ± 0.19) and males (0.07 ± 0.38; $t(30) = 2.00$, $p = .055$). Of importance, there was a significant interaction between sex (male, female) and ROI (hippocampus, V1) ($F(1, 60) = 6.31$ , $p = .015$), with males exhibiting higher magnitudes of activity in the hippocampus and females exhibiting higher magnitudes of activity in V1.

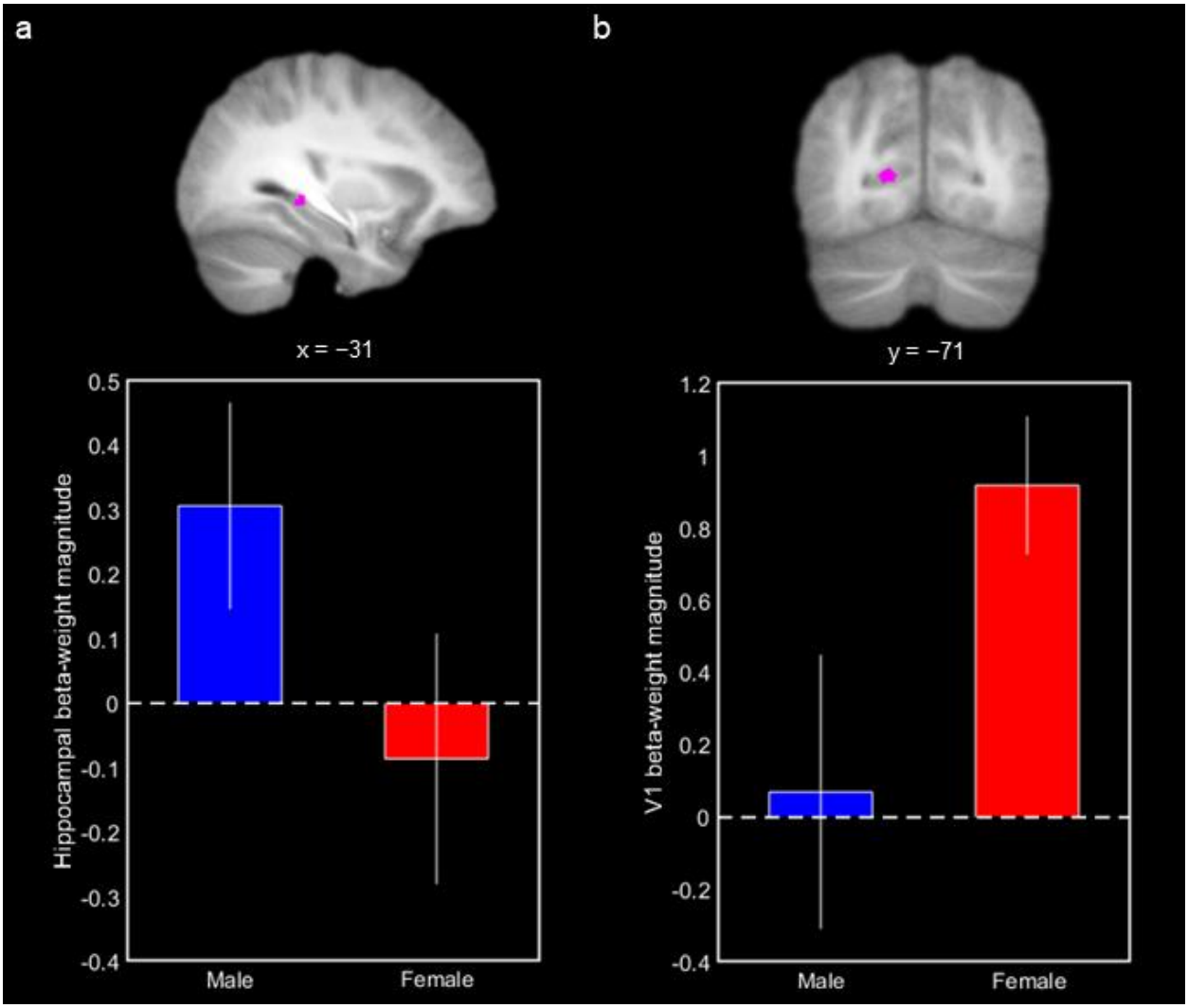


Figure 5. a) Top, hippocampal ROI identified by the group contrast of false memories versus misses (sagittal slice with x-coordinate). Bottom, mean beta-weight magnitude extracted from the hippocampal ROI for males and females. b) Top, calcarine sulcus ROI identified by the female versus male contrast of false memories (coronal slice with y-coordinate). Bottom, mean beta-weight magnitude extracted from the calcarine sulcus ROI for males and females.

## Discussion

*General false memory regions*

The current study replicates and extends previous findings on the neural correlates of false memories. The group false memory analysis produced significant activity in the prefrontal cortex and superior parietal lobule, two regions previously implicated in false memory. Increased activity in the prefrontal cortex is highly consistent with previous findings linking the prefrontal cortex to the retrieval of both true and false memories (Okado & Stark, 2003; Slotnick & Schacter, 2004a; Dennis et al., 2012). Although the prefrontal cortex is often associated with the successful selection of memory details (c.f., Rugg et al., 1999), it is more likely that activity in the prefrontal cortex during false memories reflects the evaluation of the retrieved memory (i.e., retrieval monitoring; Johnson et al., 1997; Rugg et al., 1999; Kurkela & Dennis, 2016). Activity in the superior parietal lobule has also been previously reported in studies of false memories. In a functional connectivity analysis using the anterior parahippocampal gyrus as a seed, Dennis et al. (2012) identified two distinct networks: one that supported true memory retrieval and another that supported false memory retrieval. The true memory network consisted of inferior regions including the hippocampus, anterior parahippocampal gyrus, anterior cingulate cortex, orbitofrontal cortex, and occipital cortex whereas the false memory network consisted of more superior regions including pre- and post-central gyrus, superior prefrontal cortex, posterior cingulate cortex, and superior parietal lobule. It is notable that in the current analysis, both regions associated with the group false memory analysis are regions associated with the superior false memory network.

*Male false memory regions*

Of primary interest, the current results identified a number of regions that were differentially activated in males and females during false memories . Males, for example,

displayed more activity in the precuneus, posterior cingulate cortex, and parietooccipital sulcus than females. Notably, the precuneus and the posterior cingulate cortex are associated with the superior false memory network (Dennis et al., 2012). Researchers have posited that such parietal activity may represent a sense of familiarity (e.g., Yonelinas et al., 2005), which contributes to the false memory, and others suggest that such activity may be more generally associated with memory reconstruction (Dennis et al., 2012).

The analysis also revealed that males displayed greater activity in BA18, an earlier visual processing region and the fusiform gyrus (BA37), a later visual processing region. BA18 has been identified in a number of false memory studies (for a meta-analysis, see Kurkela & Dennis, 2016). It has been proposed that the recruitment of BA18 during false memories may be specific to paradigms in which visual stimuli have high levels of perceptual similarity, and such similarity may result in sensory reactivation of the incorrect memory trace at retrieval thereby producing a false memory (Kurkela & Dennis, 2016). Previous studies employing paradigms that evoke visual false memories have similarly found that false memory retrieval was associated with activity in later visual processing regions (Slotnick & Schacter, 2004a; Kim & Cabeza, 2007; Dennis et al., 2012; Karanian & Slotnick, 2014; for a meta-analysis, see Kurkela & Dennis, 2016). Researchers have posited that the use of these later visual regions supports visual elaboration of the false memory. Thus, greater use of late visual processing regions by males suggests greater elaboration of the visual details of the false memory compared to females. Greater use of both early (BA18) and late visual processing regions (BA19/37) for males has similarly been reported in studies of true memories across a variety of long-term memory types (e.g., autobiographical, spatial, item, and facial memory; c.f., Spets & Slotnick, 2020). Together, these results suggest that visual elaboration is greater for males compared to females regardless of memory validity (i.e., during both true and false memories).

*Female false memory regions*

Our analyses also revealed regions that were preferentially active in females during false memories. Interestingly, females produced greater activity in the calcarine sulcus (BA17/V1), as compared to males. Many prior studies have suggested that V1, the earliest cortical visual processing region, is associated with the retrieval of true memories (Slotnick & Schacter, 2004a; Kim & Cabeza, 2007; Dennis et al., 2012; Karanian & Slotnick, 2014). More recent evidence, however, suggests that V1 may play a critical role in false memories for spatial location (Karanian & Slotnick, 2018). In an fMRI experiment, V1 activity displayed a retinotopic pattern such that false memories for the left spatial location were preferentially associated with activity in right V1 and false memories for the right spatial location were preferentially associated with activity in left V1. Interestingly, 75% of the participants in that experiment were female; thus, it is possible that the response in V1 was, in part, driven by the disproportionate number of female participants. However, in a follow-up transcranial magnetic stimulation (TMS) experiment, Karanian and Slotnick (2018) employed pre-retrieval inhibitory stimulation to V1 and found a reduction in the rate of false memories, relative to stimulation of the vertex (which could be interpreted as counter to the above proposal, as the number of female participants in this follow-up experiment was less disproportionate, i.e., 60%, than the fMRI experiment). These previous and the present results suggest that V1 can play an important role during the construction of false memories. Whether false memory activity in V1 is dependent on task conditions (c.f., Karanian & Slotnick, 2018) or the type of participants (i.e., female versus male) is a topic of future research. Although V1 has previously been associated with unconscious processing (c.f. Slotnick & Schacter, 2006), these results add to a growing body of literature suggesting that V1 can play a role in conscious processing (Thakral et al., 2013; Karanian & Slotnick, 2018).

Females also displayed greater activity in the medial prefrontal cortex (mPFC) and the anterior cingulate cortex. Notably, both of these regions have been commonly associated with false memory (for a meta-analysis, see Kurkela & Dennis, 2016), and it is thought that such medial frontal activity in these regions reflects monitoring and evaluation (e.g., Slotnick &

Schacter, 2004a; Dennis et al., 2014). Interestingly, it has been posited that a lack of strong sensory signal in visual regions may result in increased mPFC activity (for a discussion, see Dennis et al., 2014). Considering the present pattern of activity, it is possible that the very early visual activity observed in BA17/V1 in females does not provide a strong, conscious sensory signal in the way that more conscious later visual regions can (e.g., BA37; Crick & Koch, 1995; Tong, 2003). Accordingly, the increase observed in mPFC in females relative to males may stem from the fact that females display a relatively less conscious sensory signal in V1 as compared to males who display greater activity in more conscious (later) visual processing regions. Thus, it is possible that such sex-specific visual processing differences yield differential involvement of midline frontal regions during false memories. This is an avenue for future research.

Lastly, in the direct comparisons, females activated language processes regions (i.e., left supramarginal gyrus and bilateral lateral sulcus) to a greater extent than males. Language processing regions have previously been associated to a greater extent with false memories, as compared to true memories (Garoff-Eaton et al., 2006; Karanian & Slotnick, 2014; Kurkela & Dennis, 2016). As females have previously been shown to utilize verbal-based memory strategies to a greater extent than males (c.f. Frings et al., 2006), it is not surprising that females produced greater activity in language processing areas in the current study. Females, for example, may have assigned shapes a descriptive label (i.e., "bird" or "airplane") along with a spatial label (i.e., "left" or "right") at encoding and later evoked these labels at retrieval. Where activity in late visual processing regions for males is hypothesized to reflect visual elaboration of the false memory, activity in language processing regions for females may reflect verbal elaboration of the false memory.

*Sex x Region Interaction*

A targeted ROI analysis identified a significant interaction between sex and region (i.e., hippocampus, V1), with higher magnitudes of activity in the hippocampus for males than females

and higher magnitudes of activity in V1 for females than males. These results suggest a male specific role for the hippocampus in false memory formation and add additional evidence for a female specific role for V1. While there is a consensus that the hippocampus plays a significant role in true memories, evidence is mixed for its role during false memories (for a review, see Dennis et al., 2014). Some research suggests the hippocampus is active during both true and false memories (e.g., Cabeza et al., 2001), while others suggest that its role may be specific to true memories (e.g., Kim & Cabeza, 2007). The current findings suggest that males engage the hippocampus to a greater extent than females during false memories. These findings may, in part, explain mixed findings in the field regarding the involvement of the hippocampus in false memories. Moreover, these results complement previous findings, where using the same task and stimuli, we found greater hippocampal activity for males during true memories (Spets et al., 2019). The combination of these results suggest that males activate the hippocampus to a greater extent than females during both true and false memories.

## Conclusion

The current study suggests that sex differences exist in the neural correlates supporting false memories. Such sex differences suggest that males and females approach memory retrieval in different ways, all while yielding similar outcomes in terms of memory accuracy. Future research should explore factors such as retrieval strategy or physiological differences (e.g., hormone type or levels), which may mediate such sex differences. More broadly, the current study underlines the importance of including sex as a factor in neuroscience research.

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# Tables

Table 1. Group false memory activations

| Region | BA | x | y | z | *k* |
|---|---|---|---|---|---|
| *False memories > misses* | | | | | |
| Left precentral sulcus | 6/9/44 | −38 | 2 | 34 | 53 |
| Right superior parietal lobule | 7 | 16 | −64 | 53 | 34 |
| | | | | | |
| *False memories > true memories* | | | | | |
| *No significant activations* | | | | | |

BA refers to Brodmann area and MNI coordinate (x, y, z) refers to the center of each activation.

Table2. Male and female false memory activations

| Region | BA | x | y | z | *k* |
|---|---|---|---|---|---|
| *Male false memories > misses* | | | | | |
| Left intraparietal sulcus | 7/39 | −26 | −72 | 38 | 50 |
| Left parietooccipital sulcus | 7/18 | −14 | −63 | 27 | 113 |
| Right parietooccipital sulcus | 7/18 | 15 | −63 | 28 | 41 |
| Left fusiform gyrus | 37 | −42 | −60 | −10 | 49 |
| | | | | | |
| *Male false memories > true memories* | | | | | |
| *No significant activations* | | | | | |
| | | | | | |
| *Female false memories > misses* | | | | | |
| *No significant activations* | | | | | |
| | | | | | |
| *Female false memories > true memories* | | | | | |
| *No significant activations* | | | | | |

BA refers to Brodmann area and MNI coordinate (x, y, z) refers to the center of each activation.

Table 3. Differential male and female false memory activations

| Region | BA | x | y | z | *k* |
|---|---|---|---|---|---|
| *(Male false memories > misses) >* | | | | | |
| *(female false memories > misses)* | | | | | |
| Bilateral precuneus | 7 | −1 | −68 | 39 | 31 |
| Bilateral posterior cingulate cortex | 31 | 1 | −56 | 27 | 85 |
| Left parietooccipital sulcus | 7/18 | −13 | −64 | 27 | 52 |
| Right parietooccipital sulcus | 7/18 | 14 | −61 | 30 | 28 |
| Left fusiform gyrus | 37 | −50 | −58 | −6 | 25 |
| | | | | | |
| *(Male false memories > true memories) >* | | | | | |
| *(female false memories > true memories)* | | | | | |
| *No significant activations* | | | | | |
| | | | | | |
| *Male false memories > female false memories* | | | | | |
| *No significant activations* | | | | | |
| | | | | | |
| *(Female false memories > misses) >* | | | | | |
| *(male false memories > misses)* | | | | | |
| *No significant activations* | | | | | |
| | | | | | |
| *(Female false memories > true memories) >* | | | | | |
| *(male false memories > true memories)* | | | | | |
| Bilateral medial prefrontal/anterior cingulate cortex | 8/32 | 0 | 30 | 35 | 27 |
| Bilateral medial prefrontal cortex | 6 | 2 | 18 | 45 | 29 |
| Bilateral paracentral lobule | 4 | 1 | 1 | 53 | 29 |
| Right paracentral lobule/cingulate sulcus | 4/31 | 6 | −9 | 47 | 33 |
| Right putamen | − | 29 | 9 | −4 | 25 |
| | | | | | |
| *Female false memories > male false memories* | | | | | |
| Left supramarginal gyrus/lateral sulcus | 40 | −56 | −24 | 20 | 67 |
| Right lateral sulcus | 40 | 49 | −26 | 20 | 41 |
| Left lateral sulcus | 41/42 | −51 | −42 | 19 | 46 |
| Left calcarine sulcus | 17 | −22 | −68 | 1 | 70 |

BA refers to Brodmann area and MNI coordinate (x, y, z) refers to the center of each activation.

## CHAPTER 5

Are there sex differences in brain activity during long-term memory? A systematic review and fMRI activation likelihood estimation meta-analysis

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In press at *Cognitive Neuroscience*
DOI: 10.1080/17588928.2020.1806810

The degree to which sex differences exist in the brain is a current topic of debate. In the present discussion paper, we reviewed eight functional magnetic resonance imaging (fMRI) papers to determine whether there are sex differences in brain activity during long-term memory retrieval. The objectives were: 1) to compare the experimental parameters in studies reporting significant versus null long-term memory sex differences, and 2) to identify whether specific brain regions were associated with sex differences during long-term memory. The following experimental parameters were extracted from each paper: the number of participants, the average age of participants, stimulus type(s), whether or not performance was matched, whether or not sex differences were reported, the type of between-subject statistical test used, and the contrast(s) employed. The particular experimental parameters employed in each study did not appear to determine whether sex differences were observed, as there were sex differences in all eight studies. An activation likelihood estimation (ALE) meta-analysis was conducted to identify brain regions activated to a greater degree by females than males or males than females. This ALE meta-analysis revealed sex differences (male > female) in the lateral prefrontal cortex, visual processing regions, parahippocampal cortex, and the cerebellum. This constitutes compelling evidence that there are substantial sex differences in brain activity during long-term memory retrieval. More broadly, the present findings question the widespread practice of collapsing across sex in the field of cognitive neuroscience.

Sex differences have been exhibited during long-term memory in both behavior and neural activity and can be attributed, in part, to differences in neurochemistry and anatomy (Cahill, 2006; Andreano & Cahill, 2009). For instance, females have a relatively greater number of estrogen receptors in the dorsolateral prefrontal cortex as well as the hippocampus (Cahill, 2006), two regions associated with long-term memory (Slotnick, 2017), which may yield more optimal memory processing activity. Moreover, corrected for brain size, females have greater overall cortical volume compared to males in the dorsolateral prefrontal cortex (Andreano & Cahill, 2009; Goldstein et al., 2001). Behaviorally, there can be a female advantage in episodic memory and item memory tasks (e.g., verbal memory, facial memory) and a male advantage in spatial memory tasks (e.g., route navigation), although these effects are quite modest (Asperholm et al., 2019).

Functional magnetic resonance imaging (fMRI) studies have identified different patterns of activity for females and males across many types of long-term memory including object recognition (Canli et al., 2002; Banks et al., 2012; Frings et al., 2006; Spets & Slotnick, 2019), facial recognition (Armony & Sergerie, 2007; Loven et al., 2014), autobiographical memory (St. Jacques et al., 2011; Young et al., 2013), and spatial memory (Spets et al., 2019). However, null long-term memory sex differences have also been reported (Compere et al., 2016; Haut & Barch, 2006).

As both significant and null differences have been reported, whether and to what degree sex differences occur in the brain is a current topic of debate. In the present discussion paper, we reviewed fMRI papers to determine whether sex differences exist during long-term memory retrieval. The objectives of this systematic review were two-fold: 1) to compare the experimental parameters in studies reporting significant versus null long-term memory sex differences, and 2) to identify whether patterns of specific brain regions were associated with sex differences (female > male or male > female) during long-term memory. For this review, long-term memory was defined as any form of explicit/conscious long-term memory (which is distinct from

implicit/nonconscious long-term memory and short-term/working memory). By broadly defining long-term memory, this review encompassed many types of long-term memory including autobiographical memory (Piefke et al., 2005; Compere et al., 2016; St. Jacques et al., 2011; Young et al., 2013), memory for faces (Haut & Barch, 2006; Ino et al., 2010), memory for words (Haut & Barch, 2008), item memory (Spets & Slotnick, 2019), and spatial memory (Spets et al., 2019). The following experimental parameters were extracted from each paper: the number of participants, the average age of participants, stimulus type(s), whether or not performance was matched, whether or not sex differences were reported, the type of between-subject statistical test that was employed, and the contrast(s) employed. To identify if there were any sex-specific regions of the brain that emerged across studies, an activation likelihood estimation (ALE) meta-analysis was conducted. To anticipate the results, the present review provides strong evidence that there are substantial sex differences in brain activity during long-term memory retrieval.

## Methods

*Selection of articles*

A systematic review was conducted in accordance with the PRISMA guidelines (Moher et al., 2009, 2015). Articles were selected by entering the following search terms in PubMed: (memory[Title] OR recognition[Title] OR recall[Title]) AND (sex[Title/abstract] OR gender[Title/Abstract]) AND (fMRI[Title/Abstract] OR functional magnetic resonance imaging[Title/Abstract]). The search yielded 186 peer-reviewed articles. Articles were excluded for the following reasons: 1) the study was unrelated to long-term memory retrieval, 2) an abnormal population was studied (i.e., participants diagnosed with mental illnesses, mental disabilities, or participants prescribed medication that may alter brain function), 3) fewer than 8 female and 8 male participants were included in the analysis (c.f., Friston et al., 1999), 4) female and male brain activity was not directly compared, 5) there were any confounds, or 6) a whole-brain analysis was not conducted. Only the first experiment from Haut and Barch (2006) was

included in the analysis to maintain a consistent number of experiments across studies. Application of these exclusion criteria resulted in 8 studies with a total of 127 female participants and 119 male participants that were included in the analysis (Figure 1). Of the two studies excluded for confounds, one study did not report behavioral results making it unclear whether behavioral performance confounded the neural results (Popova et al., 2018) and the other study had perceptual confounds (Scherf et al., 2017). For one study (Spets & Slotnick, 2019), age range rather than average age of participants was reported; since we had access to the data, average age was computed for direct comparison with the other studies.

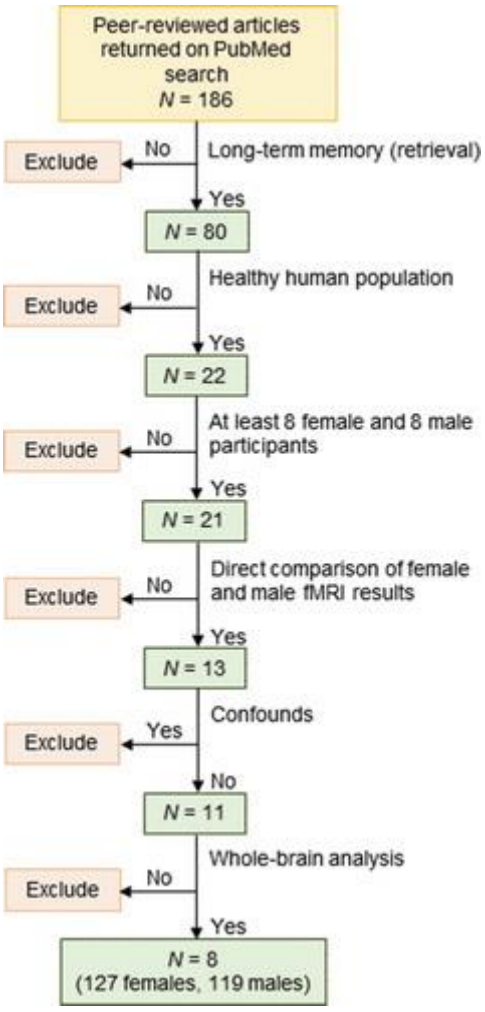


Figure 1. PRISMA flowchart outlining exclusion criteria.

*Activation likelihood estimation*

A coordinate-based meta-analysis technique (GingerALE Version 3.0.2; brainmap.org/ale) was employed to identify brain regions that were activated to a greater degree by females than males or males than females across the 8 studies included in the analysis. The activation coordinates for each between-subject contrast (females > males, males > females) were obtained from the table(s) of activations in each study. Prior to running the analyses, coordinates reported in Montreal Neurological Institute (MNI) space were transformed into Talairach space using a Lancaster Transformation implemented in GingerALE. These coordinates were used to create study-specific activation maps that were combined to produce a sample-size weighted ALE value for each voxel in the brain. These ALE values were tested against the null distribution to compute p-values, and the p-values were thresholded (Eickhoff et al., 2012, 2009). In the current analysis, an individual-voxel threshold of $p < .01$ was enforced, cluster-extent corrected to $p < .05$ (based on a Monte Carlo simulation with 10,000 iterations).

Coordinates from all contrasts specified in Table 1 were used to conduct the analyses. Piefke et al. (2005) reported five contrasts; as the contrasts were not independent, only the most general contrast (autobiographical memories > reading instructions) was included in the analysis. One male > female activation coordinate from Haut and Barch (2006; x = 35, y = 89, z = 18) was located outside of the brain. Personal communication with author K. H. confirmed that the coordinate reported in the paper should have been x = 35, y = – 89, z = 18, and this revised coordinate was used in analysis. In two of the studies (Spets et al., 2019; Spets & Slotnick, 2019), individual coordinates for sex-specific regions were not provided; these coordinates were retrieved from our archives. Results were visualized on a 1 mm isotropic anatomic Talairach template (brainmap.org) in MRIcroGL (nitrc.org).

## Results

### *The effect of different experimental parameters on sex differences*

Each experimental parameter listed in Table 1 will be discussed in turn to assess whether there was a particular parameter that may have influenced the degree to which sex differences were observed. Of importance, in the two studies that reported null sex differences (Compere et al., 2016; Haut & Barch, 2006), significant sex differences were actually observed but these findings were discounted (these studies are considered in detail in the Discussion). Haut and Barch (2006) found greater activity in visual processing regions for males than females. Compere et al. (2016), found many significant differences including greater activity for females than males in parietal cortex and visual processing regions. Thus, sex differences during long-term memory were actually observed in all eight studies.

#### *Sample size*

There was a wide range of sample sizes across studies. The average numbers of male and female participants across studies were 18.2 and 15.9, respectively. As differences were observed regardless of sample size (Table 1), it is unlikely that sample size has a major impact on the significance of results in long-term memory sex-differences studies.

#### *Age*

For the majority of studies, age was matched between female and male participants. Five of the eight studies had mean participant ages between 20.8 and 26.8 years (Piefke et al., 2005; Ino et al., 2010; Spets et al., 2019; Spets & Slotnick, 2019; St. Jacques et al., 2011). Three of the eight studies included mean participant ages between the ranges of 29.6 and 47.8 (Compere et al., 2016; Haut & Barch, 2006; Young et al., 2013). The age difference between female and male participants in one study (Haut & Barch, 2006) was marginally significant ($p < .04$). It is notable that the two studies using the oldest samples reported null differences (Compere et al., 2016; Haut

& Barch, 2006). As sex differences during long-term memory have been shown to decrease with increasing age (Supramaniapillai et al., 2019), it is plausible that the relatively older participants in these studies may have reduced the significance of the findings. As age appears to be a factor in the degree to which sex differences are observed, studies aiming to identify sex differences should match age between the sexes (to avoid a confound with age).

*Stimulus type*

Two of the articles in the present review employed faces as stimuli (Haut & Barch, 2006; Ino et al., 2010). Sex differences have been reported in facial recognition (Herlitz & Rehnman, 2008) as well as facial processing (Rennels & Cummings, 2013). Females, for example, consistently outperform males in facial recognition tasks. Additionally, females remember faces of their own sex to a greater extent than faces of the opposite sex (Herlitz & Rehnman, 2008). Outside of long-term memory, differences in facial viewing patterns exist between females and males with males exhibiting fixation patterns that suggest more holistic processing of faces (Rennels & Cummings, 2013). Moreover, facial stimuli are often affective in nature, which can introduce an additional confound as females and males respond differentially to emotional stimuli (Andreano & Cahill, 2009). Five of the eight studies employed verbal stimuli including words, pseudowords, word phrases, and sentence cues (Piefke et al., 2005, Compere et al., 2016; Haut & Barch, 2006; St. Jacques et al., 2011; Young et al., 2013). Similar to facial recognition, a female advantage has been observed across many verbal long-term memory tasks such as paired-associate learning, story recall, verbal recognition, and the California Verbal Learning Test (Andreano & Cahill, 2009). The use of verbal strategies by females has also been reported in long-term memory tasks that are not inherently verbal in nature (Frings et al., 2006; Spets et al., 2019). In one region-of-interest study (Frings et al., 2006), female and male participants performed an object/spatial memory task and then rated their strategy as more verbal or more pictorial. Females rated their strategy as significantly more verbal, as compared to males.

Moreover, females produced greater activity in the left hippocampus, while males produced greater activity in the right hippocampus, suggesting greater use of verbal strategies for females. More recently, we found marginally sex-specific activity in Broca's area for female participants during a spatial memory task, suggesting that females may employ verbal strategies to a greater degree than males when retrieving the spatial location of abstract shapes (Spets et al., 2019). The two remaining studies (Spets et al., 2019; Spets & Slotnick, 2019) employed abstract shapes as stimuli, in an effort to avoid differential verbal processing strategies (Slotnick & Schacter, 2004). Such abstract shapes have been shown to produce similar long-term memory behavioral performance for females and males (Rahman et al., 2011). Given that all of the studies reported sex differences within the brain, sex differences appear to occur regardless of stimulus type.

*Performance matched*

In the current analysis, we excluded all studies where behavioral performance between the sexes was not matched to avoid an effort confound (Figure 1). That is, if performance is not matched, differential brain activity could be due to performance differences rather than sex differences. Differences in behavioral performance may result from sex differences in stimulus processing (e.g., differential processing of faces, words, or mazes, as discussed above) or general differences in task proficiency or vigilance. It is known that females can excel in autobiographical memory and object recognition tasks, whereas males can excel in some types of spatial tasks (including three dimensional mazes and mental rotation; Andreano & Cahill, 2009). As such, it is unclear whether brain activation differences in studies where performance is not matched (e.g., Armony & Sergiere, 2007; Persson et al., 2013) are reflective of behavioral differences or sex differences. Critically, in all studies reported in Table 1, sex differences in the patterns of brain activity were observed even though there were no differences in behavioral performance.

*Test*

To determine if sex differences exist in the brain, the neural activity of females and males must be directly compared. It is not sufficient to compare the female pattern of activity with the male pattern of activity in a non-statistical manner (i.e., 'chi-by-eye'), because patterns of activity can appear different when they are statistically equivalent. For instance, if one sex shows activity in one region of the brain and the other sex does not, the null results could be slightly sub-threshold such that the activations in that region are actually similar in magnitude. In all but one study (Young et al., 2013), the statistical comparison between the sexes was conducted with a t-test, ANOVA, or ANCOVA on either the magnitude of activity or the extent of activity. Not surprisingly, given that these tests are related, there seems to be little effect of test type on whether or not significant results were found. One study (Young et al., 2013) used a mixed-effects meta-analysis (MEMA) to conduct the statistical comparison between the sexes. MEMAs may be more appropriate for studies of sex differences compared to traditional t-tests and ANOVAs as they do not make the same variability assumptions as more traditional tests. MEMAs, for example, do not assume that intra-subject variability is smaller than group variability and do not assume that intra-subject variability is equal across subjects (Chen et al., 2012). Overcoming these assumptions might make it a more reliable method for studying individual differences, such as sex differences. Although the type of test does not seem to play a role in whether or not significant results are found, if the threshold set is too conservative (e.g., a triple conjunction employed by Haut & Barch, 2006, discussed below), this would be expected to increase Type II error.

*Contrast*

As with all cognitive neuroscience studies, it is important that the contrast is carefully selected to isolate the cognitive process of interest (i.e., the comparison used to isolate a specific cognitive process and produce brain activity associated with that process). Selecting the

appropriate contrast can assuage concerns such as whether sex differences at the level of stimulus processing are influencing the results. For example, one study that investigated autobiographical memory recall used cue words as stimuli in both the experimental and control conditions (Young et al., 2013). To investigate sex differences in autobiographical memory recall they contrasted specific memories and semantic memory recall, a control condition in which a category word was presented and participants were instructed to think of examples from that category. This control condition not only controlled for general knowledge retrieval but also controlled for word processing (as words were used in both the memory and control phases). In another study (Spets et al., 2019), spatial memory was isolated by contrasting spatial memory hits (i.e., correct item memory and correct spatial memory of a previously presented shape) with spatial memory misses (i.e., correct item memory and incorrect spatial memory of a previously presented shape), where the only difference between event types was accurate spatial memory. As will be expanded on later, at least one of the null studies may have been influenced by a baseline condition that shared the same processes as the active condition (Compere et al., 2016).

### *ALE results*

The male versus female contrast produced one activation in the left lateral prefrontal cortex (that spanned the middle frontal gyrus, inferior frontal sulcus, and inferior frontal gyrus), another activation in the right middle occipital gyrus, and a third activation that spanned the right fusiform gyrus, right parahippocampal cortex, and the right cerebellum (Figure 2, Table 2). The female versus male contrast did not produce any significant activations.

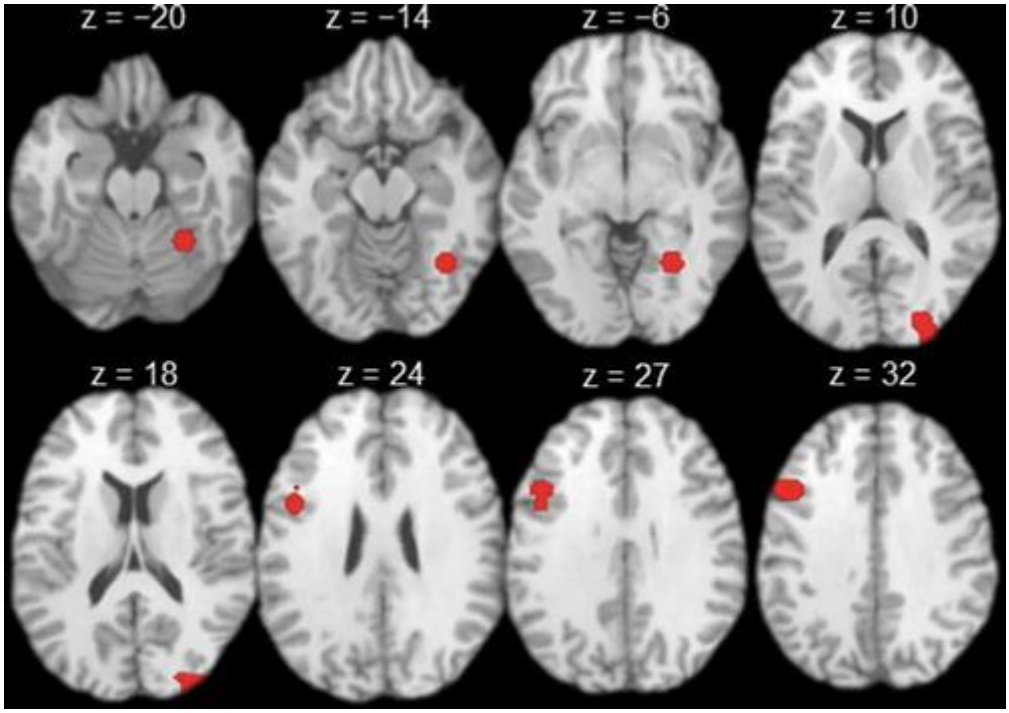


Figure 2. Results of the ALE meta-analysis. Male > female long-term memory activity (in red; there were no significant activations for female vs. male long-term memory).

## Discussion

*The effect of different experimental parameters on sex differences*

Sex differences during long-term memory have been investigated in fMRI studies with a wide range in the number of participants, the age of participants, stimuli, tasks, and contrasts (Table 1). Despite these different parameters, sex differences were observed in all eight studies. Thus, the particular experimental parameters employed in each study did not appear to determine whether sex difference were observed.

One parameter that was not examined in any of the studies was female menstruation phase or overall levels of circulating hormones. Circulating sex hormones have been shown to modulate many aspects of cognition, including memory. Levels of female sex hormones, for example, have been shown to influence object memory consolidation and water maze navigation in female rats as well as verbal memory and working memory in female humans (Andreano &

Cahill, 2009). Menstrual cycle phase has also been shown to influence fMRI activity in semantic memory (Fernandez et al., 2003). Additionally, circulating levels of testosterone in men have been shown to modulate spatial memory, verbal memory, and working memory (Andreano & Cahill, 2009). As such, recording and reporting hormone levels and menstrual cycle phases will be an important factor to consider in future fMRI studies of sex differences.

*ALE findings*

Results from the ALE meta-analysis revealed greater activity for males than females in the lateral prefrontal cortex, middle occipital gyrus, fusiform gyrus, parahippocampal cortex, and the cerebellum, suggesting that males engage these regions to a greater degree than females during long-term memory. There were no regions activated to a greater degree in females than males.

Greater activity in visual processing regions for males than females has been suggested to reflect more vivid visualization during long-term memory retrieval (St. Jacques et al., 2011). In a spatial memory task (Spets et al., 2019), males showed greater recruitment of both visual processing regions as well as hippocampus, which may have reflected greater recruitment of visual-spatial processing strategies in males than females. The parahippocampal cortex activity identified in the current meta-analysis supports this hypothesis, as both the hippocampus and parahippocampal cortex have been associated with long-term memory retrieval of visual-contextual information (Slotnick, 2013). It may be that during many forms of long-term memory (illustrated in Table 1), males are more likely to retrieve visual-contextual details than females.

Relatively greater prefrontal cortex activity in males than females has been suggested to be reflect greater engagement of the default network (Spets & Slotnick, 2019). During an item recognition memory task, female and male participants were matched for item memory accuracy. Despite equivalent behavioral performance, males produced greater activity than females in the lateral prefrontal cortex and medial prefrontal cortex, two regions associated with the default

network (Buckner et al., 2008). This may have reflected a relatively lower level of task engagement in males than females.

Beyond specific hypotheses regarding sex differences in individual brain regions, it may be that males are more likely to produce greater activity, overall, compared to females in order to achieve the same behavioral outcome, supporting the neural efficiency hypothesis. The neural efficiency hypothesis was originally postulated to explain why participants with higher intelligence quotients (IQs) produced less neural activity (typically measured with fMRI) than those with lower IQs during the same cognitive task (Neubauer & Fink, 2009). This logic has been extended to explain sex differences in previous studies (Ino et al., 2010; Li et al., 2010). For example, in a near-infrared spectroscopy study that investigated sex differences during a verbal N-back task (Li et al., 2010), despite equated behavioral performance, greater amplitudes of total hemoglobin and oxygenated hemoglobin were found for males than females, which was taken to suggest more efficient processing in the prefrontal cortex for females. The current ALE meta-analysis results should not be taken to suggest that female participants had higher IQs than male participants across studies. In fact, the equated behavioral performance in all studies suggests a similar range of IQ, and two of the studies in the present analysis matched female and male participants based on IQ (Haut & Barch, 2006; Young et al., 2013). IQ was not reported for the remaining fMRI studies included in the analysis. Still, even in instances where IQ was equated between the sexes, it is possible that memory processing regions were relatively more active in males to perform the task equivalently to females. It should be mentioned that this efficiency hypothesis and the task engagement hypotheses described immediately above are not incompatible with one another. Males, as compared to females, could be less efficient at a particular task (producing greater activity in task-related regions) and less engaged in the task (producing greater activity in default network regions). The relationship between general measures of IQ (e.g., verbal IQ, visual-spatial IQ), more specific measures of task performance, levels of task engagement, and sex differences in the brain are topics of future research.

It could be argued that sex differences might be produced by differences in overall stimulus processing rather than long-term memory. However, this seems unlikely in the present analysis. The contrasts for all studies included in the analysis successfully isolated the process of long-term memory. That is, there were no perceptual confounds in any of the studies included after the proper contrast was applied. Moreover, sex differences were observed across all stimulus types, and the ALE meta-analysis revealed significant sex-specific activations associated with long-term memory across all stimulus types. If stimulus type was a major factor in determining the results, only certain stimulus types would have produced significant sex differences and the meta-analysis results would be expected to produce null results. Since sex differences were observed across all stimulus types, this does not seem to be a major factor in determining whether there are sex differences in long-term memory studies.

Although the present review focused on sex differences in long-term memory, sex differences in the brain have also been reported in studies of working memory including auditory working memory (Goldstein et al., 2005), numerical maintenance (Bell et al., 2006), the N-back task (Li et al., 2010), and the Sternberg task (Gao et al., 2017; Zilles et al., 2016). Such findings provide evidence that sex differences in brain activity extend to other cognitive processes.

*Evidence for brain lateralization*

There are mixed results in studies reporting sex differences in brain lateralization during long-term memory. Generally, in studies of long-term memory, females have greater left laterality than males and males have greater right laterality than females in the amygdala (Canli et al., 2002; Armony & Sergerie, 2007; Cahill et al., 2004) and the hippocampus (Frings et al., 2006). However, other studies have reported null medial temporal lobe laterality differences between the sexes (Banks et al., 2012; Persson et al., 2013). A recent meta-analysis that investigated sex differences in laterality across many cognitive processes, including verbal memory and mental rotation, found no clear relationship between behavior and laterality

differences between the sexes (Hirnstein et al., 2019). More research is needed to determine the conditions under which sex differences in brain laterality emerge during long-term memory.

*A closer look at studies reporting null results*

Although the large majority of long-term memory fMRI studies reported significant sex differences (Table 1), two studies reported null results (Compere et al., 2016; Haut & Barch, 2006). These null results, however, may be explained by analysis or contrast choices. Haut and Barch (2006), sought to determine whether sex differences existed in episodic memory for both words and faces. For a region to be sex-specific, they required a conjunction of three separate effects, a triple conjunction, each at a significance level of $p < 0.02$. The first requirement was a three-way interaction between sex, material type, and condition. The second requirement was a two-way interaction between material type and condition in at least one sex. The third requirement was a main effect of condition in at least one material type in at least one sex. With such a strict triple conjunction, null results are expected. However, significantly greater activity was found for males than females during face versus word retrieval in visual processing cortex. It is likely that if a more lenient statistical threshold were enforced, additional significant differences would have been found. Another study reporting null differences (Compere et al., 2016) investigated sex differences during episodic and semantic autobiographical recall. For the control condition, participants imagined a scene given a certain context. To isolate episodic and sematic autobiographical memory, these memory conditions were contrasted against the control condition (i.e., scene construction). As remembering and imagining recruit overlapping networks (Schacter & Addis, 2007), it is plausible that meaningful activity was subtracted from the memory conditions when compared against scene construction, producing null results. As in Haut and Barch (2006), although null findings were reported, there were significant sex differences (female > male) in the Compere et al. (2016) study during semantic autobiographical memory in the parietal cortex and medial cortex. Thus, the null results can be attributed to an

overly strict analysis procedure (Haut & Barch, 2006) or a control condition that involved the same processes as the memory condition (Compere et al., 2016), and both of these studies actually produced significant sex differences during long-term memory.

A recent meta-analysis of 179 papers by David et al. (2018) concluded that there was potential reporting bias in fMRI studies of sex differences (reporting analyses that were not pre-specified), particularly in studies with smaller sample sizes. The analysis was based on the reasonable assumption that studies with larger numbers of participants (N) have more power to detect activity; therefore, the number of reported activations should show a positive relationship with sample size. Across all 179 studies, they found no statistically significant relationship between sample size and the number of activations, and the median number of activations in smaller studies ($N < 32$) did not differ from that off larger studies ($N > 32$; Figure 3; this figure, adapted from Figure 2 in David et al., 2018, contains 98% of all data points, as only 4 studies had an $N > 200$). This null finding led David et al. to conclude that there was a reporting bias in smaller N studies that produce more sex differences than truly exist. However, David et al.'s null results can be attributed to their use of highly variable cognitive processes rather than reporting bias. The 179 datasets investigated included 'studies using cognitive tasks', 'studies using mixed tasks', 'studies using motor or somatosensory tasks', and 'resting state studies' (see their Tables 1 and 2), and the primary analysis collapsed across all of these tasks. Critically, the first three task categories involve a wide range of cognitive processes, and thus brain activations, depending on the degree to which the study isolated a specific cognitive process. That is, the number of activations would be expected to be highly variable, depending on the degree to which a particular study had isolated a specific cognitive process (yielding a low number of activations) or did not isolate a specific cognitive process (yielding a high number of activations), regardless of the study N. This can be observed in the results of David et al., where even the smaller studies ($N < 32$) yielded a number of activations that ranged from 0 to 45 activations, with a cloud of data for studies with $N < 50$ (Figure 3). This data can be characterized as random data/noise that

was largely dependent on the degree to which each of the studies isolated a cognitive process, having nothing to do with participant number. Given that noise correlations are expected to be zero, it is not surprising that David et al. reported a null correlation when collapsing across all tasks. Fortunately, they also conducted subgroup analysis of specific tasks and, of particular importance, considered 11 (of the 179) studies that used a resting-state task. Resting-state tasks are known to produce activity in the default network that includes the dorsolateral prefrontal cortex, the medial prefrontal cortex, the inferior parietal cortex, and the medial parietal cortex (Buckner et al., 2008). Given that the activations for the resting-state are circumscribed (rather than highly variable), it would be expected that the number of activations should correlate with N in this case. That is what was observed, as there was a significant positive correlation in studies that used a resting-state task between the number of activations and N (Pearson R = 0.67, $p < .012$). David et al.'s null findings across all studies can be attributed to cognitive processing variability across tasks, and drawing conclusions from null findings is always speculative. Moreover, in resting-state studies, which did not suffer from the cognitive variability argument, they found a significant correlation between the number of activations and N. Thus, David et al.'s empirical findings provide no support for the conclusion that there is reporting bias in studies of sex differences.

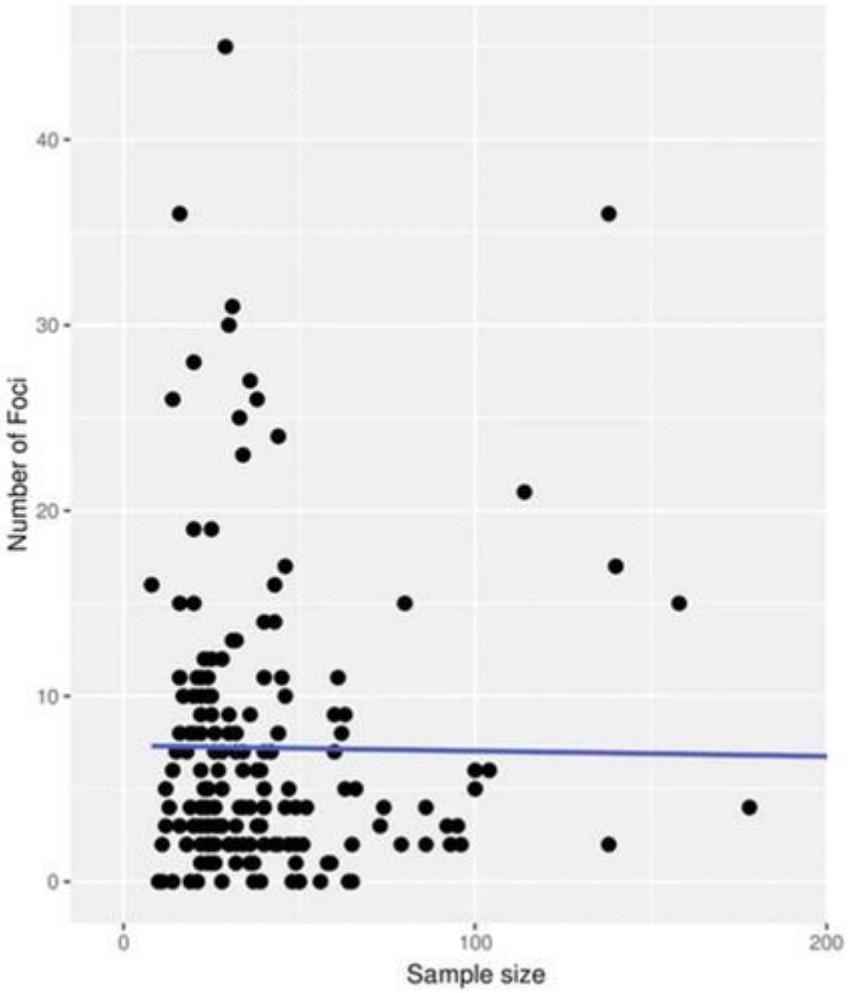


Figure 3. Relationship between sample size and identified number of foci per study. Adapted from David et al. (2018).

David et al. (2018) also highlighted the file-drawer problem (under-reporting of null results), which is another potential issue of studies with smaller N. We would argue that sex-differences studies are more immune to this issue than studies that collapse across sex, because studies investigating sex differences have multiple contrasts (and a conjunction) of theoretical interest. In particular, there are female-specific contrasts, male-specific contrasts, the conjunction (overlap) of these contrasts, and direct contrasts between females and males in addition to males and females. One meaningful set of results includes significant activations for females alone, significant activations for males alone, the conjunction of activity between females and males,

and null sex differences between females and males (in both directions). Another meaningful set of results would include significant activations for females alone, significant activations for males alone, null activity for the conjunction of these contrasts, and significant sex differences (in one or both directions) between females and males. In both of these specific examples, there are null results, but the findings would still be publishable in light of the other significant findings. In fact, there are numerous possible sets of results for the contrasts (in addition to the conjunction that would be conditional on significant sex-specific contrast results) that would produce at least one significant finding and thus would be of theoretical interest and be publishable. As such, although the degree of null results can never be known with certainty, it is unlikely that sex-differences research suffers from the file-drawer problem.

A related point to the previous two issues is whether N is sufficient to observe sex differences. In the present analysis, study Ns ranged from 20 (10 females, 10 males) to 61 (37 females, 24 males), with half of the eight studies having Ns of 20–23 participants. It is arguable that the N needs to be sufficient to produce significant sex differences, and in all these studies sex differences were observed and thus the Ns were sufficient. With that said, larger sample size does allow better generalization to the population. The required N in sex differences research reflects a more general focus in the field of cognitive neuroscience on deceasing type I error (while ignoring type II error) that has produced a systematic increase in sample size over time. From 2005 to 2015, the median N increased from about 13 participants to 28.5 participants, while the standardized effect sizes have improved by only about 25% (Poldrak et al., 2017). Button et al. (2013) estimated the median statistical power in 'neuroimaging studies' was 8%; however, these were structural/volumetric MRI studies rather than fMRI studies, such that this analysis is not relevant to the issue of sample size in fMRI studies. Button also made an extreme recommendation of suggesting over 100 participants in neuroscience studies to achieve 80% power. Their analysis clearly does not apply to the large majority of fMRI studies, given that nearly every fMRI study identifies activations in expected sensory and control regions of the

brain (e.g., visual long-term memory studies routinely activate the lateral prefrontal cortex, the parietal cortex, the medial temporal lobe, and visual processing regions; Slotnick, 2017), as is evidenced by the substantial number of significant activations in studies with Ns < 20 (this is illustrated in Figure 3). The general push to increase N in the fields of behavioral neuroscience and cognitive neuroscience begs the following question: Is it better to run two smaller studies with moderate effect sizes or one large study with a slightly improved effect size? If type II error, replication, and innovation are ignored, larger and larger studies with stricter significance thresholds will be favored. If type I error and type II error are balanced, it is not clear that larger studies are necessarily better. Related to this, Hopfinger (2017) pointed out several problems that occur when a strict statistical threshold is employed to limit type I error while ignoring type II error. Hopfinger (2017) highlighted that even at a less stringent threshold real findings will replicate across labs, that there is a danger in assuming only one analysis technique can uncover the truth (as all methods have limitations), and that if studies with only large samples are employed this will slow scientific progress and negatively impact innovation. Making some of the same points, in an earlier paper that considered the sole focus on type I error in fMRI analysis, Leiberman and Cunningham (2009) 'consider four negative consequences: (i) increased type II errors, (ii) a bias toward publishing large and obvious effects, (iii) a bias against observing effects associated with complex cognitive and affective processes, and (iv) deficient meta-analyses' (p. 424). The current study, with a combined N of 246, is the type of meta-analysis that Lieberman and Cunningham described, which employed the data from several smaller studies to make inferences to the general population.

## Conclusion

Every paper that was considered in the current review found sex differences in the brain during long-term memory. The results of the current ALE meta-analysis suggest that there are substantial sex differences in brain activity during long-term memory. More broadly, these

findings question the ubiquitous practice of collapsing across sex in the field of cognitive neuroscience.

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# Tables

Table 1. Experimental parameters and results from whole-brain long-term memory studies that investigated sex differences

| | | | | | | Between-subject analysis method | |
|---|---|---|---|---|---|---|---|
| Study | Sub. N | Average age | Stimulus type | Perform. matched | Reported differences | Test | Contrast(s) |
| Piefke et al. (2005) | 10F,10M | 25.5F,26.8M | ABM sentence cues | Yes | Yes | t-test | ABM>reading instructions |
| Haut & Barch (2006) faces>words/fixation | 26F,23M | 39.7F,33.1M | Words & faces | Yes | No | ANOVA | Words>faces/fixation, |
| Ino et al. (2010) faces | 10F,10M | 26.6F,26.7M | Faces | Yes | Yes | ANOVA | Female>male faces, male>female |
| St. Jacques et al. (2011) cues | 12F,11M | 23.1F,24.5M | ABM cues | Yes | Yes | t-test | Visual>verbal cues, verbal>visual |
| Young et al. (2013) | 20F,20M | 32.1F,29.6M | ABM word cues | Yes | Yes | MEMA | Specific memories>semantic recall |
| Compere et al. (2016) | 20F,16M | 47.8F,44.3M | ABM sentence cues | Yes | No | ANCOVA | Episodic/semantic ABM>imagery |
| Spets & Slotnick (2019) | 11F,11M | 21.3F,20.8M | Abstract shapes | Yes | Yes | t-test | Item memory hits>misses |
| Spets et al. (2019) | 18F,18M | 22.5F,22.3M | Abstract shapes | Yes | Yes | t-test | Spatial memory hits>misses |

Sub. = subject, Perform. = behavioral performance, ABM = autobiographical memory, MEMA = mixed-effects meta analysis. Note, average ages specified in hundredths were rounded up to the nearest tenth.

Table 2. Brain regions significantly more active in males than females during long-term memory

| Region | BA | x | y | z | k |
|---|---|---|---|---|---|
| Left MFG/IFS/IFG | 6/9/44 | −44 | 12 | 30 | 209 |
| Right MOG | 18/19 | 29 | −89 | 13 | 207 |
| Right FG/PHC/Cerebellum | 19/37 | 34 | −60 | −13 | 229 |

MFG = middle frontal gyrus, IFS = inferior frontal sulcus, IFG = inferior frontal gyrus, MOG = middle occipital gyrus, FG = fusiform gyrus, PHC = parahippocampal cortex. BA refers to Brodmann area, Talairach coordinate (x, y, z) refers to the center of each activation, and k refers to cluster size.

# PART 2

## SEX DIFFERENCES IN FUNCTIONAL CONNECTIVITY DURING LONG-TERM MEMORY

## CHAPTER 6

Sex differences in hippocampal connectivity during spatial long-term memory
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In press at *Hippocampus*
DOI: 10.1002/hipo.23319

Sex differences in brain activity have been reported across various types of long-term memory. To our knowledge, sex differences in functional connectivity during long-term memory have not been investigated. A previous study on the structural connectome identified that female brains have a greater degree of interhemispheric connectivity than males, whereas males have a greater degree of intrahemispheric connectivity than females. The aim of the current investigation was twofold: (a) identify which brain regions were functionally connected to the hippocampus during spatial long-term memory, and (b) determine if there were sex differences in the functionally connected regions. During the study phase, abstract shapes were presented to the left or right of fixation. During the test phase, abstract shapes were presented at fixation and participants classified each item as previously on the "left" or "right". A hippocampal region of interest (ROI) was identified by contrasting spatial memory hits and misses. The peak coordinate from this ROI was used to define the center of a sphere that was used as the seed for the functional connectivity analysis. The connectivity analysis produced many connected activations including the medial posterior frontal cortex, lateral posterior frontal cortex, left inferior frontal gyrus, posterior cingulate cortex, and caudate/putamen. Although there were no regions with greater connectivity in females than males, the male versus female comparison produced connected activations in the medial posterior frontal cortex, anterior prefrontal cortex, precuneus, and cingulate sulcus. Females also had greater interhemispheric connectivity than males. The current findings suggest collapsing across sex in cognitive neuroscience studies may not be warranted.

Sex differences have been reported during many cognitive processes, including long-term memory. At the behavioral level, females often show a slight advantage in episodic and item memory tasks, whereas males often show a slight advantage in types of memory that engage visuospatial processing strategies (Asperholm, Hogman, Rafi, & Herlitz, 2019). With regard to brain activity, sex differences have been reported during object recognition (Banks, Jones-Gotman, Ladowski, & Sziklas, 2012; Canli, Desmond, Zhao, & Gabrieli, 2002; Frings et al., 2006; Spets & Slotnick, 2019), facial recognition (Armony & Sergerie, 2007; Loven et al., 2014), autobiographical memory (St. Jacques, Conway, & Cabeza, 2011; Young et al., 2017), and spatial memory (Spets, Jeye, & Slotnick, 2019). Critically, in the large majority of these functional magnetic resonance imaging (fMRI) studies, there was no difference in the behavioral accuracy between female and male participants such that differential brain activity between the sexes could not be attributed to performance differences. Moreover, a recent meta-analysis that investigated differences in whole-brain fMRI activity between females and males during long-term memory found that males consistently activated the lateral prefrontal cortex, visual processing regions, parahippocampal cortex, and the cerebellum to a greater extent than females across a variety of long-term memory tasks (Spets & Slotnick, 2020).

Although mounting evidence indicates there are sex differences in brain activity during long-term memory, much less is known about sex differences in brain connectivity. A few studies have investigated sex differences in structural/anatomic connectivity or functional connectivity with resting-state fMRI data. One study used diffusion tensor imaging to map the structural connectome of the human brain (Ingalhalikar et al., 2014). They found that females had more interhemispheric connections than males (i.e., structural connections between the hemispheres), while males had more intrahemispheric connections than females (i.e., structural connections within each hemisphere). A study that investigated sex differences using resting-state fMRI data found higher functional connectivity in sensorimotor, visual, and anterior lateral prefrontal areas for males than females and higher functional connectivity within the default network for females

than males (Ritchie et al., 2018). To our knowledge, no studies have been conducted to determine whether functional connectivity differs between females and males during long-term memory.

The hippocampus is known to bind item and context information during long-term memory and this region is critical during many types of long-term memory (Slotnick, 2017a). The hippocampus has been shown to be functionally connected to many brain regions during successful long-term memory retrieval. In one study that used a word-recognition task, the left hippocampus was functionally connected to bilateral superior frontal gyrus, bilateral supramarginal gyrus, left precuneus, and left caudate, which suggests that the hippocampus is functionally connected to a network of brain regions that work in unison to support successful long-term memory retrieval (Geib, Stanley, Dennis, Woldorff, & Cabeza, 2017). Another study looked at patterns of connectivity with five different seed regions (medial prefrontal cortex, angular gyrus, posterior cingulate, middle temporal gyrus, and the hippocampus) across associative memory tasks that employed picture-word pairs, word pairs, or object pairs (King, de Chastelaine, Elward, Wang, & Rugg, 2015). Common regions of connectivity across the three experiments and five seed regions were found in regions of the core recollection network (medial prefrontal cortex, left angular gyrus, posterior cingulate/retrosplenial cortex, parahippocampal cortex, and the hippocampus). Moreover, the magnitude of functional connectivity between the seed regions and connected regions increased as a function of memory accuracy, further emphasizing the role of functionally connected networks during long-term memory retrieval.

The aim of the current fMRI study was twofold: (a) identify which brain regions were functionally connected to the hippocampus during spatial long-term memory, and (b) to determine if there were sex differences in the functionally connected regions (either in the degree of connectivity or whether there was differential interhemispheric vs. intrahemispheric connectivity). During the study phase, abstract shapes were presented to the left or right of fixation. During the test phase, shapes were presented at fixation and participants indicated whether each shape was previously in the “left” or “right” visual field. The contrast of spatial

memory hits (i.e., correct spatial location identification) versus misses (i.e., incorrect spatial location identification) was used to define a hippocampal region of interest (ROI). The peak activation coordinate of the hippocampal ROI was used to define a sphere with a 3 mm radius that was used as a seed for the functional connectivity analysis. This analysis was conducted to determine the regions of the brain that were connected with the hippocampal seed for all participants (females and males), to a greater degree in females than males, and to a greater degree in males than females. Based on previous findings (Geib et al., 2017; King et al., 2015), we hypothesized that the hippocampal functional connectivity analysis would produce connected activations in brain regions that support long-term memory including the lateral prefrontal cortex, parietal cortex, lateral temporal cortex, and occipital cortex (Slotnick, 2017a). Based on previous structural connectivity results (Ingalhalikar et al., 2014), we also hypothesized that females would produce more interhemispheric connections than males. We used laterality indices to calculate the degree of interhemispheric connectivity, a measure that has previously been used in studies of sex differences in laterality (Canli et al., 2002; Frings et al., 2006). In line with a greater degree of interhemispheric connections for females that can be assumed to reflect more global processing, where global refers to greater communication across hemispheres and local refers to greater communication within hemispheres (Ingalhalikar et al., 2014), we also hypothesized that females would have a greater number of connected activations than males. To preview the results, the analysis of all participants produced connected activations in regions previously associated with spatial long-term memory, which supports and extends previous findings (Geib et al., 2017; King et al., 2015). Furthermore, males produced a greater magnitude of connected activations in the medial prefrontal cortex, anterior prefrontal cortex, precuneus, and cingulate sulcus than females, and females produced more interhemispheric connections than males.

## Methods

The present study reanalyzed data from two spatial long-term memory studies (Jeye, MacEvoy, Karanian, & Slotnick, 2018; Slotnick & Schacter, 2004). Each study was comprised of two experiments (below, the experiments in Slotnick & Schacter, 2004, will subsequently be referred to as Experiments 1 and 2 and the experiments in Jeye et al., 2018, will subsequently be referred to as Experiments 3 and 4). Essential methodological details are provided here (full details can be found in Spets et al., 2019).

### *Participants*

Across the two studies there were 40 female and 18 male participants. Eighteen females were selected from the 40 female participants to best match the spatial memory accuracy and variance of the 18 male participants.

### *Stimulus protocol and task*

Each participant completed a behavioral training session prior to the scanning session, a single anatomic scan, and three to eight study-test runs. The number of runs were consistent within each of the four experiments. There was no significant difference between the number of runs for female and male participants ($F(3,35) = 2.7$, $p = .065$). During each study phase, abstract shapes were presented in pseudorandomized order to the left or right of a fixation cross for 2.5 s (shape construction details can be found in Slotnick & Schacter, 2004). Participants were instructed to remember each shape and its spatial location while maintaining fixation. Each shape was presented at fixation for 2.5–3.0 s (a constant duration for each experiment) during the test phase and participants made an old-"left", old-"right" judgment followed by confidence judgment with their left hand (Figure 1). Experiments 1 and 2 also included new items during retrieval and participants had the additional option to respond "new"; however, for all experiments, the identical item types were used in the analysis. That is, hits were defined as correct spatial location

identification (i.e., “right” responses to items previously presented on the right, or “left” responses to items previously presented on the left), and misses were defined as incorrect spatial location identification (i.e., a “right” response to an item previously on the left, or a “left” response to an item previously presented on the right). Spatial location accuracy was computed as the percentage of correct spatial location identification contingent on correct old item identification (chance = 50%). Shape sets were counterbalanced across participants using a Latin Square design.

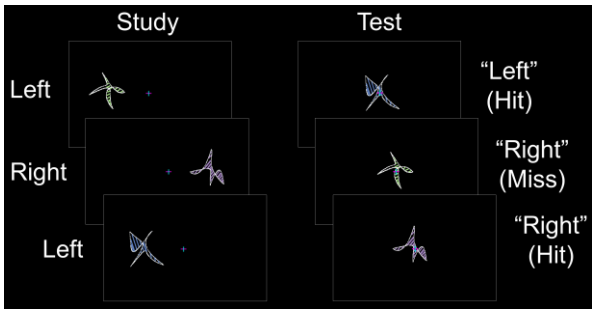


Figure 1. Stimulus and response protocol. During the study phase, abstract shapes were presented to the left of right of fixation. During the test phase, old shapes were presented at fixation and participants indicated whether each shape was previously on the “left” or “right” (example response and event types are shown to the right)

In Experiment 1, each participant completed a single anatomic scan and three study-test runs. Each session included three study-test phases with 144 shapes (16 sets of nine exemplars). Each set of exemplars alternated between presentation in the left and right visual field. Stimuli were projected onto a screen at the superior end of the scanner and were viewed through an angled mirror affixed to the head coil. Shapes were contained within a bounding square of 5.5° of visual angle in width, with the closest edge off set 3° of visual angle from fixation during the study phase. There was an approximately 7 min delay between the end of each study phase and the beginning of each test phase. The test phase consisted of 96 shapes (16 sets of two studied exemplars, two related shapes, and two nonstudied shapes). During the test phase, shapes were presented at fixation for 2.5 s followed by a confidence reminder screen for 1.4 s and a 0.1–8.1 s

fixation period. Participants responded either old and on the “left”, old and on the “right”, or “new” with their left hand, followed by an “unsure”–“sure” response.

The details of Experiment 2 are identical to Experiment 1 unless otherwise stated. Each participant completed six study-test runs. During the study phase, 32 abstract shapes were presented in the left or right visual field. During the test phase, the 32 abstract shapes from the study phase and 16 new shapes were presented at fixation.

In Experiment 3, participants completed a single anatomic scan and seven to eight study-test runs. Shapes spanned 6.7° of visual angle with the closest edge offset 3.6° of visual angle from fixation. There was an approximately 8 min delay between the end of each study phase and the beginning of each test phase. During the study phase, 32 abstract shapes were presented to the left or right visual field with random assigned so that no more than three shapes were presented on either side sequentially. During the test phase, each shape was presented at fixation for 3.0 s followed by a confidence reminder screen for 2.5 s and a 0.5–4.5 s fixation period. For each shape, participants responded either “left” or “right” with their left hand, followed by an “unsure”–“sure”–“very sure” confidence rating.

The details of Experiment 4 are identical to Experiment 3 unless otherwise stated. Shapes spanned 3.87° of visual angle with the closest edge offset 2.1° of visual angle from fixation in the upper-left, lower-left, upper-right, or lower-right visual field quadrant. Participants responded either “upper-left”, “lower-left”, “upper-right”, or “lower-right” with their left hand to indicate the quadrant in which the shape was previously presented.

Image acquisition and analysis

For Experiments 1 and 2, images were acquired using a 3-Tesla Siemens Allegra MRI scanner with a standard head coil. Anatomic data were acquired using an MPRAGE sequence (TR = 30 ms, TE = 3.3 ms, 128 slices, 1 × 1 × 1 × 1.33 mm resolution) and functional data were acquired using a T2*-weighted EPI sequence (TR = 2000 ms, TE = 30 ms, 64 × 64 acquisition

matrix, 26–30 slices in Experiment 1 and 30 slices in Experiment 2, 4.5 mm isotropic resolution). Image acquisition parameters in Experiments 3 and 4 were identical to Experiments 1 and 2 except that images were acquired using a 3-Tesla Trio Scanner with a 32-channel head coil and functional data were acquired with 34 slices and 4 mm isotropic resolution.

A random-effect general linear model (GLM) analysis was conducted in SPM12 (Wellcome Trust Center for Neuroimaging, London, UK). Functional image pre-processing included slice-time correction, motion correction to the first volume of each run, and spatial normalization to the Montreal Neurological (MNI) template, which included resampling at 2 $mm^3$. The GLM included 18 motion regressors (three translation and three rotation parameters along with their first and second derivatives) and scrubbing of all data with a framewise displacement of $\geq 0.5$ mm (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012). Spatial smoothing was not conducted in order to maximize spatial resolution. Anatomic images were normalized to MNI space with 1 $mm^3$ resolution and then averaged across participants. The following event types were entered into the GLM: encoding of items in the left visual field, encoding of items in the right visual field, accurate retrieval of items in the left visual field (left-hits), accurate retrieval of items in the right visual field (right-hits), inaccurate retrieval of items in the left visual field (left-misses), and inaccurate retrieval of items in the right visual field (right-misses; for Experiments 1 and 2, new items and the additional "new" response option was also modeled; however, the corresponding item types were not included in the subsequent analysis). For each participant, activity associated with accurate spatial memory was isolated by contrasting spatial memory hits (i.e., left-hits and right-hits) and spatial memory misses (i.e., left-misses and right-misses).

Each participant's first-level model was entered into a second-level analysis. The contrast of hits versus misses (inclusive of all participants) was thresholded at $p < .01$, uncorrected, to define a hippocampal ROI for the functional connectivity analysis. This contrast produced two hippocampal activations. A 3 mm radius sphere was extracted around the peak coordinate of the

largest and most significant of these activations and this was used as the hippocampal ROI (see Section 3). A 3 mm radius was chosen as it most effectively encompassed the ROI, allowing for the sampling of a sufficient number of voxels without sampling from surrounding regions of no interest or white matter. The voxels contained in this sphere were used as a seed for the functional connectivity analysis.

Functional connectivity analyses were conducted using a generalized psychophysiological interaction (gPPI) toolbox (Mclaren et al., 2012) using the individual-participant first-level models of accurate (i.e., left-hits and right-hits) versus inaccurate (i.e., left-misses and right-misses) spatial memory. For each participant, whole-brain t-contrasts of hippocampal functional connectivity were created and entered into a second-level model, across participants, to determine voxels functionally connected to the hippocampus. Second-level models were evaluated with independent t-tests to determine if there were sex differences in the magnitude of connectivity. When a gPPI model is built, each condition is modeled separately and all conditions are included in the analysis. The analysis outputs gPPI regressors for each condition that show the activity associated with the interaction between each event and the activity in the seed region (Mclaren et al., 2012). The regressors account for the variance unexplained by the main model. Thus, definition of the seed by the GLM contrast of hits versus misses is permissible as this original analysis and the subsequent gPPI analysis are orthogonal to one another (O'Reilly, Woolrich, Behrens, Smith, & Johansen-Berg, 2012).

All contrasts were thresholded at $p < .01$, cluster extent correct to $p < .05$ (except for the contrast to identify the hippocampal ROI). To compute the cluster extent threshold, we first computed the spatial autocorrelation for the gPPI contrast of hits versus misses for all participants in each experiment using a custom script (img_xcorr.m; Slotnick, n.d.) and employed the smallest spatial autocorrelation value (3 mm) across experiments (as larger spatial autocorrelations can be assumed to be due to true activations rather than noise). Note that we have previously obtained spatial autocorrelation values smaller than the original voxel size using the BrainVoyager (Brain

Innovation, Maastricht, The Netherlands) cluster-level statistical threshold estimator plugin and obtained values of 3.3–3.7 mm for fMRI datasets with isotropic voxel sizes that varied from 4.0 and 4.5 mm (Spets & Slotnick, 2019; Spets et al., 2019). Ten thousand Monte Carlo simulations were conducted based on the acquisition volume parameters, computed spatial autocorrelation, and the desired individual voxel and family *p* value (Slotnick, 2017b). This resulted in a cluster extent of 24 voxels, which was applied to all contrasts. Images were imported into MRIcroGL (obtained from www.nitrc.org) and overlaid on the average anatomic for viewing purposes.

To determine if there were sex differences in the number of activated clusters or the total number of voxels activated, the hippocampal connectivity maps were thresholded on an individual-participant basis (using the same individual-voxel and cluster extent thresholds specified above). To assess if there were any sex differences in interhemispheric versus intrahemispheric connectivity, laterality indices were calculated for each participant using the following formula:

$$\left|\frac{R-L}{R+L} \times 100\right|$$

R is the number of activations located in the right hemisphere and L is the number of activations located in the left hemisphere. The laterality index produces a range of values from −100 (indicating complete left hemispheric connected activations) to +100 (indicating complete right hemispheric connected activations). As our aim was to obtain a measure of interhemispheric connectivity or intrahemispheric connectivity (regardless of hemisphere), the absolute value of laterality index was employed to assess interhemispheric versus intrahemispheric connectivity, with smaller numbers (closer to 0) indicating interhemispheric connectivity and larger numbers (closer to 100) indicating intrahemispheric connectivity. Only participants with at least two activations were included in the analysis to avoid floor effects, and more than one activation was required to accurately determine whether interhemispheric or intrahemishperic connections were

predominant. Out of the 36 females and males included in the original analysis, five females and three males were excluded from these analyses based on the exclusion criteria specified above. Based on our a priori hypotheses of greater interhemispheric connectivity and a greater number of connections for females, one-tailed weighted t-tests were conducted to determine whether females and males significantly differed in the number of connected activations, the number of connected voxels, or the absolute value of the laterality index.

## Results

As expected (because the participants were matched for accuracy), there was no significant difference in the spatial memory accuracy of the 18 female participants ($74.25 \pm 0.94\%$, mean ± SE) and the 18 male participants ($73.42 \pm 1.22\%$, $t(34) < 1$). There was no significant difference between the ages of the 18 female participants ($22.54 \pm 0.68$ years) and the 18 male participants ($22.28 \pm 0.61$ years, $t(34) < 1$) and no significant difference in handedness between the female participants ($86.13 \pm 3.52$) and the male participants ($81.27 \pm 5.87$, $t(33) < 1$; handedness quotient ranged from −100 to +100 indicating completely left handed and completely right handed, respectively, computed based on responses to the Edinburgh handedness inventory; Oldfield, 1971; handedness data was not available for one female participant).

The group contrast of hits and misses produced two activations in the left hippocampus (the peak coordinate of the larger and more significant of the two activations was used in the subsequent gPPI analysis). The 3 mm sphere centered at this coordinate ($x = -24$, $y = -34$, $z = -6$) contained 13 voxels that were used as the seed for the functional connectivity analysis (Figure 2).

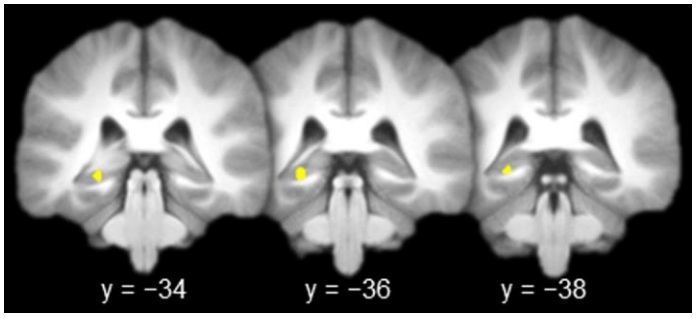


Figure 2. Hippocampal seed (identified by contrasting spatial memory hits and misses and extracting a 3 mm radius sphere around the peak coordinate in the most significant hippocampal activation; coronal slices with y-coordinates, neurological view)

Across all participants, there were many regions functionally connected to the hippocampus including bilateral medial posterior frontal cortex, bilateral lateral posterior frontal cortex (right precentral sulcus and left precentral gyrus), left inferior frontal gyrus, bilateral posterior cingulate cortex, bilateral putamen, and right caudate (Table 1 and Figure 3, in green). There were not any connected activations with the hippocampus that were greater in magnitude for females than males (Table 1). However, there were many connected activations with the hippocampus that were greater in magnitude for males than females including bilateral medial posterior frontal cortex, right anterior prefrontal cortex, bilateral precuneus, and left cingulate sulcus (Table 1 and Figure 3, in red).

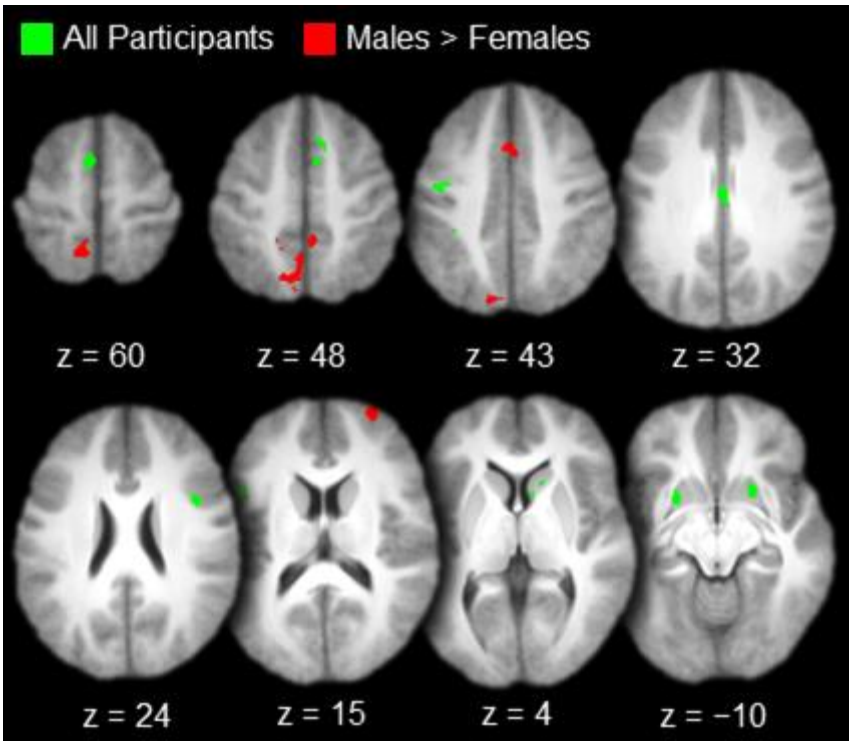


Figure 3. Hippocampal functional connectivity results (axial slices with z-coordinates; key at the top)

There was no significant difference in the number of connected activations for females (26.26 ± 6.11) and males (26.87 ± 8.43) or the number of connected voxels for females (1510.31 ± 515.12) and males (1485.53 ± 586.98, both *p* values >.2), which did not support our prediction of a greater number of connected activations in females than males. However, as predicted, the absolute value of the laterality index for females (15.23 ± 4.93) was significantly smaller than that of males (35.13 ± 9.47, weighted $t(26) = 1.78$, $p < .05$) indicating greater interhemispheric connectivity for females than males (Figure 4).

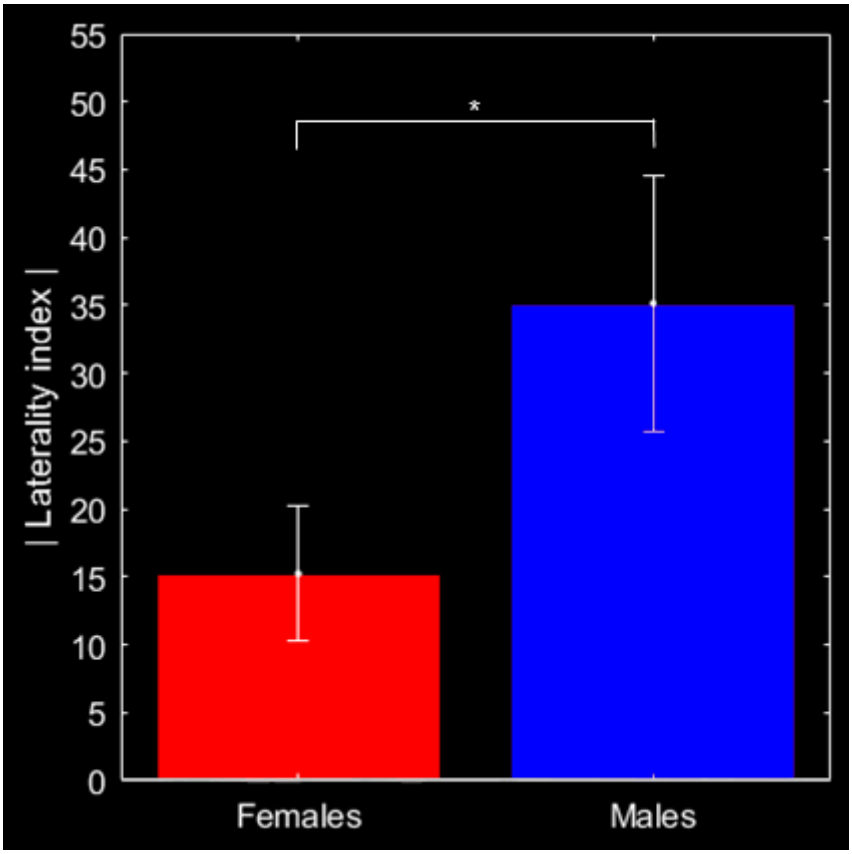


Figure 4. Average absolute value of laterality index for females and males (± 1 SE; a value of 0 indicates equally distributed connected activations across the two hemispheres, whereas a value of 100 indicates all connected activations were within a single hemisphere; *$p < .05$)

## Discussion

The hippocampal functional connectivity analysis that included all participants produced many connected activations including the medial/lateral frontal cortex, left inferior frontal gyrus, posterior cingulate, and caudate/putamen. These results suggest that the hippocampus interacts with a wide range of brain regions to support successful long-term memory, and they replicate and extend previous findings of hippocampal functional connectivity during successful long-term memory. Similar to Geib et al. (2017), who also used a left hippocampal seed region, we found hippocampal connectivity with the lateral frontal cortex, posterior cingulate gyrus, and the

caudate during successful long-term memory. The left inferior frontal gyrus activation produced by the group analysis was located within Brodmann area 44 (i.e., Broca's area), a region that has been associated with language processing (Price, 2000). The latter finding is in line with previous fMRI evidence (Frings et al., 2006) and neuropsychological evidence (Willment & Golby, 2013) indicating that the left hippocampus is associated with verbal-based retrieval.

Although we had hypothesized that the left hippocampal seed would produce connected activations in visual processing regions, there were no connected activations in these regions. Geib et al. (2017) similarly failed to find functional connectivity between the hippocampus and visual processing regions. In contrast with these results, King et al. (2015) did find functional connectivity between the hippocampus and extrastriate cortex. These results suggest that connectivity between the hippocampus and visual processing regions during long-term memory may be specific to the type of long-term memory or the task employed.

There were no regions of hippocampal functional connectivity that were significantly greater for females than males. Males, however, had greater functional connectivity with the medial posterior frontal cortex, anterior prefrontal cortex, precuneus, and cingulate sulcus. These regions have been associated with both long-term memory retrieval (Slotnick, 2017a) and default network processing (Buckner, Andrews-Hanna, & Schacter, 2008). As it is unclear whether this differential activity reflects greater retrieval (task) processes or default (non-task) processes in males than females (cf., Spets & Slotnick, 2019), this is a topic of future research.

Although females did not produce any regions of greater hippocampal functional connectivity than males, they did produce greater interhemispheric connectivity compared to males. These results support previous structural connectivity findings that suggest female brains are optimized for interhemispheric connectivity whereas male brains are optimized for intrahemispheric connectivity (Ingalhalikar et al., 2014). The fact that females produced greater interhemispheric connectivity suggests that they may engage in more global (interhemispheric)

processing during spatial long-term memory retrieval than males (who may engage a more local/intrahemispheric processing).

There are some limitations in the current study. First, there were a different number of females and males included in the laterality analysis that may have influenced the results. However, a weighted *t*-test was conducted, which corrects for a different number of participants between groups. It is also notable that data were collected from participants during different times of the day. This may have implications for the data collected from male participants, as total testosterone levels fluctuate in males over the course of a day following a circadian pattern (Plymate, Tenover, & Bremner, 1989), which may differentially influence behavior and brain function (Andreano & Cahill, 2009). However, it seems unlikely that scanning time influenced the pattern of results in the current study as there was no significant difference in the behavioral performance between males whose data were collected during the morning/early afternoon (when testosterone levels are the highest) and the evening (when testosterone levels decline; Plymate et al., 1989; spatial memory accuracy for participants in the present study during these two time periods were 75.29 ± 0.39% and 71.93 ± 0.61%, respectively, weighted $t(16) = 1.41$, $p = .18$). The current results in females may have differed as a function of cycle phase, as estrogen levels have been shown to affect the nature of the hemodynamic response (Dietrich et al., 2001) and some memory related structures contain estrogen receptors (Cahill, 2006). However, estrous cycle phase was not collected for female participants and thus this limitation cannot be addressed. Better understanding the role of testosterone and estrogen in learning and memory remains a vital area for future research.

There is an abundance of evidence that there are sex differences in the brain across many types of long-term memory (see Spets & Slotnick, 2020). The current results extend these findings by showing hippocampal connectivity is significantly different between females and males during spatial long-term memory. As sex differences in hemispheric connectivity have been reported in structural and functional connectomes (Ingalhalikar et al., 2014; Ritchie et

al., 2018), patterns of connectivity may well differ between females and males across a variety of cognitive tasks. The current, and previous, findings suggest collapsing across sex in cognitive neuroscience studies may not be warranted.

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# Table

Table 1. Regions functionally connected to hippocampus hit > miss activation

| Region | BA | x | y | z | *k* |
|---|---|---|---|---|---|
| *All Subjects (Hits > Misses)* | | | | | |
| L. Medial Prefrontal Cortex | 6 | −4 | 4 | 62 | 36 |
| R. Medial Prefrontal Cortex | 6 | 8 | 6 | 50 | 24 |
| R. Precentral Sulcus | 6/44 | 40 | 7 | 24 | 24 |
| L. Precentral Gyrus | 4/6 | −38 | −9 | 43 | 28 |
| L. Inferior Frontal Gyrus | 44 | −44 | 9 | 15 | 42 |
| L. Posterior Cingulate Cortex | 23 | −8 | −36 | 34 | 27 |
| Bilateral Posterior Cingulate Cortex | 23 | 5 | −17 | 32 | 77 |
| L. Putamen | − | −24 | 8 | −10 | 31 |
| R. Caudate/Putamen | − | 19 | 10 | 1 | 131 |
| | | | | | |
| *Female (Hits > Misses) > Male (Hits > Misses)* | | | | | |
| No activations | | | | | |
| | | | | | |
| *Male (Hits > Misses) > Female (Hits > Misses)* | | | | | |
| Bilateral Medial Prefrontal Cortex | 6 | 1 | 12 | 43 | 32 |
| R. Anterior Prefrontal Cortex | 10 | 28 | 57 | 14 | 27 |
| Bilateral Precuneus | 7 | −4 | −58 | 48 | 153 |
| L. Cingulate Sulcus | 7/31 | −17 | −43 | 48 | 24 |

BA refers to Brodmann area, MNI coordinate (x, y, z) refers to the center of each activation, and k refers to the cluster size of each activation.

## CHAPTER 7

Thalamic functional connectivity during spatial long-term memory and the role of sex
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Published in *Brain Sciences*
DOI: 10.3390/brainsci10120898

The thalamus has been implicated in many cognitive processes, including long-term memory. More specifically, the anterior (AT) and mediodorsal (MD) thalamic nuclei have been associated with long-term memory. Despite extensive mapping of the anatomical connections between these nuclei and other brain regions, little is known regarding their functional connectivity during long-term memory. The current study sought to determine which brain regions are functionally connected to AT and MD during spatial long-term memory and whether sex differences exist in the patterns of connectivity. During encoding, abstract shapes were presented to the left and right of fixation. During retrieval, shapes were presented at fixation, and participants made an "old-left" or "old-right" judgment. Activations functionally connected to AT and MD existed in regions with known anatomical connections to each nucleus as well as in a broader network of long-term memory regions. Sex differences were identified in a subset of these regions. A targeted region-of-interest analysis identified anti-correlated activity between MD and the hippocampus that was specific to females, which is consistent with findings in rodents. The current results suggest that AT and MD play key roles during spatial long-term memory and suggest that these functions may be sex-specific.

Two subregions of the human thalamus most often implicated in long-term memory are the anterior thalamic nucleus (AT) and mediodorsal nucleus (MD) (Aggleton & Brown, 1999). AT receives direct projections from the hippocampus along with other medial temporal lobe structures including the fornix and the mammillary bodies and is considered part of the "extended hippocampal system" (Aggleton et al., 1986; Aggleton & Brown, 1999). Abnormalities in AT have been identified in the prodromal phase of Alzheimer's disease and have led to evidence suggesting that amnesia presented in Alzheimer's patients is due to neurodegeneration of the Papez circuit (which includes AT, subregions of the medial temporal lobe, and the posterior cingulate cortex) (Papez, 1937), which underlines the importance of AT in episodic memory (Aggleton et al., 2016). Although AT is predominantly associated with the hippocampus (c.f. Aggleton & Brown, 1999; Papez, 1937), connections between AT and the prefrontal cortex via the anterior thalamic radiation have more recently been identified through the use of diffusion tensor imaging (Grodd et al., 2020). In one study, deep brain stimulation to AT produced a significant improvement in performance during a verbal recall test (Oh et al., 2012). In a separate study, unilateral exocytotic lesions to AT (with ipsilateral ablation of the inferiotemporal cortex/hippocampus in the opposite hemisphere) produced deficits in learning tasks that required integration of objects and spatial locations in the contralesional hemifield (Ridley et al., 2004). These results suggest AT is important in many forms of memory, including spatial memory.

Early speculation about the involvement of MD in long-term memory stems from Korsakoff patients (Benon et al., 1920), who have lesions to this thalamic nucleus and present with amnesia. However, as is often the case, lesions in many of these patients were not restricted to MD and often involved other thalamic nuclei, including AT (Harding et al., 2000). Based on the potential involvement of MD in long-term memory, anatomic connections to and from this nucleus have been mapped in rodents and non-human primates. These connections include dense reciprocal connections between MD and the prefrontal cortex, including the lateral, dorsal, and medial prefrontal cortices (Mitchel & Chakraborty, 2013). Lesions to MD in non-human primates

have been linked to deficits in spatial working memory (Isseroff et al., 1982) and object-in-place discrimination (Mitchell et al., 2007). Case studies of unilateral MD lesions in humans have linked this nucleus to both visual and verbal long-term memory in both recall and item recognition tasks (Edelstyn et al., 2012).

Functional connectivity analyses in humans have identified increased connectivity between MD with subregions of the medial temporal lobe. In one study, participants indicated their degree of familiarity (on a scale from 1 to 3) with previously studied faces, objects, or scenes (Kafkas et al., 2020). In addition to these familiarity ratings, participants also indicated whether they "recollected" the relevant stimulus or whether it was "new". Activity in MD was associated with familiarity strength across all three types of stimuli, suggesting that MD plays a role in material-general familiarity. Activity in AT, however, was consistently associated with recollection (versus strong familiarity) across all three types of stimuli, suggesting that AT plays a role in material-general recollection. In a subsequent functional connectivity analysis, MD was found to be functionally connected (i.e., a functionally connected activation produced by a connectivity analysis) with the perirhinal cortex and the parahippocampal cortex. Moreover, the degree of connectivity with these regions was found to vary with the strength of familiarity (with greater connectivity between these regions indicating a greater sense of subjective familiarity). In contrast, AT was not found to be functionally connected with any subregions of the medial temporal lobe. In another study, subjects studied face–scene pairs and, at retrieval, indicated which of three faces was originally paired with the scene of interest (Geier et al., 2020). Contrary to the results of Kafkas et al. (2020), Geier et al. (2020) did not find any difference in the strength of functional connectivity between MD or AT with subregions of the medial temporal lobe as a function of memory accuracy; however, MD did have greater connectivity to the hippocampus, perirhinal cortex, and parahippocampal cortex than AT.

AT and MD have been theorized to support parallel processes during declarative memory, where AT is thought to support the selection of memory contents and MD is thought to

support the selection of retrieval strategy (Van Der Werf et al., 2003). The roles that each nucleus plays in human memory, however, are still widely debated, with some suggesting that MD and AT work in parallel to support memory retrieval (Mitchell & Chakraborty, 2013) and others suggesting that each nucleus plays a separate role (such as familiarity versus recognition as discussed above; see Carlesimo et al., 2015; Kafkas et al., 2020; Geier et al., 2020).

Mounting evidence suggests that sex differences exist during long-term memory. Functional magnetic resonance imaging (fMRI) studies have reported sex differences in the patterns of brain activity across a variety of long-term memory types including object recognition (Canli et al., 2002; Frings et al., 2006; Banks et al., 2012; Spets & Slotnick, 2019), facial recognition (Armony & Sergerie, 2007; Loven et al., 2014), autobiographical memory (St. Jacques et al., 2011; Young et al., 2013), and spatial memory (Spets et al., 2019) (for a review see Spets & Slotnick, in press). A recent meta-analysis of sex differences in long-term memory studies identified greater activity in the lateral prefrontal cortex, visual cortex, parahippocampal cortex, and the cerebellum for males compared to females (Spets & Slotnick, in press). Greater activity for males than females has also been observed in the hippocampus during spatial memory (Spets et al., 2019), autobiographical memory (St. Jacques et al., 2011), and virtual maze navigation (Gron et al., 2000). One study that investigated the relationship between hippocampal lateralization and retrieval strategy during long-term memory found that greater activity in the left hippocampus was associated with a verbal retrieval strategy in females, whereas greater activity in the right hippocampus was associated with a visual retrieval strategy in males (Frings et al., 2006). Thus, females appear to be more likely to utilize a verbal strategy during long-term memory retrieval, whereas males are more likely to utilize a visual–spatial strategy during long-term memory and are more likely to engage the hippocampus (cf., Cahill, 2006).

Preliminary evidence from rodents suggests that the thalamus may modulate sex differences in hippocampal activity during long-term memory. Specifically, inactivation of the thalamic–hippocampal pathway rescued hippocampal activity and memory performance in

female mice, but not in male mice (Torromino et al., 2019). This suggests that the thalamus may inhibit the hippocampus during long-term memory in females, which may explain the comparatively greater hippocampal fMRI activity for males described above.

Although the functional connectivity of the human thalamus has been investigated during a resting-state task (Kumar et al., 2017) and during non-spatial long-term memory (Kafkas et al, 2020; Geier et al., 2020), to our knowledge, the functional connectivity of the thalamus during spatial long-term memory has not been investigated. The aims of the current investigation were twofold: (1) to identify functional connectivity with AT and MD during spatial long-term memory and (2) to identify whether sex differences exist in the patterns of whole-brain connectivity with each nucleus. We expected AT and MD to produce a network of connections that included regions with known anatomic connections with each nucleus as well as regions that support long-term memory such as the prefrontal cortex, parietal cortex, visual processing regions, hippocampus, and parahippocampal cortex (Slotnick, 2017a). Moreover, based on the findings in mice that suggest inhibition of the hippocampus by the thalamus in females (Torromino et al., 2019), we hypothesized that the magnitude of activity in the hippocampus and thalamus during spatial long-term memory would be anti-correlated in females (but not in males).

During encoding, abstract shapes were presented to the left and right of fixation. During retrieval, shapes were presented at fixation, and participants made an "old-left" or "old-right" judgment. We identified spatial memory hit-versus-miss activity in AT and MD and conducted a functional connectivity analysis, using activations in these two nuclei to determine which brain regions were functionally connected to the thalamus. To preview the results, activations functionally connected to AT and MD existed in regions with known anatomical connections to each nucleus as well as in a broader network of long-term memory regions, and sex differences were identified in a subset of these regions.

## Methods

The present study reanalyzed two spatial long-term memory studies, each comprised of two experiments (Slotnick & Schacter, 2004; Jeye et al., 2018). Essential methodological details are provided here (for full details, see Spets et al., 2019).

### *Participants*

There were 40 female and 18 male participants across the two studies. Eighteen females were selected from the 40 female participants to best match the spatial memory accuracy and variance of the 18 male participants. Eleven of the 18 females and males were drawn from Study 1 (Slotnick & Schacter, 2004) and the remaining females and males were drawn from Study 2 (Jeye et al., 2018). Critically, participants were matched on spatial memory accuracy and variance within each experiment such that female and male performance were matched within each experiment, and an equal number of females and males were drawn from each experiment.

### *Stimulus protocol and task*

Prior to the scanning session, each participant completed a behavioral training session. Participants also completed a single anatomic scan and a variable number of study/test runs. In Experiments 1 and 2, participants completed three study/test runs. In Experiments 3 and 4, participants completed either seven or eight study/test runs. During each study phase, abstract shapes were presented in pseudorandomized order to the left or right of a fixation cross for 2.5 s (shape construction details can be found in Slotnick & Schacter, 2004). Participants were instructed to remember each shape and its spatial location while maintaining fixation. Each shape was presented at fixation for 2.5–3.0 s during the test phase (a constant duration for each experiment), and participants made an "old-left" or "old-right" judgment followed by confidence judgment with their left hand (Figure 1). Spatial memory accuracy was calculated as the

percentage of correct spatial location identification contingent on correct old-item identification (chance = 50%). Latin square counterbalancing was used to assign shape sets across participants.

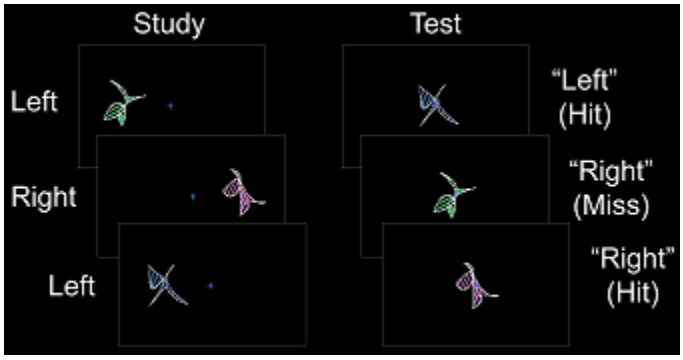


Figure 1. Stimulus and response protocol. During the study phase, abstract shapes were presented to the left or right of fixation. During the test phase, old shapes were presented at fixation and participants indicated whether each shape was previously on the "left" or "right".

*Image acquisition and analysis*

In Experiments 1 and 2, images were acquired using a 3-Tesla Siemens Allegra MRI scanner (Siemens, Erlangen, Germany) with a standard head coil. Anatomic data were acquired using a multiplanar rapidly acquired gradient echo (MPRAGE) sequence (TR = 30 m, TE = 3.3 m, 128 slices, 1 × 1 × 1.33 mm resolution). Functional data were acquired using a T2*-weighted echo-planar imaging sequence (TR = 2000 m, TE = 3.3 m, 64 × 64 acquisition matrix, 26–30 slices in Experiment 1 and 30 slices in Experiment 2, 4.5 mm isotropic resolution). In Experiments 3 and 4, image acquisition parameters were identical to those in Experiments 1 and 2 except that a 3-Tesla Trio scanner (Siemens, Erlangen, Germany) was used with a 32-channel head coil and that 33 slices and a 4 mm isotropic resolution were used to acquire the functional data.

A random-effect general linear model (GLM) analysis was conducted in SPM12 (Wellcome Trust Center for Neuroimaging, London, UK; https://www.fil.ion.ucl.ac.uk/spm/software/spm12/). Functional image preprocessing included slice-time correction, motion correction to the first volume of each run, and spatial normalization

to the Montreal Neurological Institute (MNI) template, which included resampling at 2 $mm^3$. Anatomic images were normalized to MNI space with 1 $mm^3$ resolution and then averaged across participants. The following event types were entered into the GLM: encoding of items in the left visual field, encoding of items in the right visual field, accurate retrieval of items in the left visual field (left-hits), accurate retrieval of items in the right visual field (right-hits), inaccurate retrieval of items in the left visual field (left-misses), and inaccurate retrieval of items in the right visual field (right-misses). To maximize power, events were collapsed across confidence responses. For each participant, activity associated with accurate spatial memory was isolated by contrasting spatial memory hits (i.e., left-hits and right-hits) and spatial memory misses (i.e., left-misses and right-misses).

AT and MD were identified as two regions of interest (ROIs) based on our a priori hypotheses regarding their functional connectivity with the whole brain as well as with the hippocampus during memory retrieval. Notably, the use of anatomically-defined (or in this case, guided) ROIs is permissible in functional connectivity studies given strong hypotheses regarding specific regions. To avoid selecting noisy voxels in the anatomic ROIs, task-related activity within these ROIs guided the selection of voxels that were used as seed regions for the subsequent connectivity analysis. Each participant's first-level model was entered into a second-level random-effect GLM analysis. The contrast of hits versus misses (inclusive of all participants) was first thresholded at $p < 0.01$ (without cluster extent correction) to identify whether there were any activations in AT or MD, which were to be used as a seed for the psychophysiological interaction analysis. There was one activation within the MD ROI at this threshold (see Section 3, Results). A more lenient threshold of $p < 0.05$ was then applied to identify activity within the AT ROI, and there was one activation in this region at this threshold (see Section 3, Results). The most significant voxel of activity within each of these regions was used to define the center of a 3 mm radius sphere for the generalized psychophysiological interaction (gPPI) analysis. Locations of AT and MD seeds were confirmed using a statistical

probabilistic atlas map created using a large sample of participants from the Human Connectome Project (for full methodological details on the construction of the atlas, see Najdenovska et al., 208 and Najdenovska et al., 2020).

Functional connectivity analyses were conducted using the gPPI toolbox (Mclaren et al., 2012; https://www.nitrc.org/projects/gppi) using the individual participant first-level models of hits versus misses. For each participant, whole-brain t-contrasts of AT and MD functional connectivity were created and entered into two separate second-level models, across participants, to determine voxels functionally connected to AT and MD. Second-level models were evaluated with independent t-test to determine whether there were any sex differences in the magnitude of connectivity. The gPPI toolbox first extracts time courses of activity from a specified seed region (in this case each AT and MD ROI). This creates a vector for each time point in the dataset for a particular seed region. This seed region vector acts as a regressor in a subsequent GLM analysis. Voxels in other brain regions that have a significant temporal correlation with the seed region are identified as regions that are functionally connected to the seed region (O'Reilly et al., 2012).

All functional connectivity contrasts were thresholded at $p < 0.01$, cluster extent corrected to $p < 0.05$. To compute the cluster extent threshold, we first computed the spatial autocorrelation for the gPPI contrast of hits versus misses for all participants in each experiment and employed the smallest spatial autocorrelation value (3 mm) across experiments. We conducted 10,000 Monte Carlo simulations based on the acquisition volume parameters, spatial autocorrelation, and the desired individual voxel and family *p*-value (Slotnick, 2017b). This resulted in a cluster extent of 24 voxels. This cluster extent was applied to all functional connectivity contrasts. Although it has been claimed that cluster extent threshold correction for multiple comparisons can have a relatively high false-positive rate (Eklund et al., 2016), this method of correction has been shown to produce acceptable false-positive rates (see Slotnick, 2017b and Slotnick, 2017c for a critical evaluation of Eklund et al., 2016). Images were imported

into MRIcroGL (nitrc.org), overlaid on the average anatomic for viewing purposes, and an exclusive white matter mask was employed.

In addition to the standard GLM analysis described above, a targeted/hypothesis-based ROI analysis was conducted to determine whether there was a negative relationship between the magnitude of hippocampal and thalamic activity. First, to identify whether there were any connected activations (i.e., a functionally connected activation produced by the gPPI analysis) in the hippocampus for females, we conducted the gPPI contrast of hits versus misses for MD and AT with only females. The MD contrast produced one connected activation in the hippocampus for females that was negative in magnitude ($p < 0.01$, cluster extent corrected to $p < 0.05$; see Section 3, Results). A 3 mm sphere was extracted around the peak of this hippocampal activation, which was used as the hippocampal ROI for the correlation analysis. For both ROIs (in MD and the hippocampus), beta weights were extracted for each participant using custom scripts written in MATLAB (MathWorks, Natick, MA, USA). To test for sex differences, the same procedure was repeated for males, using the hippocampal ROI identified for females. For each participant of a given sex, the average beta-weight value across spatial misses was subtracted from the average beta-weight value across spatial hits. This created a spatial hit − miss beta-weight value for each ROI for each participant. The spatial hit − miss beta-weight values in the hippocampus were plotted as a function of spatial hit − miss beta-weight values in MD for each of the sexes, and a Pearson correlation was conducted. A one-tailed test was conducted to determine whether our a priori hypothesis that the correlation between the beta-weight values in MD and the hippocampus would be anti-correlated in females (but not in males).

## Results

There was no significant difference between the spatial memory accuracy of the female participants (74.25 ± 0.94%, mean ± SE) and the male participants (73.42 ± 1.22%, $t(34) < 1$).

The group contrast of hits versus misses produced one activation in AT (Figure 2a; x = 6, y = −2, z = 2) and one activation in MD (Figure 2b; x = −6, y = −21, z = 6). A 3 mm sphere centered at each of these coordinates (containing six voxels) was used as the seed for whole-brain functional connectivity analyses with each nucleus (Figure 2). All of the voxels comprising each seed were contained within their respective nuclei (according to Najdenovska et al.'s (2018; 2020) anatomic atlas; see Methods, Section 2.3).

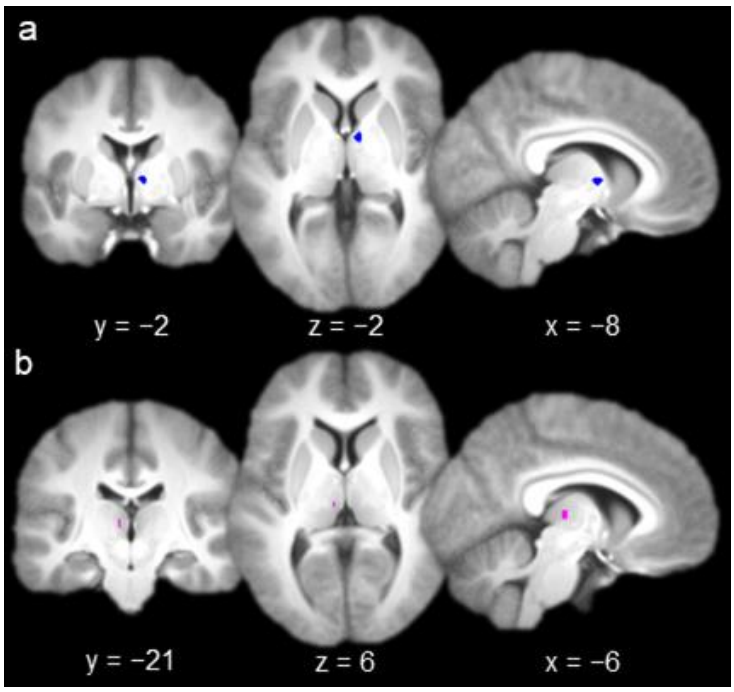


Figure 2. (a) Anterior thalamus seed (left, coronal slice; middle, axial slice; right, sagittal slice). (b) Mediodorsal thalamus seed.

Regions functionally connected to AT with positive magnitude (i.e., positive connectivity) included the left anterior prefrontal cortex, left medial prefrontal cortex, bilateral anterior cingulate gyrus, left inferior parietal cortex (angular gyrus), right lateral temporal cortex (superior temporal sulcus), and the left parahippocampal cortex (Table 1 and Figure 3, in red). There was a single activation of negative functional connectivity with AT in the left striate cortex (calcarine sulcus; Table 1 and Figure 3, in blue).

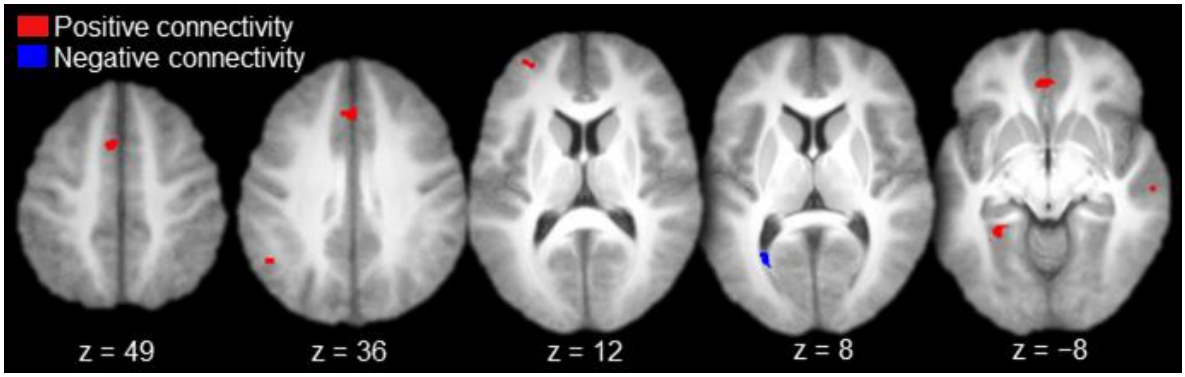


Figure 3. Anterior thalamus functional connectivity results (axial slices; key to the upper left).

The contrast between females and males produced one connected activation that spanned the right lateral prefrontal cortex (inferior frontal gyrus) and the right insula (Table 2 and Figure 4, in violet). The contrast between males and females produced one connected activation in the right striate/extrastriate cortex (calcarine sulcus/lingual gyrus; Table 2 and Figure 4, in cyan).

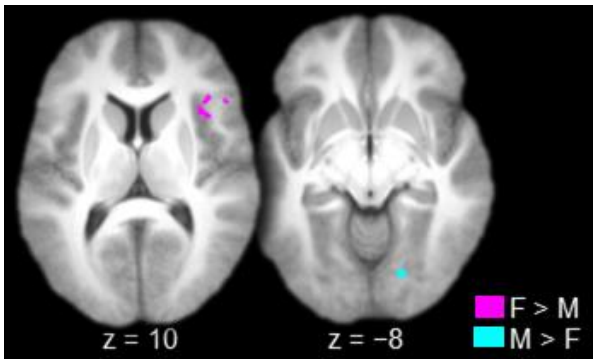


Figure 4. Regions connected to the anterior thalamus to a greater extent in females (F) than males (M; in violet) and males than females (in cyan; axial slices; key to the bottom right).

Regions with positive functional connectivity to MD included the bilateral lateral prefrontal cortex (right superior frontal sulcus and left precentral sulcus), left medial prefrontal cortex, left superior parietal cortex (intraparietal sulcus), bilateral insula, and the right putamen (Table 3 and Figure 5). There were no regions with negative functional connectivity to MD.

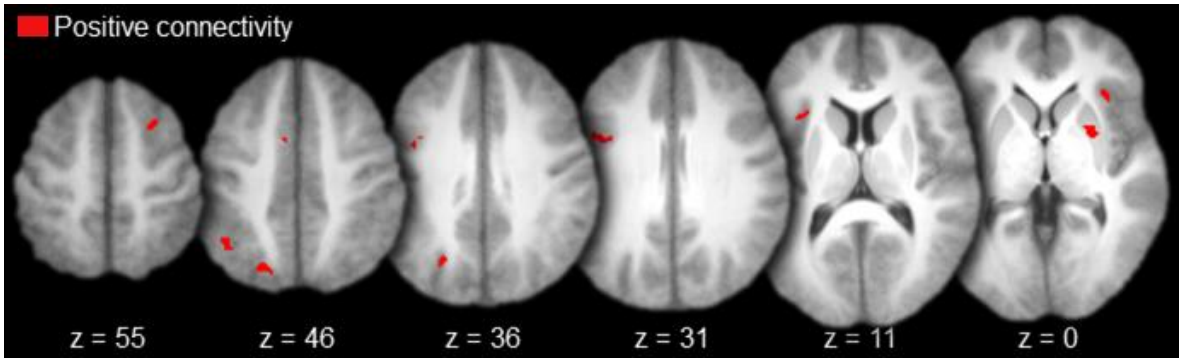


Figure 5. Mediodorsal thalamus functional connectivity results (axial slices; key to the upper left)

The contrast between females and males produced one connected activation in the left lateral temporal cortex (left superior temporal sulcus; Table 4 and Figure 6, in violet). The contrast between males and females produced many connected activations including the right inferior parietal cortex (supramarginal gyrus), bilateral superior parietal cortex (bilateral intraparietal sulcus and bilateral precuneus), and the bilateral posterior cingulate gyrus (Table 4 and Figure 6, in cyan).

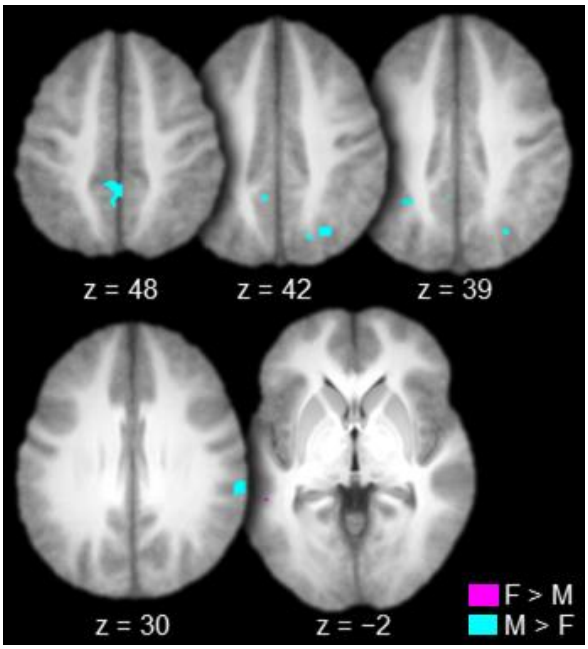


Figure 6. Regions functionally connected to the mediodorsal thalamus to a greater extent in females (F) than males (M, in violet) and males than females (in cyan; axial slices; key at the bottom).

Based on our specific hypothesis regarding thalamic inhibition of the hippocampus in females, we conducted a targeted ROI analysis to determine whether there was a negative correlation between activity in the thalamus and hippocampus for females during spatial long-term memory. In the MD gPPI contrast of hits versus misses for females, there was a single activation with negative functional connectivity with the CA1 region of the left hippocampus (x = −34, y = −32, z = −6; there were no other significant connected activations for females or males). A 3 mm sphere was extracted around the peak of this activation to create a hippocampal ROI (Figure 7a). Activity in this ROI was significantly negatively correlated with activity in MD for females ($r = -0.80$, Bonferonni corrected $p < 0.0005$) but not for males ($r = -0.25$, Bonferonni corrected $p > 0.20$; Figure 7b), and the female correlation was significantly more negative than the male correlation ($p < 0.01$). The identical pattern of results was obtained using a Spearman correlation. To determine whether the significant negative correlation for females was driven by the three participants with more extreme beta-weight values (i.e., hippocampal beta-weight values

below −2 or above 2), we conducted a follow-up correlation with these participants removed. With these three participants removed from the analysis, the negative correlation for females remained significant ($r = -0.51$, $p < 0.05$).

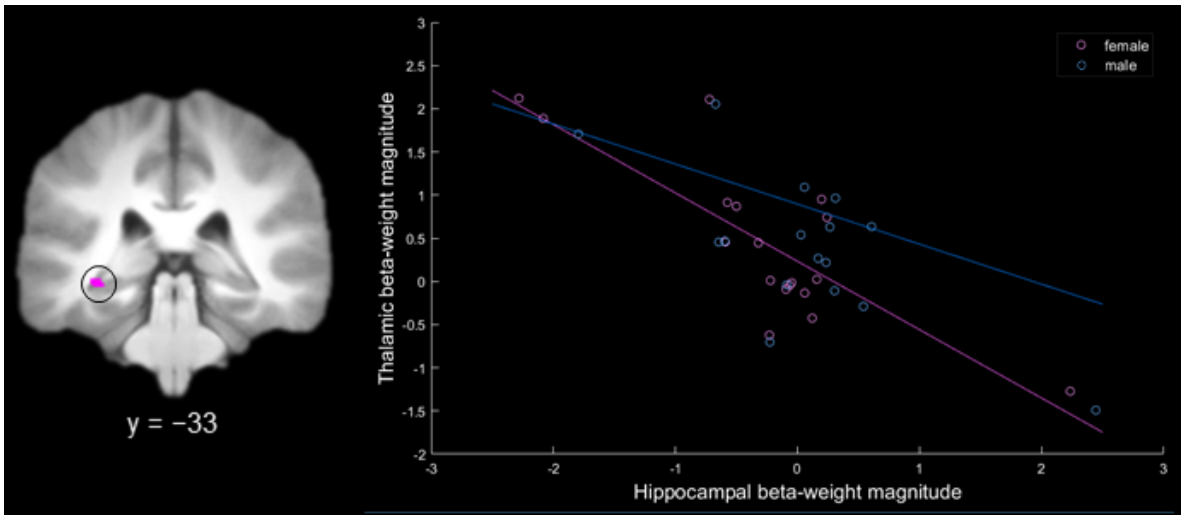


Figure 7. Left, hippocampal activation produced by the contrast female hits > misses (circled). Right, correlation between the hit minus miss beta-weight values for the hippocampal ROI activation and mediodorsal thalamic activation for females (in pink) and males (in blue; each point represents a participant; key at the upper right).

## Discussion

In the present study, we found that AT had positive functional connectivity with the prefrontal cortex (anterior prefrontal cortex and medial prefrontal cortex), the anterior cingulate cortex, inferior parietal cortex (angular gyrus), super temporal cortex (superior temporal sulcus), parahippocampal cortex, and the inferotemporal cortex (fusiform gyrus), along with negative connectivity with V1 (i.e., striate cortex). Many of the positively connected activations are known to share anatomic connections with AT, including the prefrontal cortex (Grodd et al., 2020) and regions of the Papez circuit, which is thought to support explicit memory (Vertes et al., 2001). Both the cingulate cortex and the parahippocampal cortex (two regions functionally connected to AT in the current study) are critical elements of the Papez circuit, as AT receives inputs from the

hippocampus and mamillary bodies and relays these inputs to the cingulate gyrus, parahippocampal gyrus, and back to the hippocampus (Shah et al., 2012).

The parahippocampal cortex has been linked to many cognitive processes, including visuospatial processing and episodic memory and is particularly important for processing item context (Slotnick, 2013). Parahippocampal cortex activation in the current study is most likely due to the nature of the spatial memory task, which requires an item (abstract shape) to be associated with a given context (spatial location). Although direct connections between AT and angular gyrus are not known to exist in humans, anatomical tracer studies in non-human primates have identified direct connections between the parahippocampal gyrus and the angular gyrus (Seghier, 2013). Moreover, connectivity between the parahippocampal cortex and the angular gyrus has been shown to increase during the identification of novel objects (Howard et al., 2013). Thus, activation of the angular gyrus in the connectivity map may be due to downstream activation from the other components of AT circuit (such as the parahippocampal cortex).

In the direct comparison of females and males, females produced a greater magnitude of connected activity with AT in the lateral prefrontal cortex (inferior frontal gyrus) and insula. The lateral prefrontal cortex is often implicated in spatial long-term memory and has been thought to aid in selection of memory contents either by inhibiting related items or selecting relevant targets (Slotnick, 2017a; Place et al., 2016). Males produced a greater magnitude of activity in the striate and extrastriate cortex (calcarine sulcus and lingual gyrus). Such activity in early visual processing regions can be assumed to reflect reactivation of early visual contents during memory retrieval (Slotnick & Schacter, 2006). Thus, males may rely on early visual processing during long-term memory construction than females. This is supported by recent evidence from a long-term memory meta-analysis that identified greater activity in visual regions for males compared to that in females across a variety of long-term memory types (Spets & Slotnick, in press). It has been hypothesized that AT is involved in the selection of memory contents (Van Der Werf et al., 2003). Thus, AT may aid in selecting memory contents in females by inhibiting unrelated or

closely related memory items, whereas AT may aid in selecting memory contents in males by selecting relevant visual memory components. The current findings suggest that this operation may involve coordination between AT and the lateral prefrontal cortex in females and between AT and the striate/extrastriate cortex in males.

MD had positive functional connectivity with the prefrontal cortex (superior frontal sulcus, precentral sulcus, and medial prefrontal cortex), superior parietal cortex (intraparietal sulcus), insula, and the putamen. MD shares dense reciprocal connections with the prefrontal cortex, thus, the current functional results are supported by a collection of anatomic evidence (Mitchell & Chakraborty, 2013). Although the intraparietal sulcus does not share any direct connections with MD, it is often activated in long-term memory processes, and this region may be related to sustained visual attention (Thakral & Slotnick, 2009). In the current task, the intraparietal sulcus likely mediates attention to the relevant aspects of a memory. MD has recently been shown to amplify prefrontal cortex connectivity in rodents, effectively sustaining attentional control (Schmitt et al., 2017). Thus, MD may play a role in sustaining attention in humans as well via connections with the prefrontal cortex and intraparietal sulcus. This is a topic of future research.

In the direct comparison of females and males, females produced a greater magnitude of connected activity with MD in the superior temporal cortex (superior temporal sulcus). The left superior temporal cortex has been associated with language processing (Price, 2000). It may be that during spatial long-term memory, females evoke a verbal retrieval strategy, which involves activity in the superior temporal cortex. This hypothesis is in line with literature that suggests that females utilize verbal memory strategies to a greater extent than males do (Cahill, 2006; Frings et al., 2006; Spets et al., 2019). Males produced a greater magnitude of activity in the inferior parietal cortex (supramarginal gyrus), superior parietal cortex (intraparietal sulcus and precuneus), and the posterior cingulate gyrus. A greater magnitude of activity in the intraparietal sulcus for males may suggest greater attention to memory contents compared to that in females.

Overall, males produced a greater number of connected activations with MD relative to females. Thus, outside of specific hypotheses regarding the activation of particular brain regions, it may be that males produce overall greater activity during spatial long-term memory compared to females to achieve the same behavioral result. The "neural efficiency hypothesis," is often cited in sex difference studies of long-term memory to potentially explain greater levels of neural activity in males compared to that in females (for a review, see Spets & Slotnick, in press). Although many of the regions differentially connected for females and males do not share direct connections with MD, it is possible that these are regulated secondarily by other regions directly connected to this thalamic nucleus.

Recent evidence in rodents has identified that inactivation of the thalamic–hippocampal pathway can rescue hippocampal activity and memory performance in female (but not in male) mice (Torromino et al., 2019). Based on this evidence, we hypothesized that activity in the thalamus would be anti-correlated with activity in the hippocampus for females, but not for males, which is what was observed. These results suggest that MD may play an inhibitory role in regulating hippocampal activation during spatial long-term memory that is specific to females. The hippocampal activation was localized to the CA1 subregion of the hippocampus (Yang et al., 2008; Slotnick, 2017a), which has previously been associated with autobiographical memory (a cognitive process closely related to spatial memory). Since MD does not share any direct connections with the hippocampus, this inhibition may take place via a secondary structure, such as the prefrontal cortex (Place et al., 2016). Despite the lack of direct connections, functional connectivity between MD and subregions of the medial temporal lobe have previously been reported during long-term memory (Kafkas et al., 2020), including with the hippocampus (Geier et al., 2020). The current results provide evidence that MD regulates hippocampal activation in a manner that is specific to females. The relationship between MD and hippocampal inactivation may explain why females often employ verbal strategies in tasks that are not necessarily verbal in nature (Spets et al., 2019). Of course, as we cannot assess causality in the current study, it may

also be the case that hippocampal inhibition is a consequence of the employment of verbal strategies in females. This hippocampal inhibition may also explain why the magnitude of hippocampal activity during long-term memory is sometimes greater in males than in females (St. Jacques et al., 2011; Spets et al., 2019) and why females more often employ verbal strategies (Cahill, 2006; Frings et al., 2006). More generally, these results support the hypothesis that MD aids in the selection of a memory retrieval strategy (Van Der Werf et al., 2003).

The current study has some limitations. First, data were collected on two different MRI scanners, which would be expected to increase variance and yield null results. Of relevance, a recent study investigated scanner reliability during resting-state scans collected from three different scanners (Siemens Trio 3T, GE 3T HDx, and GE 3T discovery) that were analyzed using three different functional connectivity methods (seed based, intrinsic connectivity distribution, and matrix connectivity) (Noble et al., 2017). There were no major variability effects in the results of the connectivity analyses based on the scanner location (i.e., site), scanner manufacturer, or time of day the scans were collected. Moreover, the effect of subject was found to be much greater than any of the other measured effects. It was noted that when using a single 5 min scan as a sample, the reliability in connectivity measures was poor; however, when the duration of the scan was increased to 25 min, the reliability increased. It was suggested that when collecting data from multiple scanners, a minimum scan time of 25 min should be employed, and that this is sufficient to aggregate functional connectivity data across multiple scanners. As the average scan time in the current study was 42.25 min, the results of the current study are unlikely to be affected by differences across the two scanners. Noble et al. (2017) also found that seed-based connectivity approaches, which the current analysis employed, are more reliable than other types of connectivity approaches. It should also be noted that between-scanner variability would be expected to increase variance and produce null results. Since significant (rather than null) results were observed in the present study, such variability was not a major issue. That said, acquiring data on two different scanners was not ideal, and this is a limitation of the current

study. Second, the correlation analysis contained 18 participants per group. It would of course have been preferable for such a correlation analyses to have a larger *N* (Yarkoni, 2009; Button et al., 2013). It is not uncommon, however, for correlation analyses in long-term memory fMRI studies to have sample sizes comparable to that of the present study (Wang et al., 2010; Wang et al., 2013; Tompary et al., 2016; Tambini et al., 2017; Roberts et al., 2017; Shanahan et al., 2018). Nevertheless, the correlation results in the current study should be viewed as preliminary, and future studies should employ larger sample sizes.

## Conclusions

The current results contribute to a growing literature supporting the role of the thalamus in cognition. Functional connectivity was identified between AT and MD and many regions associated with memory including the prefrontal cortex, parietal cortex, visual processing regions, hippocampus, and the parahippocampal cortex. Many of the regions functionally connected to AT and MD shared direct connections supported by anatomic evidence, while others may be related to these nuclei via secondary connections. Moreover, we identified that sex differences exist in functional connectivity between MD and the hippocampus, with greater magnitudes of activity in MD relating to lower magnitudes of activity in the hippocampus for females (but not for males). More broadly, the present results point to an important role of the thalamus in human memory, which to some extent is modulated by sex. These sex differences argue against the common practice of collapsing across sex in cognitive neuroscience studies.

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## Tables

**Table 1.** Regions functionally connected to the anterior thalamus during spatial memory hits > misses.

| Region | BA | x | y | z | *k* |
|---|---|---|---|---|---|
| *All participants* | | | | | |
| *Positive activations* | | | | | |
| L. Anterior Prefrontal Cortex | 10 | −32 | 51 | 12 | 31 |
| L. Medial Prefrontal Cortex | 6 | −5 | 11 | 48 | 50 |
| Bilateral Anterior Cingulate Gyrus | 32 | 0 | 24 | 38 | 30 |
| Bilateral Anterior Cingulate Gyrus | 32 | 0 | 39 | −10 | 32 |
| L. Angular Gyrus | 39 | −44 | −54 | 34 | 51 |
| R. Superior Temporal Sulcus | 21/22 | 60 | −21 | −7 | 29 |
| L. Parahippocampal Cortex | 19/37 | −27 | −46 | −7 | 27 |
| *Negative activations* | | | | | |
| L. Calcarine Sulcus | 17 | −26 | −62 | 8 | 30 |

BA refers to Brodmann area and MNI coordinate (x, y, z) refers to the center of each activation.

**Table 2.** Regions differentially connected to the anterior thalamus between females and males during spatial memory hits > misses.

| Region | BA | x | y | z | *k* |
|---|---|---|---|---|---|
| *Female (Hits > Misses) > Male (Hits > Misses)* | | | | | |
| *Positive activations* | | | | | |
| R. Inferior Frontal Gyrus/Insula | 44/45 | 39 | 25 | 7 | 74 |
| *Male (Hits > Misses) > Female (Hits > Misses)* | | | | | |
| *Positive activations* | | | | | |
| R. Lingual Gyrus | 18 | 19 | −76 | −5 | 32 |

BA refers to Brodmann area and MNI coordinate (x, y, z) refers to the center of each activation.

**Table 3.** Regions functionally connected to the mediodorsal thalamus during spatial memory hits > misses.

| Region | BA | x | y | z | *k* |
|---|---|---|---|---|---|
| *All participants* | | | | | |
| *Positive activations* | | | | | |
| R. Superior Frontal Sulcus | 6/8 | 27 | 12 | 53 | 29 |
| L. Precentral Sulcus | 6 | −37 | 3 | 32 | 48 |
| L. Medial Prefrontal Cortex | 6 | −7 | 8 | 50 | 37 |
| L. Intraparietal Sulcus | 19/39 | −19 | −68 | 45 | 50 |
| L. Intraparietal Sulcus | 7/40 | −39 | −55 | 45 | 27 |
| L. Insula | − | −31 | 16 | 4 | 32 |
| R. Insula | − | 34 | 24 | −2 | 43 |
| R. Putamen | − | 27 | 3 | 0 | 41 |
| *Negative activations* | | | | | |
| No activations | | | | | |

BA refers to Brodmann area and MNI coordinate (x, y, z) refers to the center of each activation.

**Table 4.** Regions differentially connected to the mediodorsal thalamus between females and males during spatial memory hits > misses.

| Region | BA | x | y | z | *k* |
|---|---|---|---|---|---|
| *Female (Hits > Misses) > Male (Hits > Misses)* | | | | | |
| *Positive activations* | | | | | |
| L. Superior Temporal Sulcus | 22 | −48 | −41 | −2 | 31 |
| *Male (Hits > Misses) > Female (Hits > Misses)* | | | | | |
| *Positive activations* | | | | | |
| R. Supramarginal Gyrus | 40 | 61 | −31 | 29 | 40 |
| L. Intraparietal Sulcus | 7/40 | −28 | −48 | 40 | 24 |
| R. Intraparietal Sulcus | 19/39 | 28 | −67 | 42 | 37 |
| Bilateral Precuneus/Post. Cingulate Gyrus | 7/31 | 0 | −42 | 48 | 55 |

BA refers to Brodmann area and MNI coordinate (x, y, z) refers to the center of each activation.

# PART 3

## USING MULTIVOXEL PATTERN ANALYSIS TO PREDICT SEX

## CHAPTER 8

Sex is predicted by spatial memory multivariate activation patterns
Dylan S. Spets and Scott D. Slotnick

Under review

Whether or not sex differences exist in the brain is a topic of debate. The present spatial long-term memory fMRI study is the first to classify sex based on task-related patterns of activity (using multivoxel pattern analysis). Moreover, using a novel approach, we identified voxels that were most diagnostic for predicting sex. The current results suggest that the brain processes mediating spatial long-term memory are sexually dimorphic. The present findings add to the growing body of evidence that there are functional sex differences in the brain and, more broadly, question the widespread practice of collapsing across sex in the field of cognitive neuroscience.

Sex differences exist in brain anatomy and neurochemistry (Cahill, 2006). For example, corrected for brain size, females have higher gray matter-to-white matter ratios, whereas males have larger ventricle volumes (Goldstein et al., 2001). Despite differences in anatomy and neurochemistry, it is still debated whether or not sexual dimorphism exists in the brain (Joel et al., 2015; Cahill, 2019). To illustrate, Joel et al. (2015) defined female characteristics as the largest gray matter volumes in 33% of females and male characteristics as the largest gray matter volumes in 33% of males. Far more brains were classified as having characteristics of both sexes rather than characteristics of only one sex, which led Joel et al. to conclude that female brains and male brains are not sexually dimorphic (i.e., average female brains and male brains are indistinguishable; Joel, 2011; Joel et al., 2015). However, Joel et al.'s findings hinge on their particular, potentially biased, definitions and method of analysis (Cahill, 2019).

Multivariate prediction analyses can provide an unbiased method to classify sex. In the field of cognitive neuroscience, such analyses are typically conducted by training a classifier to identify the relationship between sex and a set of brain features (e.g., voxel morphometry, functional connectivity) on a subset of training data. Next, the classifier is tested on new data and identifies the sex of each participant based on learned associations from the training phase. Classification accuracy is defined as the proportion of times the classifier was successful (i.e., correctly predicted the sex of each participant in the test set). When Joel et al.'s (2015) anatomic data was re-analyzed by separate groups of researchers, classifiers were able to predict sex approximately 80% of the time (Rosenblatt, 2016; Del Giudice et al., 2016). Another group of researchers conducted a similar prediction analysis on differences in cortical thickness and subcortical volume using a separate dataset and achieved a classification accuracy of 70% (Chekroud et al., 2016). Two other studies classified sex based on patterns of resting-state functional connectivity and achieved similar classification accuracies (Zhang et al., 2017; Weis et al., 2019). These studies provide compelling evidence that female brains and male brains can be distinguished well above chance.

Although sex differences have been reported in functional magnetic resonance imaging (fMRI) studies across a variety of cognitive tasks, including long-term memory (for a review, see Spets & Slotnick, in press), no studies have employed multivariate sex classification using task-related data. Recently, we provided evidence for robust sex differences in the brain during spatial long-term memory (Spets et al., 2019). For both sexes, spatial memory was associated with activity in regions commonly associated with visual long-term memory, such as the dorsolateral prefrontal cortex and the parietal cortex; however, the activations were almost completely distinct between the sexes. Sex-specific activity for males was identified in the left hippocampus, bilateral middle occipital gyrus, right collateral sulcus, left fusiform gyrus, right caudate, and bilateral cerebellum. Sex-specific activity for females was identified in the right superior parietal lobule and marginally significant activity was identified in language processing cortex.

In the present study, we reanalyzed data from Spets et al. (2019) to assess whether sex could be classified using multivoxel pattern analysis (MVPA) at above-chance levels. Using task-related data, we developed a novel sex-classification approach by creating functional regions of interest (ROIs), which eliminated the vast majority of task-irrelevant voxels in the analysis. To determine which voxels were most predicative (i.e., diagnostic) of sex, we conducted a spotlight analysis within the functional ROIs. Based on our previous fMRI general linear model (GLM; Spets et al., 2019) and meta-analysis (Spets et al., in press) results, we predicted female diagnostic voxels would be located in superior parietal lobule and language processing cortex and male diagnostic voxels would be located in visual processing regions and the cerebellum.

## Methods

The present study reanalyzed data from two spatial long-term memory studies (Slotnick & Schacter, 2004; Jeye et al., 2018). Each study was comprised of two experiments (below, the two experiments in Slotnick & Schacter, 2004, will be referred to as Experiments 1 and 2, and the two experiments in Jeye et al., 2018, will be referred to as Experiments 3 and 4). Essential

methodological details are provided here (full details can be found in Spets et al., 2019).

*Participants*

Across the four experiments, there were 40 female and 18 male participants. Eighteen females were selected to best match the spatial memory accuracy and variance of the eighteen males. Participants were matched within each experiment such that female and male performance was equated within each experiment as well as across all experiments. The age range across all thirty-six participants included in the analysis was 18–29 years. Informed consent was provided by each participant before the experiment commenced.

*Stimuli protocol and task*

Each participant completed a behavioral training session prior to the fMRI session. During fMRI, in Experiments 1, 2, and 3/4, participants completed six, three and either seven or eight study/test runs, respectively. During each study phase, abstract shapes were presented to the left or right of fixation in a pseudorandom order for 2.5 s (shape construction details can be found in Slotnick & Scacter, 2004). During each test phase, shapes were presented at fixation for 2.5−3.0 s and participants made "old-left" or "old-right" judgments (Fig. 1). Spatial location accuracy was computed as the percentage of correct spatial location identification contingent on correct old item identification (chance = 50%). Shapes sets were counterbalanced across participants according to Latin square design.

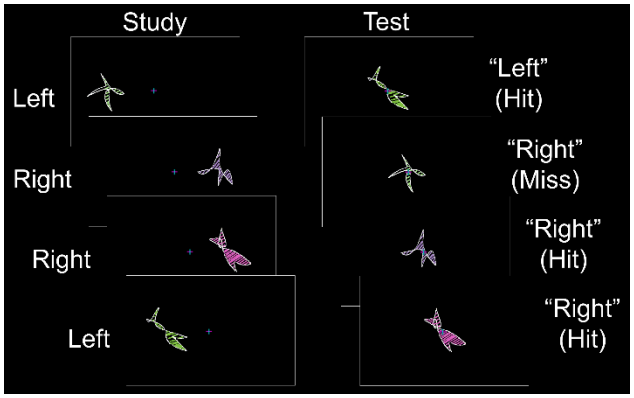


Figure 1. Stimulus and response protocol. Left, during the study phase, abstract shapes were presented to the left or right of fixation. Right, during the test phase, old shapes were presented at fixation and participants indicated whether the shapes were previously on the "left" or "right" (example responses are shown to the right with corresponding response types shown in parentheses).

*Image acquisition and analysis*

In Experiments 1 and 2, images were acquired using a 3-Tesla Allegra MRI scanner (Siemens, Erlagen, Germany) using a standard head coil. Anatomic data were acquired using a multiplanar rapidly acquired gradient echo (MPRAGE) sequence (TR = 30 ms, TE = 3.3 ms, 128 slices, 1 x 1 x 1.33 mm resolution). Functional data were acquired using a T2*-weighted echo planar imaging sequence (TR = 2000 ms, TE = 3.3 ms, 64 x 64 acquisition matrix, 26-30 slices in Experiment 1 and 30 slices in Experiment 2). The image acquisition parameters in Experiments 3 and 4 were identical to those of Experiments 1 and 2 except that a 3-Tesla Trio scanner (Siemens, Erlangen, Germany) was used with a 32-channel head coil and functional data had 33 slices with 4 mm isotropic resolution.

Analyses were conducted with BrainVoyager (Brain Innovation, Maastricht, Netherlands) and custom scripts written in MATLAB (MathWorks, Natick, MA). Following standard pre-processing (including slice-time correction, motion correction, and spatial normalization to Talairach space), individual-participant first-level models were created. Accurate spatial memory was isolated for each participant by contrasting spatial memory hits versus spatial memory misses (i.e., old-left-"left", responding "left" to an item previously presented in the left visual field, and

old-right-“right” versus old-left-“right” and old-right-“left”).

An MVPA leave-one-out classification procedure was conducted (following Haxby et al., 2001). For each pair of left-out participants (1 female, 1 male), an independent functional ROI based on the remaining participants (17 females, 17 males) was defined as the union of activity produced from the contrasts of female spatial memory hits versus misses and male spatial memory hits versus misses. Each contrast was thresholded at $p < .001$ and the union of activity was cluster-extent corrected for multiple comparisons to $p < .01$. A cluster extent threshold of 10 voxels based on 10,000 Monte Carlo simulations was enforced, computed using the functional volume acquisition parameters and a spatial autocorrelation value of 3.72 mm (computed by contrasting female hits versus male hits to estimate the null activation volume). We employed the largest spatial autocorrelation value across experiments (as larger values can be attributed to spatial autocorrelation due to true activations rather than noise, this cluster threshold can be considered conservative). A female template was created from the remaining 17 female participants by averaging the response magnitude at each voxel and a male template was created from the remaining 17 male participants by averaging the response magnitude at each voxel (i.e., a leave-one-out procedure was employed). The left-out female (i.e., female test) and left-out male (i.e., male test) patterns were then classified as female or male depending on whether they were most highly correlated with the female or male template. That is, if the test pattern was more correlated with the template pattern of the same sex, the classification for that test pattern was recorded as ‘correct’, while if the test pattern was more correlated with the template pattern of the opposite sex, the classification for that test pattern was recorded as ‘incorrect’. This procedure was repeated for all participant combinations. That is, the left-out participant was classified based on the template of the remaining participants of the same sex as well as the 17 templates of the other sex (e.g., for left-out female 1, females 2–17, as well as males 2–18, males 1 and 3–18, males 1–2 and 4 –18, and so on). If, across these individual tests, the participant’s sex was correctly classified more than 50% of the time, that participant’s classification accuracy was

recorded as ‘correct’ in a winner-take-all strategy. The average classification accuracy was then taken across all participants to determine the overall classification accuracy.

We next determined which voxels were most predicative/diagnostic of sex. Following normalization of all functional and anatomic data to MNI space, for each left out participant, we recorded the average difference of the within-sex and between-sex correlations for each voxel (within the corresponding functional ROI). One-tailed t-tests ($p < .05$) were employed to determine which voxels significantly predicted sex, and these diagnostic voxels were projected onto the average anatomic volume (an inclusive grey matter mask was applied for viewing purposes).

## Results

As expected, spatial memory performance was matched for females (74.25 ± 0.94%) and males (73.42 ± 1.22%, $t(34) < 1$, chance = 50%). The average functional ROI size was 481.04 voxels.

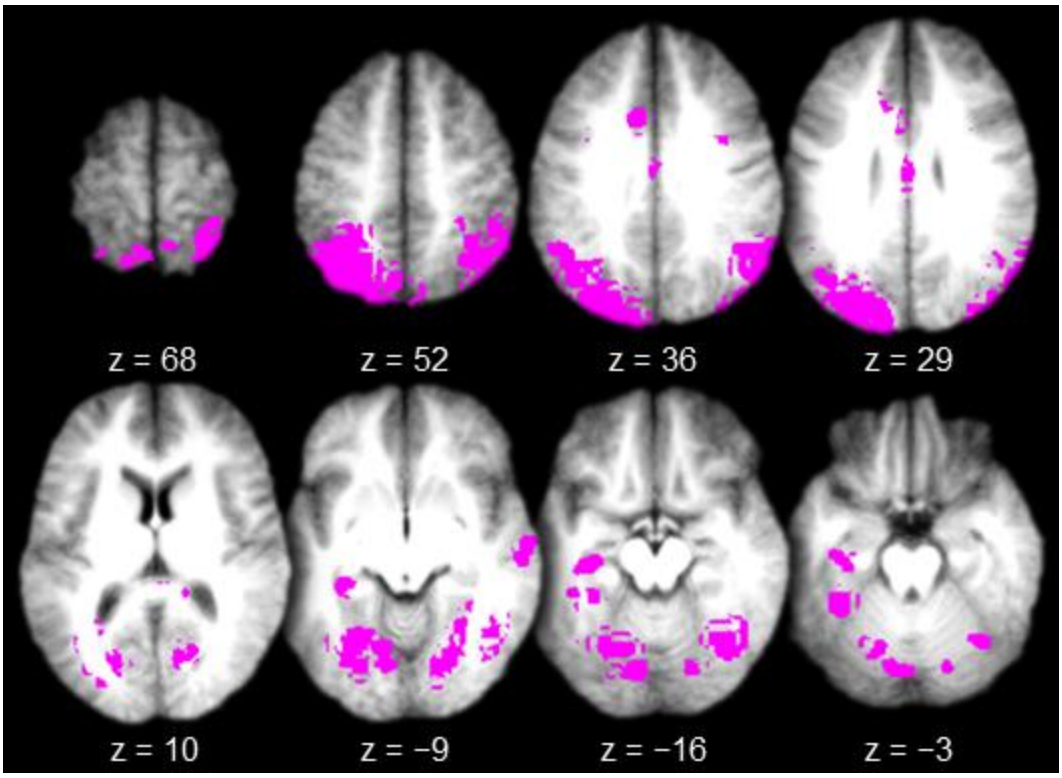


Figure 2. Functionally-defined (spatial memory) ROIs (in magenta; axial slices with z-coordinates).

The union of all functional ROIs spanned a number of long-term memory regions including, but not limited to, the prefrontal cortex, the parietal cortex, visual processing regions, and the hippocampus (Slotnick, 2017; Fig. 2). For the majority of participants, the average correlation was higher for within-sex test-template comparisons than between-sex test-template comparisons (Fig. 3A). Across all participants, the average classification accuracy was significantly above chance (63.89 ± 8.12%, $t(35) = 1.71$, $p < .05$, chance = 50%; Fig 3B). There was no significant difference between the classification accuracy for females (61.11 ± 11.82%) and males (66.67 ± 11.43%, $t(34) < 1$).

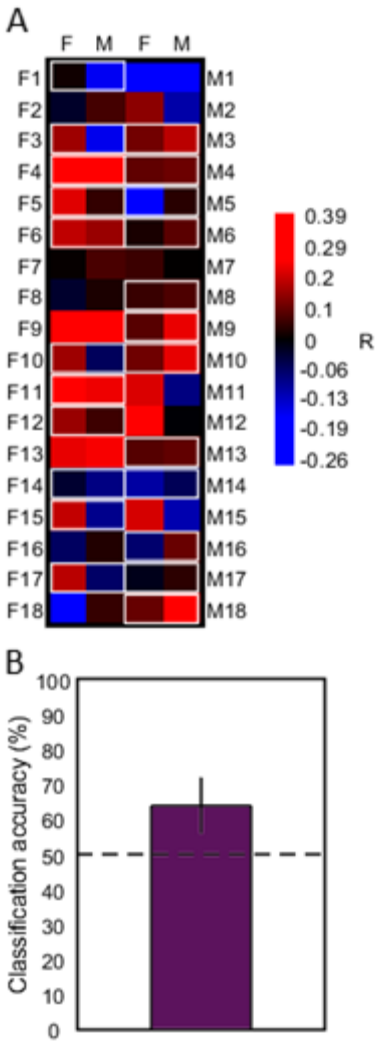


Figure 3. MVPA classification results. (A) Average correlation between each subject (F1-18 on the left y-axis and M1-18 on the right y-axis) and all combinations of the female (F) and male (M) templates (x-axis). White boxes indicate a participant was classified correctly. (B) Average classification accuracy (± 1 standard error).

There were many regions diagnostic of females and males. For females, diagnostic voxels were located in bilateral superior parietal lobule, bilateral intraparietal sulcus, right precuneus, bilateral angular gyrus, right posterior cingulate cortex, right superior temporal sulcus, left fusiform gyrus, left parieto-occipital sulcus, and left superior occipital gyrus (Table 1 and Fig. 4 in red/yellow). For males, diagnostic voxels were located in left superior parietal lobule, left precuenus, right angular gyrus, left anterior cingulate cortex, right inferior temporal sulcus, left

cuneus, left superior occipital gyrus, right middle occipital gyrus, and left cerebellum (Table 1 and Fig. 4 in blue/green).

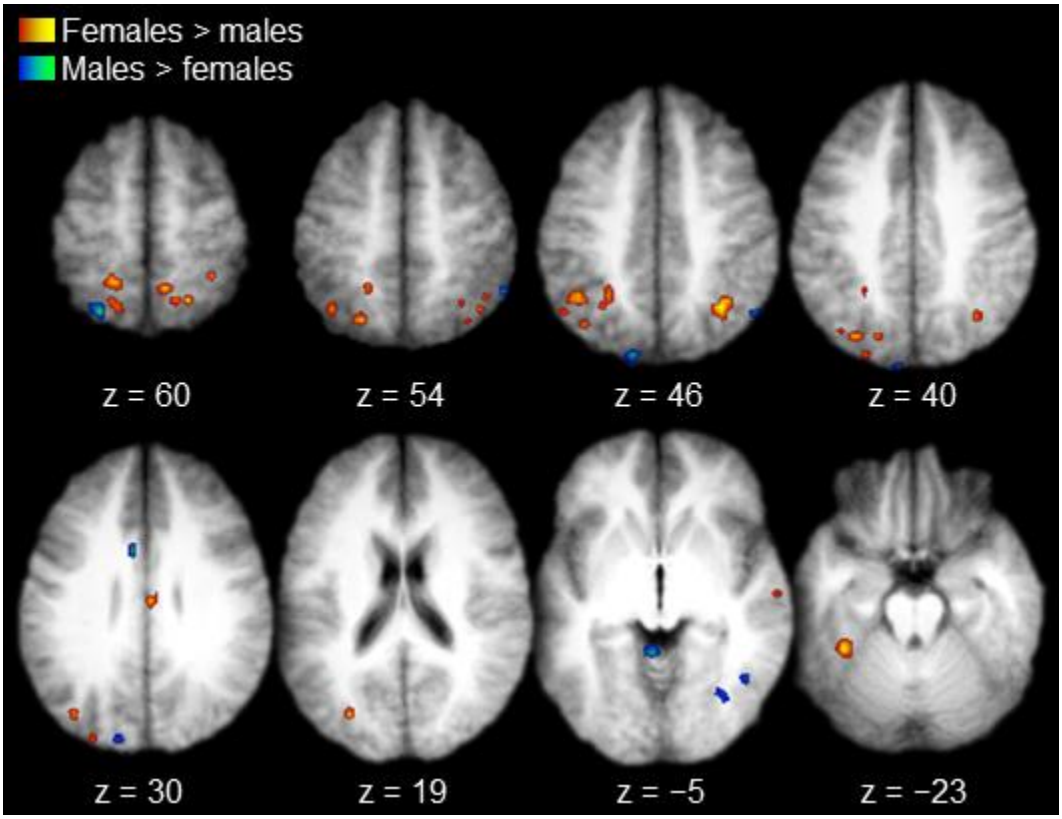


Figure 4. Diagnostic voxels for females and males (key at the top left, axial slices with z-coordinates).

## Discussion

In the present study, MVPA was able to classify sex at above-chance levels. These results provide evidence that patterns of brain activity during spatial long-term memory are different for females and males. This is the first time, to our knowledge, that sex has been successfully classified using task-related data, as past studies have classified sex based on brain structure (Chekroud et al., 2016; Del Giudice et al., 2016; Rosenblatt, 2016) or resting-state functional connectivity (Zhang et al., 2015; Weis et al., 2019). The current classification accuracy is similar to previous classification accuracies reported in structural (Chekroud et al., 2016) and resting-

state functional connectivity (Weis et al., 2019) studies.

The voxels that were diagnostic for sex identified in the current study replicated and extended our previous GLM (Spets et al., 2019) and meta-analysis (Spets & Slotnick, in press) results. In the current study and in Spets et al. (2019), we identified sex-specific activity for females in the right superior parietal lobule and sex-specific activity for males in the right middle occipital gyrus and left cerebellum. Male greater than female activity within visual processing regions and the cerebellum were also observed in our meta-analysis (Spets & Slotnick, in press).

In support of our hypothesis, greater activity in the superior parietal lobule for females may reflect a retrieval strategy requiring shifts in attention (Yantis et al., 2002; Thakral & Slotnick, 2013; Spets et al., 2019). It may be that when a shape is presented at the center of the screen during retrieval, females are more likely to shift their attention to the left and/or right to determine whether the shape was presented in a previous spatial location. Also in support of our hypothesis, female-diagnostic voxels were identified in the right angular gyrus (i.e., the right hemisphere homologue of Wernicke's area; Price et al., 2000). This finding is supported by previous evidence that females tend to utilize verbal retrieval strategies to a greater extent than males (Frings et al., 2006; Herlitz & Rehnman, 2008; Spets et al., 2019; Spets & Slotnick, 2019). Past findings, however, have not yet identified greater use of right hemisphere language areas, as was found here. The use of the right hemisphere homologue of Wernicke's area may be related to the nature of the spatial memory task employed.

Although there were sex-diagnostic voxels for males in the right middle occipital gyrus (proving support for our hypothesis in this specific region), females produced an overall greater number of visual activations than males (6 activations versus 4 activations, respectively) including the left fusiform gyrus, left parieto-occiptal sulcus, and left superior occipital gyrus (which was counter to our hypothesis based on our previous GLM results). Of importance, although we identified greater magnitudes of activity in visual processing regions for males (including right middle occipital gyrus) in Spets et al. (2019), we also identified that the extent of

visual processing activity was greater for females than males (i.e., there were more active voxels across visual processing regions for females). The use of MVPA in the current investigation may explain the greater number of female than male diagnostic voxels in visual processing regions, as MVPA is able to capture lower, but consistent, response magnitudes across voxels. These smaller magnitude–but meaningful–differences, may have been overwhelmed by noise in the GLM analysis (Weaverdyck et al., 2020). A greater extent of visual processing activity in the present study for females may reflect more vivid recollection of retrieved information (Andreano & Cahill, 2009). Greater activity in visual processing regions has also been reported for females in the left fusiform cortex during a picture naming task (Garn et al., 2009). Sex differences have also been identified in multiple visual event related potential components. One study investigating sex differences in face perception identified a larger N170 component amplitude (which has previously been linked to face perception) for females compared to males (Sun et al., 2010). In addition, a spatial attention study identified greater P1 and N1 amplitudes for females compared to males, indicating greater extrastriate attention effects in females (Feng et al., 2011).

It is notable that the current MVPA prediction analysis identified a greater number of sex-specific activations than the GLM analysis we employed in Spets et al. (2019; 40 activations versus 10 activations, respectively). This suggests MVPA may be more sensitive than GLM analysis at identifying sex differences in the brain. This may be because GLM analyses averages across and wash out reliable patterns that are differential between groups, which can be captured using MVPA (Weaverdyck et al., 2020).

Sex differences were identified in a wide range of brain regions in the current study (see Table 1). Moreover, sex could be classified based on functional patterns of spatial long-term memory activity. Together, these results suggest that the brain regions involved in spatial long-term memory are sex-specific. As there is mounting evidence that sex differences in brain structure and function exist (Andreano & Cahill, 2009; Chekroud et al., 2016; Del Giudice et al., 2016; Rosenblatt, 2016; Zhang et al., 2018; Spets et al., 2019; Weis et al., 2019; for a review, see

Spets & Slotnick, 2020), collapsing across sex, which is widely done in the field of cognitive neuroscience is questionable. By continuing to collapse across sex in cognitive neuroscience studies, we may be missing vital information that could ultimately inform the way we understand the human brain and/or cognitive processing. Failure to treat sex as a factor could lead to false conclusions because results were driven by one sex. One study, for example, investigated the effects of stress on memory for pictures and found that post-learning stress enhanced memory for men but not for women (Yonelinas et al. 2011). Importantly, if sex had not considered, their result would have led to incorrect conclusions about the overall effect of stress on memory (cf., Cahill, 2012).

The National Institute of Health (NIH) has recently developed policies to ensure preclinical research investigates, or at least accounts for, differences between the sexes (Arnegard et al., 2020). These critical policies follow decades of research in which (animal and human) females have been underrepresented in biomedical and preclinical research (Beery & Zucker, 2011; Berlin & Ellenberg, 2016). At this point in time, there is compelling evidence that sex should be treated as a factor in all neuroscience research (Cahill, 2006, 2012; Andreano & Cahill, 2009).

## Conclusion

The current spatial memory study adds to a growing body of evidence indicating there are significant sex differences in the human brain. This is the first study, to our knowledge, that successfully classified sex using task-related patterns of activity. Such multivariate classification methods provide an unbiased approach to identify whether or not sex differences exist in the brain. Moreover, we were able to identify which brain regions were diagnostic of sex. The results of these two analyses suggest that the brain regions involved in spatial long-term memory are sex-specific. More broadly, the current and previous results question the widespread practice of collapsing across sex in the field of cognitive neuroscience.

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## Table

Table 1. Sex predictive activations

| Region<br>BA | x | y | z |
|---|---|---|---|
| *Females > males* | | | |
| Bilateral superior parietal lobule | | | |
| 7 | −16 | −61 | 60 |
| 7 | 21 | −58 | 60 |
| 7 | 33 | -46 | 59 |
| 7 | −17 | −48 | 59 |
| 7 | 34 | −67 | 57 |
| 7 | 30 | −58 | 56 |
| 7 | −37 | −61 | 55 |
| 7 | −22 | −66 | 53 |
| Bilateral intraparietal sulcus | | | |
| 7 | −37 | −61 | 55 |
| 7 | 40 | −61 | 53 |
| 7 | 33 | −59 | 45 |
| 7 | −24 | −56 | 44 |
| 7 | −29 | −73 | 42 |
| Right precuneus | | | |
| 7 | 10 | −53 | 58 |
| Bilateral angular gyrus | | | |
| 39 | 42 | −54 | 56 |
| 39 | −46 | −61 | 48 |
| 39 | −40 | −54 | 47 |
| 39 | −36 | −70 | 38 |
| 39 | −37 | −75 | 31 |
| Right posterior cingulate cortex | | | |
| 23 | 3 | −16 | 30 |
| Right superior temporal gyrus | | | |
| 22 | 62 | −18 | 1 |
| Right superior temporal sulcus | | | |
| 22 | 61 | −15 | −7 |
| Left fusiform gyrus | | | |
| 37 | −35 | −43 | −23 |
| Left parieto-occipital sulcus | | | |
| 7/19 | −17 | −74 | 42 |
| Left superior occipital gyrus | | | |
| 19 | −13 | −90 | 44 |
| 19 | −23 | −83 | 39 |
| 19 | −26 | −87 | 32 |
| 19 | −27 | −75 | 20 |
| *Males > females* | | | |
| Left superior parietal lobule | | | |
| 7 | −23 | −64 | 62 |
| Left precuneus | | | |
| 7 | −14 | −84 | 46 |
| Right angular gyrus | | | |
| 39 | 53 | −52 | 52 |
| 39 | 50 | −62 | 46 |
| 39 | 59 | −62 | 34 |
| Left anterior cingulate cortex | | | |
| 24 | −6 | 10 | 28 |
| Right inferior temporal sulcus | | | |
| 37 | 44 | −58 | −3 |
| Left cuneus | | | |
| 19 | −6 | −89 | 39 |
| Left superior occipital gyrus | | | |
| 19 | −13 | −86 | 28 |
| 19 | −14 | −87 | 27 |
| Right middle occipital gyrus | | | |
| 19 | 39 | −65 | 5 |
| Left cerebellum | | | |
| − | −4 | −46 | −4 |

BA refers to Brodmann area and MNI

coordinate (x, y, z) refers to the center of each activation

# GENERAL DISCUSSION

*Sex differences in the patterns of brain activity during long-term memory*

In Part 1, we investigated sex differences in the patterns of activity during long-term memory. Critically, by utilizing neutral stimuli and an event-related design, we were able to successfully isolate the cognitive process of long-term memory. Previously, the majority of studies investigating sex differences in the brain during long-term memory were confounded by these, and other factors, that we were able to control for here (see Spets & Slotnick, in press for a review). In Chapter 1, we identified many sex-specific brain regions associated with spatial long-term memory. These included visual processing regions for males (bilateral middle occipital gyrus, left inferior occipital gyrus, right collateral sulcus, and left fusiform gyrus) and the parietal cortex for females (right superior parietal lobule). We also identified male specific activity in the left hippocampus and marginally significant female activity in Wernicke's area. These results are in line with previous literature suggesting greater use of visuospatial processing strategies in males (indicated by the greater activity in visual regions and the hippocampus) and greater use of verbal processing strategies for females (indicated by a marginally significant difference in activity in Wernicke's area) (Goldstein et al., 2001; Cahill, 2006; Herlitz & Rehnman, 2008; Garn et al., 2009; St. Jacques et al. 2011). Although males produced a greater magnitude of activity compared to females in visual processing regions, females produced a greater extent of activity in these regions which may lend support to the finding that females often report more vivid visualization of past events (Andreano & Cahill, 2009). In Chapter 1, the differences far outweighed the similarities between the sexes; only three regions were commonly activated in females and males. Moreover, a multivariate correlation analysis suggested that the observed differences were due to sex rather than other individual differences.

In Chapter 2, we identified sex-specific brain regions associated with item memory. There were not, however, as many differences identified during item memory as in spatial

memory (described above; Chapter 1). Specifically, we identified greater activity for males in the prefrontal cortex (left medial prefrontal cortex, left inferior frontal sulcus, and left inferior frontal gyrus) and parietal cortex (left angular gyrus) and the frontal cortex for females (right precentral gyrus). We also identified marginally significant sex-specific activity for females in Wernicke's area. Despite these differences, there were far more common regions of activity between females and males compared to our spatial memory investigation (ten compared to three regions commonly activated). The regions that were sex-specific for males were mostly located within the default mode network (DMN), which includes the dorsolateral prefrontal cortex, the inferior parietal cortex, and the medial parietal cortex (Buckner et al., 2008). These results suggest greater task disengagement in males during the item memory task. They could also, however, suggest the use of a distinct memory network as the same regions associated with the DMN also support long-term memory (Sestiero et al., 2011). Broadly, the results from Chapter 2 suggest that item memory is a more similar, than dissimilar, process for females and males.

In Chapter 3, we investigated the neural basis of memory confidence in females and males. In Chapter 2, we identified a numerically higher number of high confidence responses for males compared to females and so we sought to identify the neural basis of this difference. Many of the regions activated by the contrast of high confidence versus low confidence memories were regions of the long-term memory network including parietal and visual regions, suggesting that high confidence memories may be associated with amplification of signal in long-term memory regions (Slotnick, 2017). There were no regions activated to a greater extent for females during high confidence memories. However, there were many regions activated to a greater extent in males including the lateral prefrontal cortex, sensorimotor cortex, parietal cortex, and visual processing regions. The lateral prefrontal cortex has been previously associated with both post-retrieval monitoring as well as the subjective feeling of confidence (Chua et al., 2004; Bona & Silvanto, 2014). In order to distinguish between these two hypotheses, we extracted beta-weights from a region of interest (ROI) in the lateral prefrontal cortex and correlated the beta-weight

magnitudes associated with high confidence to the proportion of confident hits. The correlation was significantly more positive for males than females, suggesting that greater activity in the lateral prefrontal cortex is associated with the subjective feeling of confidence in males.

In Chapter 4, we investigated the neural basis of sex differences in false memories. As false memories and true memories rely on similar brain regions (including the prefrontal cortex, parietal cortex, late visual processing regions, and the hippocampus), we posited that sex differences would exist in similar brain regions during false memories as true memories (Cabeza et al., 2001; Okado & Stark, 2003; Slotnick & Schacter, 2004a; Kim & Cabeza, 2007; Dennis et al., 2012; Gutchess & Schacter, 2012; Slotnick, 2017; Karanian et al., 2020; for a review, see Schacter & Slotnick, 2004b). Perhaps most notably, we identified sex-specific false memory activity in the hippocampus for males and in V1 for females, two regions where involvement in false memories is often debated (Dennis et al., 2014). This sex-specific relationship may help explain, at least to some extent, the disparate findings in the literature and underline the importance of considering sex as a factor in neuroscience research.

Finally, in Chapter 5, we looked at whether certain experimental parameters influence the outcome of sex differences research. That is, whether certain parameters produce a null result. Sex differences were observed in all included studies and close examination of the articles suggested that there was no influence of experimental parameters on whether or not null differences were found. A subsequent meta-analysis identified consistently greater activity for males in the lateral prefrontal cortex, visual processing regions (middle occipital gyrus and fusiform gyrus), parahippocampal cortex, and the cerebellum. There were no regions consistently activated to a greater extent in females. These results support the hypothesis that males utilize visuospatial processing strategies to a greater extent than females (as was observed in Chapter 1). However, since there were no regions activated to a greater extent in females, it may also be the case that males are more likely to produce greater overall activity and that the increases are not isolated to specific brain regions. This viewpoint supports the neural efficiency hypothesis which

posits that lower levels of brain activity reflect more efficient processing (Neubauer & Fink, 2009; Ino et al., 2010; Li et al., 2010).

The evidence presented in Part 1 suggests that sex differences exist in patterns of brain activity during long-term memory. Although the differences seem to be dependent on the type of task and stimuli that are employed, there are some consistencies in the brain regions that show sex-specific responses. Namely, males tend to produce greater magnitudes of activity in visual processing regions as well as the hippocampus lending support for the hypothesis that males may utilize visuospatial processing strategies to a greater extent than females (Chapters 1, 2, 4, and 5). There is also some consistency in the greater magnitudes of activity for females in verbal processing regions which may suggest that females utilize verbal strategies to a greater extent than males (Chapter 1 and 2). Moreover, we identified sex differences across a variety of tasks and stimuli types in our meta-analysis (Chapter 5), providing further support for sex differences in the brain across different types of long-term memory. More broadly, the results from Part 1 suggest that sex should be considered as a factor in cognitive neuroscience studies.

*Sex differences in functional connectivity during long-term memory*

In Part 2, we investigated sex differences in the patterns of functional connectivity during long-term memory. We focused on the functional connectivity with two brain regions: the hippocampus (Chapter 6) and the thalamus (Chapter 7). Critically, these were the first long-term memory studies, to our knowledge, to look at task related differences in functional connectivity between the sexes.

In Chapter 6, we looked at whether sex differences existed in the patterns of functional connectivity with the hippocampus during spatial long-term memory. Compared to females, males had greater hippocampal connectivity with the medial frontal cortex, anterior prefrontal cortex, precuneus, and cingulate sulcus. Although there were no regions with greater hippocampal connectivity for females, we did find evidence supporting our hypothesis that there

would be greater interhemispheric connectivity for females and greater intrahemispheric connectivity for males. Notably, these results are backed by structural connectivity findings that identified that white matter tracts in female brains are optimized for interhemispheric connectivity and that white matter tracts in male brains are optimized for intrahemispheric connectivity (Ingalhalikar et al., 2014). The laterality findings suggest that females may engage in more global processing during long-term memory compared to males who may engage in more local processing. In line with previous findings (c.f., Chapter 2), the brain regions that were preferentially connected to the hippocampus for males are not only associated with long-term memory (Slotnick, 2017) but also with the DMN (Buckner et al., 2008). Future research is necessary to disseminate whether this increase in connectivity is reflective of long-term memory or DMN processing. Chapter 6 provides valuable insights into sex differences in the functional connectivity of the hippocampus during long-term memory which is critical to understanding long-term memory and had never before been investigated.

In Chapter 7, we investigated the role of the thalamus during long-term memory. Previous evidence from mice suggests that the thalamus may inhibit the hippocampus during spatial long-term memory in females but not in males (Torromino et al., 2019). This sex-specific relationship between the hippocampus and thalamus may, in part, help explain the mechanism underlying the relative decrease in hippocampal activity that is often observed in females (c.f., Chapters 1 and 4). The findings from this chapter support and extend past findings. General regions of connectivity with the thalamus were identified in both memory and anatomic networks (Vertes et al., 2001; Slotnick, 2017). We identified many regions that were differentially connected to the thalamus for females and males but, critically, we found evidence for the sex-specific hippocampal-thalamic relationship described above. Specifically, beta-weight magnitudes extracted from hippocampal and thalamic ROIs were more negatively correlated for females than males with higher magnitudes of activity in the thalamus correlating with lower magnitudes of activity in the hippocampus. In addition to providing further insight into the role of

the thalamus in long-term memory, Chapter 7 provided evidence for the involvement of the thalamus in the often observed decrease in hippocampal activity in females (c.f., Chapters 1 and 4).

*Using multivoxel pattern analysis to predict sex*

Despite robust sex differences in brain anatomy, neurochemistry, and (most recently) functional activity, it is still widely debated whether sex differences exist in the brain (Joel et al., 2015; Cahill, 2019). Of particular relevance is Joel et al. (2015) in which it was concluded, based on their arguably biased methods of analysis, that the average female and male brain were not significantly different. However, when their data were reanalyzed by two separate groups of researchers using unbiased classifiers, female and male brains were able to be predicted well above chance suggesting that the average female and male brain are significantly different (Rosenblatt, 2016; Del Giudice et al., 2016). In order to identify whether the differences that we had observed during spatial long-term memory (in Chapter 1) were consistent enough to support sex classification, we re-analyzed the data using multi-voxel pattern analysis (MVPA). Using functional data to define the ROIs, we were able to classify sex above chance, suggesting that the average female and male brain during long-term memory are significantly different. Moreover, we conducted a spotlight analysis within the functional ROIs to determine which voxels were most predicative of sex.

The results of Chapter 8 support and extend past findings (i.e., Chapter 1). Notably, we identified a greater number of sex-specific regions for females in the spotlight analysis compared to the general linear model (GLM) analysis employed in Chapter 1. Interestingly, we identified far more sex-specific voxels in visual processing regions for females than males in Chapter 8. In Chapter 1, we found greater magnitudes of activity in visual processing regions for males but a greater extent of activity in these regions for females. The comparison of these results underlines the potential benefit of using MVPA to study sex differences in the brain. As MVPA is able to

capture responses that are lower in magnitude, but more consistent across participants, it could be a useful tool to study subtle, but important, sex differences in the brain that could otherwise be undetected using a typical GLM analysis (Weaverdyck et al., 2020). The results from Chapter 8 lend strong support to the hypothesis that the average female and male brain are significantly different in the patterns of activity during spatial long-term memory. As MVPA may be more sensitive to sex differences in the brain compared to other methods, this method of analysis should be applied to investigate other types of memory as well.

*General conclusions*

The studies presented in this dissertation investigated sex differences in the brain during long-term memory both in terms of the patterns of activity as well as functional connectivity. Part 1 provided evidence that sex differences exist in patterns of brain activity during spatial long-term memory, item long-term memory, memory confidence, false memory, and across many types of long-term memory via our meta-analysis. Although the differences in activity seemed to be task and stimuli specific, males tended to activate visual processing regions and hippocampus to a greater extent than females, which supports the hypothesis that males employ visuospatial processing strategies to a greater degree than females during long-term memory. The findings presented in Part 1 also lend some support to the hypothesis that females employ verbal strategies to a greater degree than males during long-term memory. More generally, males often presented greater overall magnitudes of activity compared to females, which may suggest that females engage in more efficient processing during long-term memory.

The findings presented in Part 2 extend those of Part 1. Specifically, Part 2 looked at sex differences in functional connectivity during long-term memory. Functional connectivity with the hippocampus most notably differed in the number of inter- versus intrahemispheric connections with females producing a greater number of interhemispheric connections than males. These findings support the hypothesis that females engage in more global processing during long-term

memory. A sex-specific relationship was also observed between the hippocampus and thalamus with higher magnitudes of activity in the thalamus correlating with lower magnitudes of activity in the hippocampus for females, but not males. These results may shed some light on the mechanism underlying the lower levels of hippocampal activity that are often observed in females during long-term memory (including those observed in Chapter 1).

In Part 3, we provided evidence that patterns of brain activity observed during spatial long-term memory are significantly different between females and males. These results provide undeniable evidence that sex differences exist in the brain during long-term memory. Recently, the National Institute of Health (NIH) has implemented policies to ensure sex differences are considered in preclinical research (Arengard et al., 2020). These policies are preceded by decades in which females have been severely underrepresented in biomedical and preclinical research (Beery & Zucker, 2011; Berlin & Ellenberg, 2016). The studies presented within this dissertation support the ongoing effort to consider sex in all elements of neuroscience research.

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