

**SEX DIFFERENCES IN FUNCTIONAL CONNECTIVITY OF EPISODIC MEMORY
NETWORKS USING NATURALISTIC STIMULI**

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DEDICATION

To my parents who have supported all my endeavours with their whole hearts.

ABSTRACT

Males and females exhibit differences in episodic memory, both behaviourally and neurally. Previous research suggests that females have a general episodic memory advantage, however the neural correlates underlying this advantage remain unclear. There are significant advantages to using naturalistic stimuli for uncovering memory networks, however, there remains a gap in the literature examining recognition related network differences between older males and females using such stimuli. In the present study, 35 older adults (age 55-75 years, 17 females) encoded six narrative-driven, naturalistic scenes. Seven days later, all participants completed a delayed recognition task during functional magnetic resonance imaging (fMRI), in which they viewed three previously encoded and three novel scenes. To identify differences in functional connectivity during recognition, we used functional connectivity multivariate pattern analysis (fc-MVPA) followed by post-hoc seed-based correlations (SBC). Fc-MVPA revealed eight clusters exhibiting significant differences in functional connectivity between females and males, including the left postcentral gyrus, bilateral precuneus/posterior cingulate cortex, left hippocampus, left parietal operculum cortex, left cerebellum 4 5, right posterior middle temporal gyrus, left paracingulate gyrus, left superior frontal gyrus. SBC from these clusters showed widespread differences in whole brain memory networks between males and females. Notably, the left hippocampal region of interest showed significantly greater connectivity with the default mode network (DMN) in males than females. These findings suggest older females and males exhibit distinct patterns of functional connectivity during recognition of naturalistic stimuli despite comparable recall performance. More broadly, we provide evidence for different episodic memory network architecture between older females and males that may help inform more global episodic memory systems.

ETHICS STATEMENT

Work described in this thesis received research ethics approval from the University of Alberta Research Ethics board, Project Name “Real-life recall: An fMRI exploration of episodic memory in the real-world,” Study ID: Pro00144671.

USE OF GENERATIVE AI

I used generative AI tools in a limited way to support the writing of this thesis document. AI was not used to generate research ideas, design the study or stimuli, analyze the data, or interpret the results. AI was used as noted in methods for Whisper transcription of recall and was thoroughly checked by study team members. In some cases, I used AI to look for synonyms, rephrase sentences, and help improve grammar and overall flow. All AI suggestions were carefully reviewed and edited to make sure it is an accurate reflection of my work. All decisions, analyses, and conclusions are my own. I take full responsibility for the content of this thesis, including the accuracy of all information and citations.

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LIST OF ABBREVIATIONS

ACC	Anterior Cingulate Cortex
AD	Alzheimer's Disease
AG	Angular Gyrus
BOLD	Blood Oxygen Level Dependent
Cereb45	Cerebellum lobule 4/ lobule 5
CSF	Cerebrospinal Fluid
DMN	Default Mode Network
DOF	Degrees of freedom
fc-MVPA	functional connectivity- multivariate pattern analysis
FD	Framewise displacement
fMRI	functional Magnetic Resonance Imaging
FOV	Field of view
FWHM	Full width half mass
GLM	General Linear Model
HC	Hippocampus
MCI	Mild Cognitive Impairment
MNI	Montreal Neurological Institute
MoCA	Montreal Cognitive Assessment
mPFC	Medial Prefrontal Cortex
MTG	Middle Temporal Gyrus
MTL	Medial temporal lobe
MRI	Magnetic Resonance Imaging
NIH	National Institute of Health
PCC	Posterior Cingulate Cortex
PaCiG	Paracingulate Gyrus
PFC	Prefrontal Cortex
pMTG	Posterior Middle Temporal Gyrus
POpC	Parietal Operculum Cortex
POV	Point of View
PHG	Parahippocampal Gyrus
PostCG	Post Central Gyrus
PreCG	Precentral Gyrus
PSM	Picture Sequence Memory
QC	Quality Control
ReHo	Regional Homogeneity
ROI	Region of interest
RSC	Retrosplenial Cortex
SFG	Superior Frontal Gyrus
STG	Superior Temporal Gyrus
TE	Echo time
TR	Repetition time
WM	White matter
3T	3 Tesla

CHAPTER 1: INTRODUCTION

1.1 BACKGROUND

Episodic memory is a form of long-term explicit memory that supports the conscious recollection of personally experienced events and the context in which they occurred. These memories are not factual accounts of what happened, but include contextual details such as where and when the event occurred, who was present, and the perceptual features that make the experience distinct (Baddeley, 2001), such as a holiday or graduation. Schacter and Tulving's (1982) distinction between semantic and episodic memory emphasized that episodic memory is uniquely tied to events situated in time and space. Remembering an episode therefore depends not only on storing information, but on binding, organizing, and reconstructing the perceptual, emotional, and circumstantial features of prior experiences. Studying episodic memories requires the distinction between two process involved in recognition: recollective recognition and familiarity detection. Aggleton & Brown (2006), suggest that only recollective recognition relies on episodic memory and define recollective recognition as the process of recognizing a specific and distinct event beyond familiarity by a process they refer to as “mental time travel”. In contrast, familiarity is associated with semantic “knowing,” and does not include the conscious awareness of the context in which the memory was formed. Rodent research has shown simultaneous assessment of what (object), where (place), and when (temporal order; Dere et al., 2005), suggesting a common evolutionary process encapsulating some elements of episodic memory. However, given the inability of rodents to communicate any process of introspection, the comparative research lacks the ability to confirm the element of “mental time travel.” Additionally episodic memory relies on the merging of contextual components and coupling

them specifically with an event (Aggleton & Brown, 2006). Together, these features make episodic memory a fundamentally integrative process, requiring the brain to link event content with the spatial, temporal, and contextual details that allow past experiences to be remembered as specific episodes.

Modern theories of episodic memory are deeply rooted in classic neuropsychological evidence showing that memory for personally experienced events can be selectively and profoundly disrupted by brain injury. The most influential of these cases is H.M., who had severe anterograde amnesia following bilateral medial temporal lobe (MTL) resection surgery, which included the hippocampus (HC; Scoville & Milner, 1957). This demonstrated that damage to these structures can eliminate the formation of new declarative memories while leaving many perceptual, intellectual, and procedural abilities relatively preserved. This landmark case transformed the scientific study of memory by linking declarative memory formation to the MTL and by demonstrating that different forms of memory can be differentially affected by brain damage.

Consistent with the case of H.M., subsequent lesion studies showed that damage to the HC is strongly associated with impairments in memory formation and retrieval, with hippocampal lesions affecting multiple facets of episodic memory (Jarrard, 1993). Similarly, damage to specific regions of the MTL, including the parahippocampal gyrus (PHG), and entorhinal and perirhinal cortices, can produce further memory impairment, consistent with the broader role of the MTL in supporting declarative memory (Borbély et al., 2013). The prefrontal cortex (PFC) has also been linked to more specific episodic memory processes, where damage is associated with deficits in the organization and retrieval of contextual details, such as when and where an event occurred (Fletcher et al., 1997). In contrast, damage to medial parietal regions (such as the

precuneus) has been associated with deficits in visual imagery ability, which is an important facet of episodic memory retrieval (Fletcher et al., 1997). The distinction between familiarity and recollective recognition also is supported by different subdivisions of the MTL, with the HC supporting recollective recognition and the perirhinal cortex supporting familiarity responses (Yonelinas, 2002). Together, these findings demonstrate that episodic memory depends not on a single memory centre, but on interactions among medial temporal, prefrontal, and parietal systems that support the formation, contextual organization, and conscious retrieval of personally experienced events.

Work published in 2015 by Ritchey et al. expanded the understanding of episodic memory beyond individual brain regions by identifying interconnected cortical pathways that work alongside the HC and demonstrated coordinated activity for different tasks. One pathway, which includes the PHG, retrosplenial cortex (RSC), posterior cingulate cortex (PCC), angular gyrus (AG), precuneus, anterior thalamus, and medial PFC (mPFC), plays an important role in representing the context of autobiographical events, including their temporal and spatial context in a memory. This representation enables scene perception and the storage of scene-related information in long-term memory. A second pathway, consisting of the perirhinal cortex, anterior ventral temporal cortex, amygdala, and lateral orbitofrontal cortex, is associated with object recognition and forming associations between objects and features. The amygdala further contributes to affect processing and integrating emotional information into episodic memory. The involvement of these interconnected pathways laid the groundwork for the increasingly prevalent perspective that episodic memory arises from coordinated activity across distributed neural systems.

1.2 DEFAULT MODE NETWORK

In the early 2000's, human neuroscientists began to look more deeply at coordinated activity and coupling of activation during different tasks. Functional connectivity using fMRI refers to the temporal correlation of BOLD signal fluctuations between spatially distinct brain regions or voxels and provides a means of identifying large-scale functional networks (Fox & Raichle, 2007). Research has identified the default mode network (DMN) as a key large-scale network supporting episodic memory and other internally directed cognitive processes (Huo et al., 2018; Kim, 2010b; Menon, 2023). Initially discovered as a set of regions that were regularly suppressed during externally directed processing in a study using positron emission tomography (Shulman et al., 1997), the DMN is characterized by deactivation during active tasks (Raichle et al., 2001). The DMN consists of a set of functionally connected cortical and subcortical brain regions associated with internally focused cognition. This is the process of directing your attention towards your thoughts, memories, or mental imagery (Dixon et al., 2014). Cortical regions of the DMN include the PCC, RSC, and PFC (including the ventrolateral, ventromedial, and anteromedial and dorsal PFC), as well as the PHG, middle temporal gyrus (MTG), posterior parietal cortex, and temporal pole. Subcortical components of the DMN include the HC, amygdala, caudate, basal forebrain, thalamus, and midbrain (Menon, 2023). The average DMN mask generated from a Neurosynth meta-analysis is shown in Figure 1.

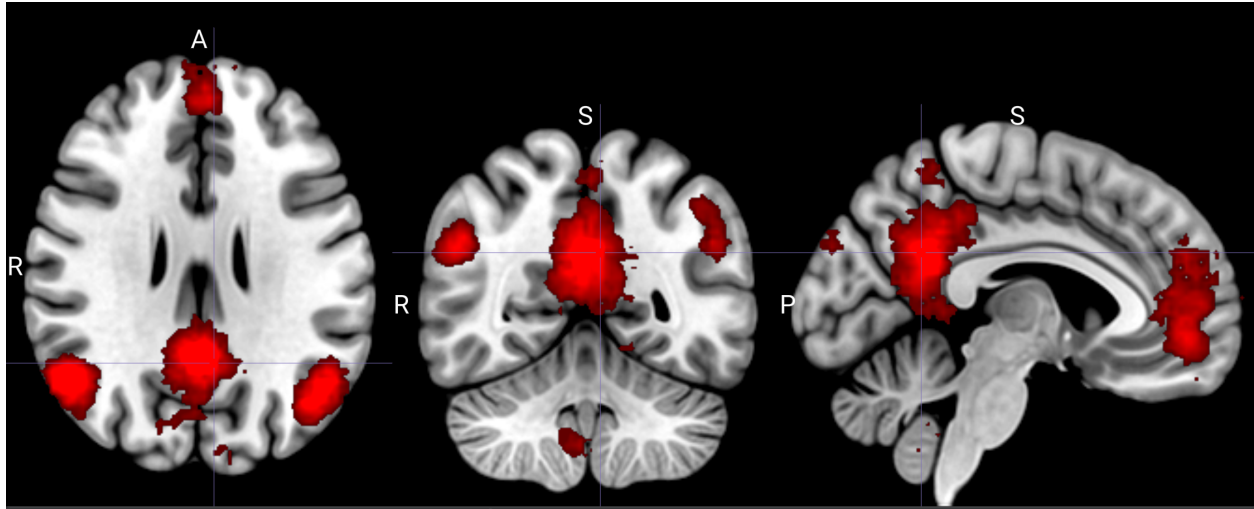


Figure 1: *Automated Meta-Analysis of the Default Mode Network*

An automated meta-analysis of 777 studies generated with Neurosynth using the keyword “default mode”. The statistical map represents the association test map, thresholded at [FDR .01], generated using Neurosynth <https://neurosynth.org/analyses/terms/default%20mode/> (accessed June 26, 2026) [Yarkoni et al., 2011]. Statistical maps were visualized using MRICroGL (version 1.2.20220720b; Rorden, 2025).

Functionally, the DMN is associated with autobiographical recollection, future-oriented thought, and self-referential processing (Menon, 2023). Given the presence of many memory regions in the DMN, a strong link between episodic memory and the DMN is not unexpected. Research suggests the DMN plays a particular role in episodic memory recollection (Kim, 2010) and episodic memory retrieval processes (Sestieri et al., 2011), highlighting its contribution to the conscious reconstruction of past experiences. Further evidence for the DMN’s role in memory retrieval comes from a meta-analysis by Kim et al. (2010), which identified consistent DMN activation in the anterior and posterior midline cortex, AG, and MTL regions, and associated them with recollection-based memory judgements. Taken together, these findings

indicate that activation within the DMN is, in some cases, a neural correlate of episodic memory, and the contributions extend beyond isolated regional activity and depend on coordinated interactions among distributed memory areas. Beyond its role in episodic retrieval, evidence suggests that connectivity within the DMN is also associated with successful memory encoding. For example, Li et al. (2015) investigated the relationship between DMN connectivity during an fMRI emotional face-name encoding task and subsequent recognition memory assessed outside the scanner. Their results showed that connectivity from the PCC, HC, and amygdala to other DMN regions during encoding as well as during rest, was linearly correlated with recognition memory performance in older adults. These findings suggest that stronger communication among key DMN regions supports successful memory formation.

1.3 SEX DIFFERENCES IN MEMORY

Memory is one of several cognitive domains that sex differences warrant consideration, as females and males often exhibit behavioural differences that may reflect different underlying neurological mechanisms. Of note, prior research reports a general episodic memory advantage for females that persists into older adulthood (Agneta & Johanna, 2009; Herlitz et al., 1997; Herlitz & Johanna, 2009). This advantage is most evident in verbal and narrative-based memory tasks. During recall, females tend to produce longer, more coherent narratives, with greater recall of details, people, and contextual information (J. P. Buckner & Fivush, 1998). This pattern remains consistent on a range of verbal tasks (Agneta & Johanna, 2009; Herlitz et al., 1997; Lewin et al., 2001), including delayed and immediate recall, memory recognition, and memory for concrete pictures (Herlitz et al., 1997). Women also outperform men in autobiographical (Bloise & Johnson, 2007; Seidlitz & Diener, 1998) and narrative (Hultsch et al., 1991) recall.

Importantly, this episodic memory advantage for females cannot be fully explained by hormones (Herlitz & Johanna, 2009) or superior performance on verbal tasks (Herlitz et al., 1999). Herlitz et al., (1997) tested many laboratory variations of episodic and semantic tasks with 1000 adults (530 females) between 35-80 years of age and found a consistent female advantage in episodic memory domains. Females performed better in free and cued recall of subject performed tasks, sentences and words, as well as face and name recognition, however the female bias had moderately low effect sizes ranging from $d = 0.05$ to 0.34 . Interestingly, evidence from outside the laboratory suggest that these sex differences may not necessarily generalize to all types of real-world episodic memory. For example a review by Russell et al., (2024) of sex differences in eye witness testimonies suggest that neither females nor males have superior performance in the total amount of accurate information reported. Instead, the review suggest that females may have better memory for person-related details and males may have better performance for details relating to the surroundings. Together, these findings indicate that biological sex differences reported for memory may differ depending on the type of episodic details being recalled.

Behavioural differences in episodic memory provide only a partial picture, as similar memory performance does not necessarily imply identical neural mechanisms. Functional neuroimaging provides a powerful approach to examine whether females and males recruit different neural systems during memory retrieval. In a meta-analysis, Piefke et al. (2005) reanalyzed data from fMRI studies of autobiographical memory to assess whether sex differences in BOLD signal were evident during the recall of life events. Females showed greater activation than males in the right dorsolateral PFC and right insula, whereas males showed

greater activation than females in the left PHG. These findings suggest that sex differences in memory may extend to the neural systems engaged during retrieval.

Because episodic memory is supported by coordinated activity across distributed brain systems, sex differences in regional activation may also be reflected in broader patterns of network organization. Previous research suggests that females and males differ in functional connectivity within the DMN, with these differences showing variability across brain regions and lifespan. For example, Ficek-Tani et al. (2023) examined the relationship between functional connectivity patterns in the DMN, memory performance, and sex differences using a large resting-state fMRI dataset spanning multiple decades. This study used DMN intrinsic connectivity distribution as a measure of global correlation and within DMN connectivity. Results from this study showed that females had greater within DMN connectivity than males for the bilateral PCC and AG. In DMN-to-whole-brain seed-based analyses, females also showed greater connectivity between DMN regions and the bilateral HC, bilateral AG, insula, ventral PFC, and anterior cingulate cortex (ACC). Overall, this pattern was characterized by relatively higher posterior DMN connectivity and lower anterior DMN connectivity in females compared with males of the same age. In contrast, males had a greater within DMN connectivity from the mPFC to the rest of the DMN across the lifespan, as well as stronger connectivity between DMN regions and the left premotor cortex and superior temporal sulcus. Together, these findings suggest that sex differences in memory-related brain function may be evident at multiple levels, from regional recruitment during retrieval to large-scale network organization.

1.4 AGING AND MEMORY

Episodic memory is one of the cognitive systems most susceptible to age-related decline, even in otherwise healthy adults (Baddeley, 2001). Because females are more susceptible to

diseases of episodic memory (Filon et al., 2016), it can be difficult to categorize changes associated with healthy aging and changes that may be predictors or early indicators of disease. Age-related changes affect both encoding and retrieval processes and are often reflected in behavioural differences in the quality and quantity of information remembered. For example, older adults are more likely to retain general categorical information (gist) than specific episodic details (Grilli & Sheldon, 2022). Further, Launay et al. (2025) compared episodic memory recall of young adults (20-35 years), young-old adults (60-74 years), and oldest-old adults (75-91 years) following exposure to a short movie. The results indicated that, although the oldest adults reported more action-related episodic content than the youngest group, they recalled fewer details overall. Importantly, recall declined gradually with age and did not differ significantly across qualitative categories, suggesting a broad reduction in episodic memory performance rather than an abrupt decline in a specific class of remembered information.

These behavioural changes are associated with age-related differences in the neural systems involved in episodic memory. Neuroimaging studies suggest that memory decline in older adulthood is associated with altered regional activation in memory regions, including the dorsolateral and ventrolateral PFC, HC, and superior frontal gyrus (SFG; Dennis et al., 2008; Grady et al., 2006.) For example, Daselaar et al. (2006) used fMRI to examine the effects of age on familiarity and recollection memory-related brain activity by presenting old words or new words. Their results showed that older adults had reduced HC and parietotemporal activation during recollection for old words, which was correlated with decreased memory scores. Similarly, Persson et al. (2012) set out to determine if intraindividual activation changes in the MTL were associated with longitudinal change in memory performance. The results showed that age-related decline in memory performance was with an associated decline in left HC activation

and increased activation in the PHG. These findings suggest that altered engagement of medial temporal memory systems may contribute to poorer episodic memory performance in older adults.

Beyond regional activation, aging is also associated with changes in connectivity among memory-relevant brain regions at distinct points in and across the lifespan. In a comprehensive review of functional neuroimaging research, Nyberg (2017) concluded that healthy aging is associated with altered connectivity between the PFC and MTL, as well as reduced HC and MTL activity during memory tasks after approximately 65 years of age. Further, Nyberg (2017) suggested that, although many functional networks show reduced resting-state connectivity with age, the HC may show increased resting state to whole-brain connectivity and decreased task-related HC to whole-brain connectivity, representing an inefficiency in functional connectivity. Consistent with this idea, Salami et al., (2014) examined HC-DMN connectivity in a large adult sample ranging from 25 to 80 years of age and found that greater resting-state HC-cortex connectivity was associated with poorer episodic memory performance and longitudinal memory decline. They also reported that increasing age was positively associated with left and right HC connectivity and HC-cortex connectivity at rest but negatively associated with HC-cortical connectivity during memory encoding. These findings suggest that aging is associated with complex, state-dependent changes in HC connectivity. Critically, this pattern indicates that age-related neural reorganization is not limited to medial temporal memory systems but also extends to large-scale network connections within and beyond the DMN. Building on this, researchers have begun to examine how connectivity across the DMN changes with aging and relates to memory performance.

Given the central role of the DMN in episodic memory, understanding how DMN changes happen as function of time and the overall lifespan trajectory in regards to functional connectivity provides a more comprehensive picture of age-related memory systems. Staffaroni et al. (2018) conducted a longitudinal study with the goal of establishing a profile of DMN connectivity over a period of decades. In this study, they assessed older adults (46 females) for three patterns: within DMN connectivity, anterior vs. posterior DMN connectivity, and MTL to DMN connectivity. They used a minimum of three scans from each subject to establish that DMN connectivity follows a non-linear age-related trajectory. Results showed that DMN connectivity was associated with episodic memory performance and increased from 50-66 but took a sharp decline after age 74. Collectively, these findings suggest that age related changes in DMN connectivity contribute to memory decline and underscore the importance of determining whether these trajectories differ with biological sex.

Changes in network organization do not follow the same trajectory for aging females and males. To investigate the relationship between changes in DMN connectivity and sex, Scheinost et al. (2014) studied DMN resting state connectivity using intrinsic connectivity distribution (ICD) as a measure of seed to whole-brain connectivity. Results showed a decline in connectivity for both females and males for PCC and medial PFC ICD values with increasing age. However, the decline of ICD for the PCC differed by sex, with females exhibiting a more gradual and linear decline, whereas males showed a steeper reduction in connectivity over time. They concluded that females have a more linear trajectory of DMN connectivity decline with respect to aging and males have a greater rate of DMN ICD decline overall. These findings indicate that sex differences in the DMN are both region specific and dynamic across networks and lifespan. However, because these measures come from scans at rest rather than during memory tasks, the

full modulation of memory tasks by sex and age on connectivity patterns remains unclear. Further research is required to understand how these connectivity differences may translate to sex-specific patterns beyond resting state, and how the effects of age may moderate sex differences.

1.5 EPISODIC MEMORY IMPAIRMENT IN NEURODEGENERATIVE DISEASE

One important reason to study episodic memory is to better understand disorders associated with episodic memory impairment, including mild cognitive impairment (MCI) and Alzheimer's disease (AD). Behaviourally, these conditions are characterized by difficulties in encoding, storing, and retrieving information about recent experiences (Ally et al., 2009; Barba, 1997; Tromp et al., 2015). These impairments often affect memory for contextual details (Ritchey et al., 2015; Shallice et al., 1994), including where an event occurred, when it occurred, and whether previously encountered information is familiar or recollected (Yonelinas, 2002). For example, individuals with AD often show impairments on recognition and recall tasks, including difficulty distinguishing previously studied items from distractors (Ally et al., 2009). Because episodic memory supports the ability to remember personally experienced events, disruptions to this system can affect orientation, daily functioning, and sense of continuity over time (Gilmour et al., 2019).

Diseases of episodic memory have a higher prevalence in females, and females with AD show greater total brain atrophy across the cortex (Filon et al., 2016). These sex differences suggest that biological and genetic factors may interact with functional brain networks to influence disease progression. Evidence for such interactions is provided by Williamson et al., (2024) who investigated the interaction between genetic risk factors and functional connectivity biomarkers of AD in females and males. Using resting state-fMRI (rs-fMRI) data from AD and

non-AD participants with different ApoE-4 genotypes (which have previously been associated with reduced HC functional connectivity to the PCC and precuneus), they showed that intrahippocampal connectivity differed by sex when AD participants had at least one ApoE-4 allele. Specifically, AD males had significantly greater connectivity between the left and right HC, demonstrating a sex difference in interhemispheric HC connectivity in AD pathology.

At the network level, AD pathology is associated with progressive disruption of functional connectivity across memory systems. For example, early in the disease course, DMN abnormalities are evident in preclinical populations, with PCC-HC connectivity being associated with successful encoding and recognition in MCI individuals (Papma et al., 2017). As the disease progresses, network dysfunction becomes more widespread, primarily trending towards decreased intra-network connectivity across resting state networks (Brier et al., 2012). Given the relationship between AD pathologies and biomarkers with functional connectivity profiles, understanding how functional memory networks differ by sex across the lifespan has important implications for the early detection and treatment of neurodegenerative diseases.

1.6 NATURALISTIC STIMULI

A central challenge in episodic memory research is balancing experimental control with ecological validity. Traditional episodic memory tasks and resting state studies have been highly valuable because they allow researchers to isolate specific encoding and retrieval processes under controlled conditions. Many studies have used visually presented word lists, word–location associations, object or scene images, and face-recognition paradigms to characterize the neural mechanisms supporting memory (Buckner et al., 2001; Kirchhoff et al., 2000; Uncapher & Rugg, 2005; Wagner et al., 1998; Brewer et al., 1998; Qin et al., 2007). These paradigms have produced important insights into memory systems, including the role of MTL, PFC, and visual

association regions. However, they are limited in their ability to capture the richness of everyday episodic memory, which typically involves continuous events embedded in spatial, temporal, social, emotional, and perceptual contexts.

Naturalistic stimuli (such as podcasts, audiovisual movies, or videogames) offer a more true-to-life approximation of real-world experiences and are especially well suited for studying episodic memory, which naturally unfolds in multimodal, contextualized settings. Movies are particularly useful because they contain continuous narratives, dynamic perceptual information, and affective content while still allowing experimental control during neuroimaging (Sonkusare et al., 2019). Naturalistic stimuli also engage brain regions commonly implicated in episodic memory. For example, fMRI studies of movie watching have linked successful subsequent memory recall to patterns of activation in the temporal pole, STG, temporal parietal junction, and mPFC (Hasson et al., 2008). Further, Lui et al. (2020) compared auditory narrative presentation with combined audiovisual presentation and found that multimodal encoding improved later episodic retrieval and was associated with stronger activation in the AG. These findings suggest that naturalistic, multimodal stimuli may better engage the distributed neural systems involved in forming and retrieving event memories.

1.7 THE CURRENT RESEARCH

In summary, previous research suggests that episodic memory depends on distributed interactions among medial temporal, prefrontal, parietal, and DMN regions. Further, these systems are altered during aging, implicated in memory impairment, and may differ between biological females and males. However, relatively little research has examined whether older females and males differ in task-related whole-brain connectivity during episodic memory of naturalistic events. This represents an important gap, as sex differences in memory performance

and DMN connectivity may not be fully captured by conventional memory tasks or by resting-state analyses alone. This gap is particularly relevant in the context of aging. Much of the literature on memory and aging has examined general age-related decline without explicitly testing whether females and males show different neural profiles. When sex is considered, evidence suggests that females and males may show distinct patterns of DMN connectivity across the lifespan. For example, Ficek-Tani et al. (2023) reported that females showed relatively higher posterior DMN connectivity, including connectivity involving the AG, whereas males showed patterns more consistent with previously reported age-related decreases in overall DMN connectivity. These findings suggest that sex may be an important source of variability in memory-related network organization during aging.

Thus, the goal of the present study is to examine whether females and males differ in whole-brain functional connectivity during recognition of previously encoded naturalistic scenes. To test this, participants viewed six short everyday narrative vignettes designed to approximate real-world episodic events. Seven days later, participants returned for a recall task and a fMRI recognition task involving previously viewed and novel scenes. This design allows task-related connectivity to be examined during recognition of naturalistic event memories after a delay. A whole-brain data driven connectivity analysis (functional connectivity multivariate pattern analysis; fc-MVPA; Nieto-Castanon, 2022) was used to identify regions of the brain that showed significantly different patterns of whole-brain functional connectivity between males and females. Regions identified to have significantly different whole-brain connectivity patterns between females and males were further analyzed to characterize the network connectivity differences driving significant effects of each identified region of interest (ROI). Based on the well-established female advantage in episodic memory, we hypothesized that females would

demonstrate superior free recall of the encoded events compared with males. Based on previous evidence linking sex differences to DMN and HC connectivity (Ficek-Tani et al., 2023; Spets et al., 2024), we further hypothesized that females and males would differ in functional connectivity in memory-relevant regions within and beyond the DMN and HC. By identifying sex-specific memory networks in older adults, this study aims to advance our understanding of the neural mechanisms that may contribute to cognitive aging and the disproportionate burden of memory-related disorders in women.

CHAPTER 2: METHODS

2.1 OVERVIEW

The current thesis aims to examine sex differences in patterns of functional connectivity used for recognition memory. Specifically, our experiment investigated female and male whole brain patterns of connectivity from fMRI during viewing of previously encoded or novel naturalistic scenes. This experiment is one component in a larger project comparing naturalistic encoding modalities on functional connectivity and episodic recall. As a result, some decisions were made in accordance with Liu et al. (2020) which analyzed memory differences between three different encoding modalities using a seven day gap between encoding and retrieval tasks. To determine whether sex differences influence episodic memory networks, we had participants view naturalistic audiovisual vignettes outside of the scanner and return seven days later to recall what they remembered and contrast their brain activity when they viewed scenes they had watched a week before or new scenes. We compared free recall as one measure of episodic memory. Additionally, as a measure of recognition, we analyzed the fMRI data using a data driven approach (fc-MVPA) that determined regions with different whole brain connectivity patterns for females and males during the memory task. To further characterize these patterns, we used a post-hoc analysis (seed-based connectivity) for each identified region to the rest of the brain.

2.2 PARTICIPANTS

A total of 38 healthy older adults (age range 55-75) participated in the current study. Two participants dropped out during scanning and data from one person was removed because of an incidental finding. This resulted in 35 participants in the final analysis (17 females; $M = 68.0$ years old, $SD = 5.24$ years, 18 males; $M = 65.9$ years old, $SD = 5.12$ years). Participants were

recruited from the University of Lethbridge and the broader Lethbridge community via posters, flyers, emails, listservs, in-person recruitment, and referrals from community organizations. All participants were screened for neurological or vision conditions that would prevent them from completing the task or could be associated with abnormal neuroanatomy or brain function. All participants provided written informed consent prior to participation. Participants received monetary compensation of \$25/hr for participation in the study (\$50 per session for two sessions). Approval for experimental procedures was acquired through the University of Alberta Research Ethics Board (protocol ID: Pro00144671).

2.3 EXPERIMENTAL PROCEDURE AND STIMULI

All participants took part in two sessions, set seven days apart. Both sessions took place at the U3T MRI Center at the University of Lethbridge. The flow of experimental design is pictorially outlined in Figure 2.

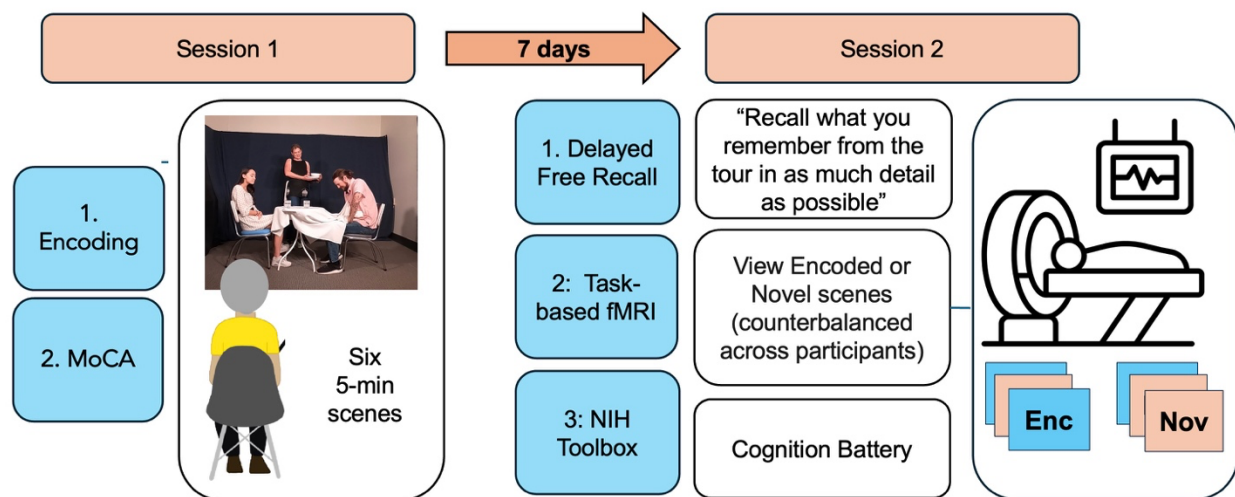


Figure 2: *Experimental Design*

During Session 1, participants viewed the stimuli, completed the Montreal Cognitive Assessment (MoCA), and completed consent and demographic questionnaires. During Session 2, participants

verbally completed the delayed free recall task, fMRI recognition task, a structural MRI scan, and the NIH Toolbox Cognition Battery (Weintraub et al., 2013).

Session 1

In the first session, participants arrived and were led to a room where they were briefed on the experiment and pre-screened for MRI eligibility. Before beginning the experiment, participants provided informed consent and then completed a comprehensive demographic questionnaire. The participants were then led to a viewing room and told, “You will watch a tour that is about 40 minutes. You will later be asked to recall as much as you can remember about the tour and the individual scenes.” They were directed to a chair where they were seated approximately 2 m from a large screen (1.98 m x 2.90 m) on which they viewed an audiovisual movie of six different vignettes filmed from a first-person perspective. Video audio was delivered via a Bluetooth speaker placed out of sight below the projection. Manual keystone correction was used to ensure the screen focused to the same size each time, and the viewing angle was consistent across experimental trials. Following the encoding activity, participants completed the Montreal Cognitive Assessment (MoCA; Nasreddine et al. 2005) administered by a researcher who had completed the official MoCA training.

Session 2

Seven days later, participants returned for a second session where they completed free recall, a task-based MRI scan, and additional behavioural testing. When they arrived, they completed delayed free recall, where they were asked to “Recall what you remember from the tour in as much detail as possible” while a researcher recorded their audio using a Sony ICD-UX670 digital audio recorder. Instructions were presented both on a screen and verbally. They

were encouraged to talk at least five minutes, with no time limit. When they were finished, they were asked if they would like to add anything else. Participants then changed into MRI safe clothing and were provided with MRI safe prescription goggles to correct their vision (if necessary). Any participants with visual impairment were required to read at least three of four letters on line 4 of the Snellen Chart from 10 ft away with the MRI safe prescription goggles.

In the scanner, participants completed a passive movie watching task where they viewed previously encoded scenes from the first session (Encoded Scenes) or novel foils filmed under the same conditions (Novel Scenes). Stimuli were displayed on a 40-inch MRI compatible LCD monitor (Nordic Neuro Lab, 2020) and viewed via a mirror attached to the head coil. Stimulus presentation was controlled using PsychoPy (Version 2021.2.1) and the presentation order of the scenes was randomised across participants. Video audio was delivered through an MRI-safe headphone system, which was also used by researchers to provide instructions and check in with participants throughout the experiment. To ensure consistent screen positioning across participants, the researchers aligned the screen with tape markers on the floor for each session and researchers adjusted the mirror so that participants could clearly view the display. Following the MRI scan, participants completed the entire NIH Toolbox Cognition Battery (Weintraub et al., 2013) administered on a 10th generation iPad (iPadOS Version 18.5).

2.4 STIMULUS DEVELOPMENT

The recorded scenes for both the encoding and recognition conditions were designed by a drama class at the University of Lethbridge specifically organized for this study. Students in this class were given neuroscience lectures on memory and naturalistic stimuli. The class was instructed to write 5-minute narratives that were fictitious but potentially observed in everyday settings. The full assignment they were given is included in Supplementary Materials A. Briefly,

the students were required to develop scenes that had a beginning, middle, and end and were directed to focus on memorable “and then” plot points, which were defined as causal and sequential links necessary to advancement of the narrative. Each scene had 6-8 events that were accompanied by intentional actions and dialogue to mimic dramatized versions of encounters people may experience in the real world. Each scene had two or three characters and was set in a common social setting, some public and some private. In total, the students wrote twenty scripts, with nine scripts ultimately selected to be refined and used as stimuli. Table 1 lists the scenes and describes the general narrative for each scene.

Table 1.

Scene List and Description of Main Events

Scene 1	A date at a restaurant. A waitress comes in and out of the scene. A rejected proposal/breakup.	Encoding/ Recognition
Scene 2	A gender reveal party featuring a young couple and a mother-in-law. A fight about the paternity of the child.	Encoding/ Recognition
Scene 3	A couple at home in the late evening arguing about the husband's hobby horse obsession.	Encoding
Scene 4	A mother in a doctors office discussing the death of her child and their decision to be an organ donor.	Encoding
Scene 5	A camping break-up scene between an organized young adult (female) and a frantic disorganized young adult (male)	Encoding/ Recognition
Scene 6	A library patron witnesses another patron trying to steal books from the library and alerts the librarian.	Encoding

Foil 1	A patron of a bar notices a strange noise and tries to draw attention to it but is dissuaded by the regular and the bartender.	Recognition
Foil 2	A wedding scene in which the vows and following argument are constantly interrupted by a sneezing priest.	Recognition
Foil 3	An elderly woman is instructing her daughter on how to divide her sentimental belongings upon her entrance into a nursing home.	Recognition

Note: Scenes 1-6 were viewed during encoding. During the recognition scan scenes 3, 4, and 5 were replaced by Foils 1-3. The main event of the scene is summarized in the second column. The third column shows which scenes were presented during the session 1 (“Encoding”) and which scenes were presented in session 2 (“Recognition”). Scenes with both “Encoding/Recognition,” represent the three previously encoded scenes used in subsequent analyses to elicit recognition.

To perform the scenes, eight actors were hired from both the class and the broader Lethbridge community. Scenes were recorded in a live version of this protocol (not discussed in this thesis) where participants walked through the building, viewing each scene with a camera mounted on their chest. All videos were recorded on three alternating GoPro Max Sports (GoPro Inc., San Mateo, CA, USA) video cameras set to “linear frame” and “30 fr/1080 resolution” mounted on each participant’s chest. Before the tour, the participant sat in a chair and the camera was adjusted to catch the same frame marked on the wall for each participant. They then completed the tour, where they moved through a building to six rooms and sat in seats 40cm from the floor and 200 cm from the frontmost area where actors would appear. Practical constraints such as actor availability on scan days, coordinating 6-8 actors for 6 scenes with

overlapping participant slots, maintaining consistent performances, and minimizing how long the scanner was empty between participants led us to select three scenes that would be used as foils/replacement scenes during recognition. Video quality was reviewed by study team members. 6/40 videos were considered unusable for the current study due to the following reasons: one was erroneously recorded with different camera parameters, one had lag that could not be fixed, and four had footage that was unusable (two were crooked and two were obstructed by the participants body or clothing). The scenes were performed and filmed on 40 separate runs corresponding with 40 participants that were matched with a participant from this study who watched their counterpart's video footage. The 40 participants who saw the scenes live were part of a larger project and none of the 40 participants used in the stimuli creation were part of the current analysis.

2.5 BEHAVIOURAL TESTING AND SCORING

Free recall analysis was performed similarly to Liu et al. (2020). Free recall was given verbally, and audio was recorded during Session 2 and later scored by a team of researchers using the following steps. First, recall recordings were transcribed using Whisper, an open-source automatic speech recognition tool developed by OpenAI (Radford et al., 2023) and all transcriptions were reviewed and edited by study team members, who corrected omissions or errors. Following corrections, all recall transcripts of Encoded Scenes were scored by the primary researcher. The free recall scoring procedure was developed to capture episodic details such as the key events in each narrative. For each event, internal details were scored based on the definition given by Levine et al., (2002), "Internal details were those that pertained directly to the main event described by the participant, were specific to time and place, and were considered to reflect episodic reexperiencing." During scene creation, each 5-minute scene was designed with

6-8 events considered necessary for the progression of the narrative, scripts were segmented to reflect actions and dialogue relating to each of the events and every action or line belonged exclusively to one event.

Each event was scored out of one based on whether it was fully (1.0) or partially (.25, 0.5, .75) recalled in gist/core events, regardless of additional details. Full points were given if the context of the recall made it apparent that the participant was referring to the correct characters and actions. Figure 3 shows how events were described based on each section of the script, and how points were allocated. Figure 4 shows two examples of recall transcriptions from the event in Figure 3, with any information that earned partial points highlighted and scores for the event below the transcript. For each participant, recall scores for events and for the three encoded scenes were combined and averaged, resulting in a recall percent across all previously encoded scenes. We then used JASP statistical software (JASP Team, 2026) to perform an independent samples t-test to determine if males and females differed on overall recall performance.

Event	Script
1.0- The server asks if they will have dessert. They order coffee and cheesecake	Server Can I interest you in some dessert? A coffee? Julia I'd love a coff – Chad (Interrupts) Yeah we'll get a piece of the cheesecake but can we get it with the chocolate <i>and</i> caramel?
0.5- only mentions cheesecake (or cake)	Server Yes, definitely!
Or	Chad Okay great and I'll get a coffee. Babe, are you sure you want one? It might keep you up. You know how you are with your sleep.
0.25- mentions any other desert	<i>Julia stares at Chad silently. Without breaking eye contact, she says:</i>
0.5- only mentions coffee	Julia I'd love a coffee, please. Black's fine. Server Okay. Two coffees and a chocolate caramel New York cheesecake.
0.25- Server offers desert	<i>Julia breaks eye contact with Chad to smile at the server. The server walks away.</i>

Figure 3: Scene 1 Event 2 Scoring Rubric

Note: Each participant received an event score for every event within the scene. These were combined for total scene score for each previously encoded scene.

Transcription examples:
“And the waitress comes to ask them what they'd like for dessert, and even though they've had some discussion about his GI upset, then maybe it's some kind of bowel disorder, he still orders a lemon cheesecake, and I think she orders maybe a coffee with nothing in it.” Event score: 1.0/1.0
“As they carried on through their meal and the server came in and out of the, came in and out from their table offering desserts and whatnot, he ordered cheesecake, which again, cheese.” Event Score: 0.75/1.0

Figure 4: Scene 1 Event 2 Scored Transcription Examples

Note: Participants were given partial points up to a total of 1.0 for each scene. Providing additional information including inaccurate information was not penalized. Only information relevant to the predetermined rubric was counted.

Additionally, the Montreal Cognitive Assessment (MoCA) was administered and scored by researcher who completed the official MoCA Training and Certification program prior to participant testing (Nasreddine, 2020). For verification, a second researcher with equivalent training checked all the newly administered MoCA scores at the end of each day. Lastly, we administered the NIH Toolbox Cognition Battery (Weintraub et al., 2013), which includes Picture Sequence Memory, Flanker, List Sorting Working Memory, Dimensional Change Card Sort, Oral Reading Recognition, Pattern Comparison, and Picture Vocabulary. Administration was led by a researcher on an iPad (10th generation) and scores were automatically calculated using the NIH Toolbox V3.30.1.2. iPad application. For this thesis, analysis of MoCA and NIH included independent samples t-tests split by sex using JASP statistical software (JASP Team, 2026). We used NIH age-adjusted standard scores for all NIH toolbox statistics, allowing for standardized comparison across participants.

2.6 MRI DATA ACQUISITION

MRI data were acquired using a 3T Skyra Siemens Magnetom MRI system (Siemens Medical Systems, Erlangen, Germany) scanner at the University of Lethbridge, Community Center for Wellbeing in the U3T MRI Center, equipped with a 32-channel head coil. Each participant underwent a high resolution T1-weighted anatomical scan and a task-based T2*-weighted functional scan. T1-weighted images were acquired using a magnetization-prepared rapid gradient echo (MPRAGE) sequence (192 sagittal slices, 1.0 mm thickness, 256×256

matrix, field of view = 256 mm, voxel size = $1.0 \times 1.0 \times 1.0$ mm; TR = 2300 ms, TE = 2.26 ms, flip angle = 8°). Participants then completed a task based functional block-design scan during which T2*-weighted images were acquired using an echo-planar imaging (EPI) pulse sequence (TR = 1500 ms, TE = 33.00 ms, voxel size = $2.5 \times 2.5 \times 2.0$ mm; 72° flip angle, 85×85 matrix, field of view = 256 mm, multiband factor = 4). During this scan, participants performed a passive audiovisual movie viewing task, where they viewed six scenes, three of which that were previously seen at encoding seven days prior (Encoded Scenes), and three novel foils (Novel Scenes). The order of the scenes was randomised for each participant. The entire functional run consisted of 1295 volumes.

2.7 MRI PREPROCESSING

Initial preprocessing was conducted using fMRIPrep version 25.1.4. (see Supplementary Materials B for full preprocessing details; Esteban et al., 2019). In summary, anatomical images were skull-stripped and normalized to MNI152NLin2009Asym space using Advanced Normalization Tools (ANTs; Avants et al., 2008). Functional images underwent slice-timing correction, motion correction, co-registration to anatomical images, and normalization to MNI space. Motion metrics, physiological noise regressors (aCompCor), and motion outliers (framewise displacement > 0.5 mm or standardized DVARS > 1.5) were estimated for subsequent denoising.

Preprocessed data from fMRIPrep was imported into CONN (Whitfield-Gabreli and Nieto-Castanon, 2012) release 22.a (Nieto-Castanon and Whitfield-Gabreli, 2022) and SPM (RRID:SCR_007037) release 12.7771(Penny et al. 2011) for further preprocessing and analysis. Functional data was denoised using CONN's standard denoising pipeline, including regression of potential confounds: white matter time series (5 CompCor noise components), CSF time series (5

CompCor noise components), motion parameters with 1st order derivatives (12 factors), session and task effects with first order derivatives (4 factors), outlier scans (below 494 factors), and linear trends (2 factors) within each functional run, followed by band pass filtering of the BOLD timeseries between .008 Hz and .09 Hz. Importantly, task effects for both blocks (Encoded Scenes and Novel Scenes) were modeled as variables of non-interest during denoising to reduce task evoked co-activation to the functional connectivity estimates to increase confidence that observed differences reflect changes in connectivity profiles.

2.8 FUNCTIONAL CONNECTIVITY ANALYSIS

To detect brain regions that differed in patterns of functional connectivity between females and males during previously viewed scenes, the following steps were implemented: 1) fc-MVPA of pairwise connectivity between all measured voxels; 2) second-level between condition analyses testing for differences in functional connectivity between the groups using an F-test; and 3) post-hoc seed-based correlation analysis (SBC) on each of the identified ROIs from the second-level results.

First-Level Analysis

Functional connectivity analyses were performed in CONN (RRID:SCR_009550) release 22.a and SPM (RRID:SCR_007037) release 12.7771. Functional connectivity multivariate pattern analysis (fc-MVPA; Nieto-Castanon, 2022) was performed to estimate the first ten eigen patterns characterizing the principal axes of heterogeneity in functional connectivity across participants and conditions. The first four eigen patterns were then chosen for analysis based on a recommendation of one component to every ten participants (Nieto-Castanon, 2022; Vittinghoff and McCulloch, 2007). Eigenpatterns and eigenpattern-scores were computed separately for each individual seed voxel and the rest of the brain by singular value decomposition of matrix of

functional connectivity values between each seed voxel and the rest of the brain (a matrix with one row per target voxel, and one column per participant and condition). Individual connectivity values were computed from the matrices of bivariate correlation coefficients between the BOLD time series and each pair of voxels, estimated using as singular value decomposition of the z-score normalized BOLD signal with 64 components separately for each participant and condition.

Second Level Analysis

Group level analyses were performed using a GLM. For each individual voxel, a separate GLM was estimated with first level connectivity measures at this voxel as dependent variables (one independent sample per participant and one measure per task), and sex as an independent variable. Additionally, our female and male groups differed in scores on the MoCA, $t(33) = 2.204, p = .035, d = 0.362$, so it was added to the GLM as a covariate. Voxel-level hypotheses were evaluated using multivariate parametric statistics with random-effects across subjects and sample covariance estimation across multiple measurements. Inferences were performed at the level of individual clusters (groups of contiguous voxels). Cluster-level inferences were based on parametric statistics from Gaussian Random Field Theory (Worsley et al., 1996; Nieto-Castanon, 2020). Results were thresholded using a cluster-forming $p < .01$ voxel-level threshold, and a familywise corrected $p\text{-FWE} < .05$ cluster mass threshold (Chumbley et al. 2010).

Seed-Based Connectivity

Next, we performed post-hoc SBC analysis on the identified regions of interest. SBC were estimated to characterize the spatial pattern of functional connectivity associated with the Females > Males contrast with conditions set to Encoded Scenes > Novel Scenes. Functional connectivity strength was represented by Fisher-transformed bivariate correlation coefficients

from a weighted GLM estimated separately for each seed and target voxel modelling the correlation between their BOLD signal time series. Group-level analyses were performed using a GLM. For each individual voxel, a separate GLM was estimated, with first level connectivity measures at this voxel as the dependent variable. Voxel-level hypotheses were evaluated using multivariate parametric statistics with random effects across subjects and sample covariance estimation across multiple measurements. Cluster level inferences were based on nonparametric statistics from randomization/permutation analyses (Bullmore et al., 1999; Nieto-Castanon, 2020), with 1000 residual-randomization iterations. Results were thresholded using a combination of a cluster-forming $p < .01$ voxel-level threshold and an adjusted cluster-mass corrected $p\text{-}FWE < .05$.

Radar Plot Network Assignment

To examine the functional network distribution of seed-based connectivity (SBC) results, we used the Yeo 17-network cortical atlas (Thomas Yeo et al., 2011). The Yeo 17-network atlas parcellates the cerebral cortex into seventeen distinct functionally coupled networks large scale networks derived from and validated in two independent samples of 500 participants each. These networks include Central Visual (Vis A), Peripheral Visual (Vis B), Somatomotor A (SomMat A), Somatomotor B (SomMat B), Dorsal Attention A (DAN A), Dorsal Attention B (DAN B), Ventral Attention A (VAN A), Ventral Attention B (VAN B), Limbic A (Lim A), Limbic B (Lim B), Control C (Con C), Control A (Con A), Control B (Con B), Temporoparietal (TempPar), Default C (DMN C), Default A (DMN A), and Default B (DMN B). The atlas was selected because it provides a more fine-grained subdivision of the DMN than the commonly used 7-network atlas while maintaining stability. This level of network specificity will help us visualize connectivity patterns within the DMN and between the DMN and other networks.

To visualize the results on a network level, the unthresholded masks created from each fc-MVPA seed were overlaid onto a version of the Yeo 17-network parcellation (Thomas Yeo et al., 2011a) that had been fit to standard MNI152 cortical space. Each voxel within the SBC map was assigned to one of the Yeo-17 functional networks. The resulting unthresholded SBC maps contain voxel-wise *t*-statistics where positive values represented greater connectivity in females than males and negative values represented greater connectivity in males than females. Voxels were classified according to the direction of the group difference based on their individual *t*-stat. The total count of voxels in Female > Male and Male > Female contrasts in each network were converted to a percentage for that network. The distribution of the network percentages was visualized on radar plots for each SBC. The radar plots therefore illustrate the percentage of voxels for females and males separately that belong to each Yeo network and allow us to visualize sex differences in whole brain patterns of connectivity for each seed region.

CHAPTER 3: RESULTS

3.1 BEHAVIOURAL RESULTS

Overall, no significant sex differences were observed in free recall performance or on most cognitive measures. Specifically for our primary measure of task-related retrieval, using percent scores to quantify free recall of previously encoded scenes, a Welch's t-test revealed no significant sex differences ($t(32.87) = 0.13, p = .900$). Means and distribution of the free recall scores are depicted in Figure 5.

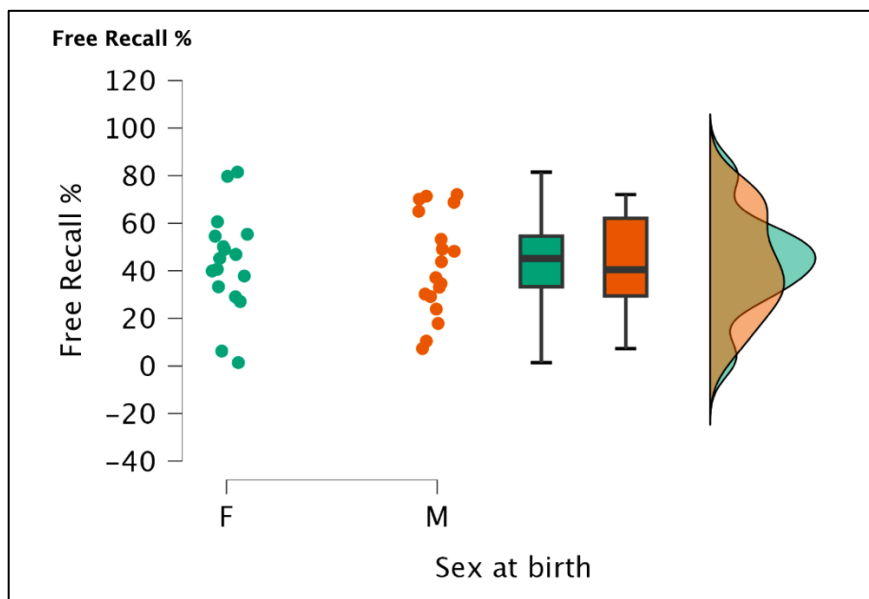


Figure 5: *Free Recall Scores as a Function of Sex*

Note: Scatter plot depicts all participants. Box plot depicts minimum and maximum and means. Raincloud plot depicts density of results.

Independent samples Welch's t-tests revealed no significant sex differences on the MoCA ($t(32.76) = 0.510, p = .613, d = 0.17$), Flanker Inhibitory Control Attention Test ($t(31.51) = 0.027, p = .979, d = .009$), List Sorting Working Memory Test ($t(32.80) = 0.653, p = .518, d = .220$), Dimensional Change Card Sort Test ($t(30.38) = 0.899, p = .376, d = .302$), Oral Reading

Recognition Test ($t(31.94) = .821, p = .418, d = .342$), Pattern Comparison Processing Speed Test ($t(28.70) = .175, p = .862, d = .060$), and Picture Vocabulary Test ($t(32.87) = 0.622, p = .538, d = .210$). However, females ($M = 116.9, SD = 12.17$), performed significantly better than males ($M = 104.2, SD = 11.35$) on the Picture Sequence Memory Test ($t(32.46) = 3.193, p = .003, d = 1.08$). Means and range of the above behavioural test are depicted in Figure 6.

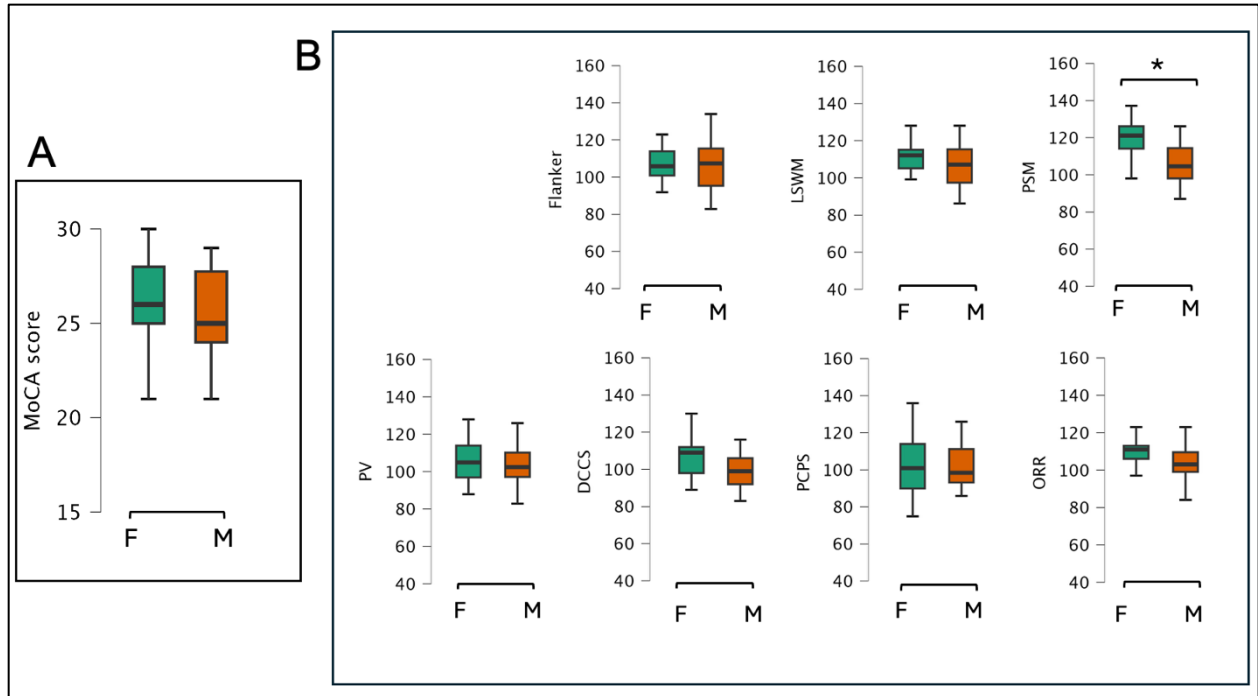


Figure 6: Female and Male MoCA and NIH Toolbox Scores

Note: **A** depicts box plots of Female (F) and Male (M) Montreal Cognitive Assessment scores with the minimum, maximum and mean. **B** depicts box plots of the different NIH Toolbox tests administered split by sex. The top row includes results for the Flanker Inhibitory Control Attention Test, List Sorting Working Memory Test and Picture Sequence Memory Test. The second row includes Picture Vocabulary Test, Dimensional change Card Sort Test, Pattern Comparison Processing Speed Test and Oral reading Recognition Test. Significant differences between groups are marked by an asterisk.

3.2 FC-MVPA RESULTS

Results from the fc-MVPA group-level GLM identified 8 significant clusters of differential functional connectivity between Females and Males using a cluster-forming $p < .01$ voxel-level threshold and a familywise corrected p -FWE $< .05$ cluster-mass threshold using nonparametric statistic with 1000 random permutations. These clusters included the left postCG, precuneus/PCC, left HC, left POpC, left cereb 4 5, right pMTG, left PaCiG and left SFG. According to the Yeo 17 Network Atlas (Thomas Yeo et al., 2011b), four of our clusters were part of the DMN, falling into either Default A (Precuneus/PCC, left PaCiG, left SFG) or Default B (right pMTG) networks. The other clusters fell partially into the Somatomotor A (left PostCG) or Somatomotor B (left POpC). Although the HC is not explicitly included in the Yeo 17 atlas, it is a core component of the default mode network. Fc-MVPA cluster features are included in Table 2. Fc-MVPA clusters are projected in MNI space for visualization in Figure 7.

Table 2.

fc-MVPA Females > Males for Encoded Scenes > Novel Scenes

Cluster Location	Max Voxel Coordinates (x, y, z)			Cluster size	F-value	Size p -FWE
L PostCG	-22	-44	+74	175	3.28	< .001
Bilateral precuneus/ PCC	00	-54	+30	142	2.73	0.002
L HC	-26	-30	-10	131	10.34	0.004
L POpC	-44	-40	+10	122	4.01	0.007
L Cereb 4 5	-14	-44	-32	112	1.18	0.014
R pMTG	+58	-30	-08	108	1.58	0.018
L PaCiG	-10	+50	+14	104	3.70	0.023

L SFG	-22	+50	+44	96	5.59	0.039
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Note: Results from fc-MVPA omnibus analysis for the 2D encoding condition for Females > Males, controlling for MoCA score, for recognition scenes > novel scenes. Coordinates are in MNI space. Abbreviations: PostCG = post central gyrus, HC = Hippocampus, POpC = Parietal Operculum Cortex, Cereb 4 5= Cerebellum crus 4/crus 5, pMTG = posterior middle temporal gyrus, PaCiG = Paracingulate gyrus, SFG = superior frontal gyrus.

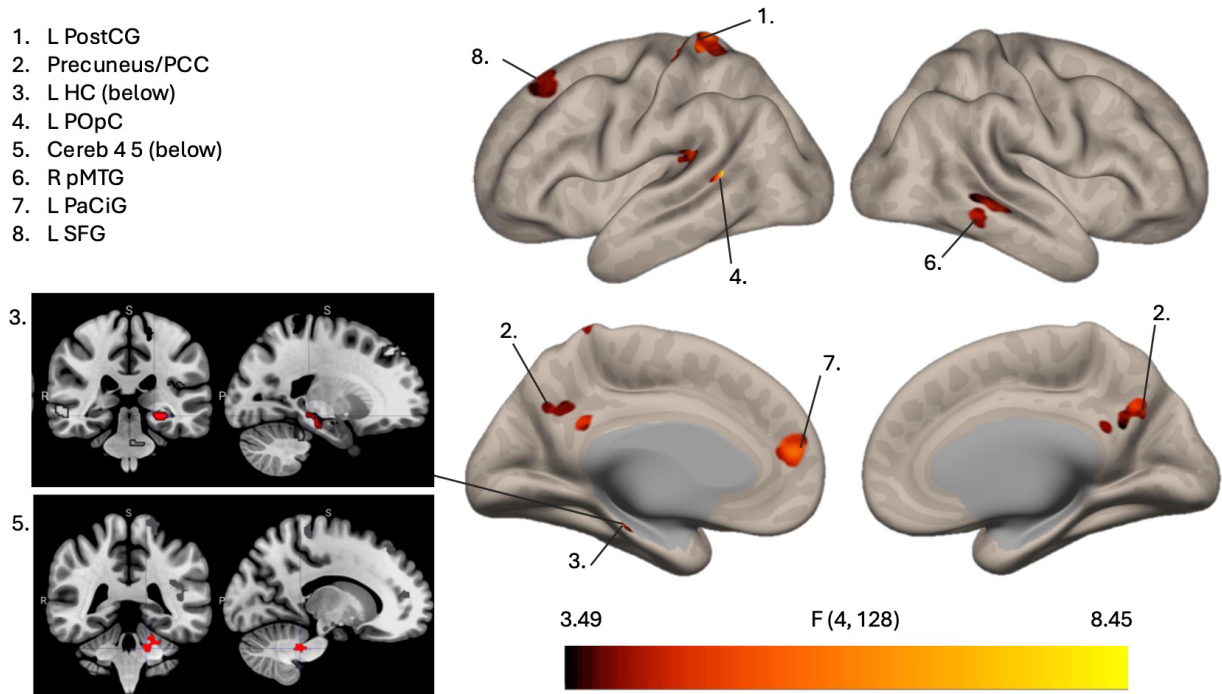


Figure 7: *fc-MVPA results for Females > Males for Encoded Scenes > Novel Scenes*

Note: fc-MVPA clusters in MNI space. Results from fc-MVPA omnibus analysis for the 2D encoding condition for Females > Males, controlling for MoCA score, for recognition scenes > novel scenes. Cluster-forming $p < .01$ voxel-level threshold and an adjusted cluster-mass corrected $p\text{-}FWE < .05$. Abbreviations: PostCG = post central gyrus, HC = Hippocampus, POpC = Parietal Operculum Cortex, Cereb 4 5 = Cerebellum crus 4/crus 5, pMTG = posterior middle temporal gyrus, PaCiG = Paracingulate gyrus, SFG = superior frontal gyrus.

3.3 SBC RESULTS

Post-hoc SBC analyses were completed for the 8 significant ROIs identified from the fc-MVPA analysis (left PostCG, Bilateral Precuneus/PCC, left HC, left POpC, left Cereb 4 5, right pMTG, left PaCiG, left SFG) and are summarized below. SBC masks of significant clusters are presented in Figure 8 for each ROI used as a source seed. SBC results were thresholded at $p < .01$ (voxel level) and $p\text{-}FWE < .05$ (cluster-size corrected). SBC analysis was intended to characterize the patterns of differences for each fc-MVPA seed but should be considered exploratory. Additionally, the radar plots using the SBC results are intended to be illustrative of broad patterns.

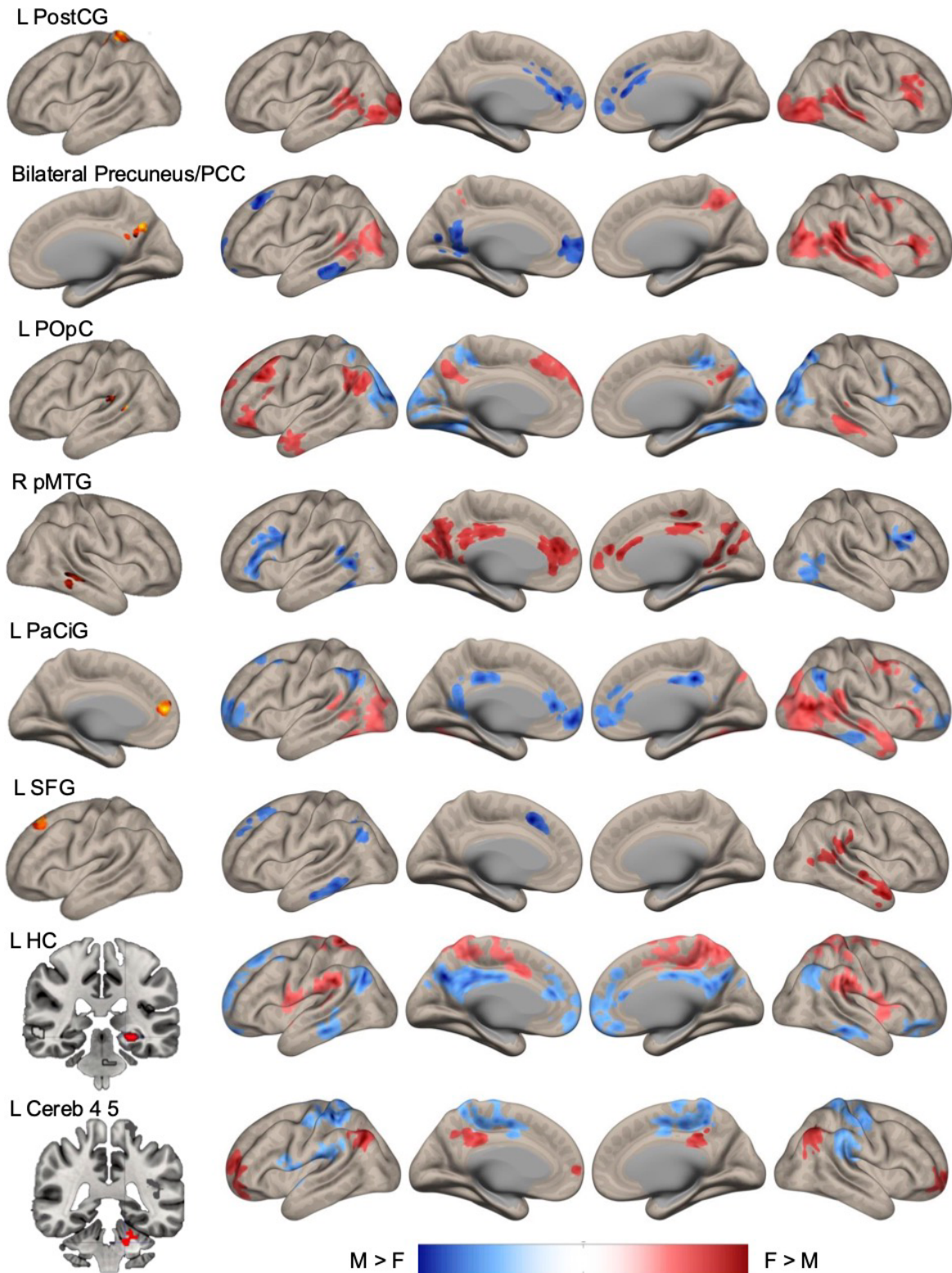


Figure 8: Results from seed-based correlation analysis Females > Males

Note: ROIS with significant differences in connectivity between Females and Males from the fc-MVPA were used as seed regions for a seed-to-voxel connectivity analysis. Seed regions are shown on the left side of the panel and significant regions of connectivity are shown to the right in the following order: left lateral view, left medial view, right medial view, right lateral view. Regions shown in red showed greater connectivity with the seed region for females than males. Regions shown in blue showed greater connectivity from the seed region for males than females. Results were thresholded using a combination of a cluster-forming $p\text{-FWE} < .01$ voxel-level threshold and an adjusted cluster-mass corrected $p\text{-FWE} < .05$. Abbreviations used in the image are Post CG = post central gyrus, HC = Hippocampus, POpC = Parietal Operculum Cortex, Cereb 4 5= Cerebellum crus 4/crus 5, pMTG = posterior middle temporal gyrus, PaCiG = Paracingulate gyrus, SFG = superior frontal gyrus.

L Post Central Gyrus

The SBC analysis using the left PostCG ROI as a seed for whole brain connectivity incorporating both Females > Males and Encoded > Novel contrasts identified 5 regions with significantly different connectivity patterns. The left PostCG showed greater connectivity for the females bilaterally in the inferior LOC, the right IFG triangularis and the left occipital pole. Males showed greater connectivity from the left PostCG to the ACC. The clusters associated with this SBC are presented in Table 3.

Table 3

Seed-Based Connectivity for Left Post Central Gyrus

Cluster Location	Contrast	Max Voxel Coordinates	Cluster size	<i>t</i> -value	Size <i>p</i> -FWE
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		(x, y, z)					
L inferior LOC	Female > Male	-14	-80	-22	2732	8.12	< .001
R inferior LOC		+48	-40	+02	2540	6.01	< .001
R IFG triangularis		+60	+26	+08	807	6.41	< .001
L Occipital Pole		-16	-106	+06	624	5.16	< .001
ACC	Male > Female	-04	+46	+10	930	-5.74	< .001

Note: Results from SBC analysis for source voxel (-22 -44 74) Females > Males, controlling for MoCA score. Coordinates are in MNI space. Abbreviations: LOC = Lateral occipital cortex, IFG = Inferior frontal gyrus, ACC = Anterior Cingulate Cortex.

Precuneus/Posterior Cingulate Cortex

The SBC analysis using the Precuneus/PCC ROI as a seed for whole brain connectivity incorporating both Females > Males and Encoded > Novel contrasts identified 9 regions with significantly different connectivity patterns. The PCC showed greater connectivity for females to the right inferior lateral occipital cortex, left superior lateral occipital cortex, right inferior frontal gyrus triangularis, right precuneus, and the right precentral gyrus. Males showed greater connectivity between the precuneus/PCC ROI to the left frontal pole, left precuneus, left pMTG, and left SFG. The clusters associated with this SBC are presented in Table 4.

Table 4

Seed-Based Connectivity for Bilateral Precuneus/PCC

Cluster Location	Contrast	Max Voxel Coordinates (x, y, z)			Cluster size	t-value	Size p-FWE
R inferior LOC	Female > Male	+62	-40	+24	3436	5.45	< .001
L superior LOC		-46	-82	+24	1009	4.77	< .001
R IFG triangularis		+50	+28	+08	884	5.89	< .001

R Precuneus		+08	-54	+48	491	4.43	< .001
R PreCG		+48	+04	+46	373	4.98	< .001
L Frontal Pole	Male > Female	-06	+48	+06	549	-4.89	< .001
L Precuneus		-04	-54	+14	422	-4.54	< .001
L pMTG		-68	-36	-14	317	-4.45	0.013
L SFG		-20	+32	+48	310	-4.89	0.015

Note: Results from SBC analysis for source voxel (0 -54 30) Females > Males, controlling for MoCA score. Coordinates are in MNI space. Abbreviations: LOC = Lateral occipital cortex, IFG = Inferior frontal gyrus, PreCG = precentral gyrus, pMTG = posterior middle temporal gyrus, SFG = superior frontal gyrus.

L Hippocampus

The SBC analysis using the left HC ROI as a seed for whole brain connectivity incorporating both Females > Males and Encoded > Novel contrasts identified 12 regions with significantly different connectivity patterns. Females had greater connectivity between the left hippocampus and clusters in the precuneus, bilateral POpC, and the bilateral central operculum. Males also showed greater connectivity between the left HC and a cluster in the left precuneus, but at a slightly more medial cluster overlapping with voxels in the PCC. Males also had greater connectivity to the bilateral superior LOC, bilateral pMTG, and the right cerebellum Crus2. The clusters associated with this SBC are presented in Table 5.

Table 5

Seed-Base Connectivity for the Left Hippocampus ROI

Cluster Location	Contrast	Max Voxel Coordinates (x, y, z)			Cluster size	t-value	Size <i>p</i> -FWE
L Precuneus	Female > Male	-20	-46	+66	4126	10.42	< .001

R POpC		+56	-28	+28	905	6.50	< .001
L POpC		-56	-40	+32	658	6.10	< .001
L Central Operculum		-62	+06	+10	546	5.97	< .001
R Central Operculum		+48	+04	+08	546	5.83	< .001
L Frontal Pole	Male > Female	-14	+56	-18	2928	-10.39	< .001
L Precuneus/PCC		-02	-70	+34	2158	-6.52	< .001
L sLOC		-44	-76	+42	855	-5.49	< .001
R sLOC		+50	-60	+50	581	-4.67	< .001
R pMTG		+62	-28	-18	512	-7.29	< .001
R Cerebellum Crus2		+46	-76	-36	421	-4.84	0.001
L pMTG		-62	-36	-12	400	-5.95	0.002

Note: Results from SBC analysis for source voxel (-26 -30 -10) Females > Males, controlling for

MoCA score. Coordinates are in MNI space. Abbreviations: POpC = parietal operculum cortex, PCC = posterior cingulate cortex, sLOC = superior lateral occipital cortex, pMTG = posterior middle temporal gyrus.

L Parietal Operculum Cortex

The SBC analysis using the left POpC ROI as a seed for whole brain connectivity incorporating both Females > Males and Encoded > Novel contrasts identified 13 regions with significantly different connectivity patterns. Females had greater connectivity from the left POpC to the left superior lateral occipital cortex, left middle frontal gyrus, right pMTG, right precuneus, left temporal pole, and two clusters the right cerebellum (Crus 1 and 2), as well as two clusters in the left frontal pole. Both the right precuneus and the left superior LOC had clusters that were Female > Male and Male > Female. Additionally, males showed greater connectivity than females between the left parietal operculum and the left SPL and right precentral gyrus. The clusters associated with this SBC are presented in Table 6.

Table 6*Seed-Based Connectivity for Left Parietal Operculum Cortex*

Cluster Location	Contrast	Max Voxel Coordinates (x, y, z)			Cluster Size	t-value	Size p-FWE
L sLOC	Female > Male	-56	-60	+28	917	5.26	<0.001
L MidFG		-54	+22	+36	869	6.62	<0.001
L Frontal Pole		-14	+66	+18	757	6.49	<0.001
L Frontal Pole		-46	+36	-16	503	5.84	<0.001
R Cerebellum Crus 1		+24	-82	-28	424	5.65	0.001
R pMTG		+70	-40	+10	348	4.73	0.005
R Cerebellum Crus 2		+38	-72	-48	335	6.17	0.007
Precuneus		+04	-56	+32	332	4.04	0.007
L Temporal Pole		-56	+04	-22	326	5.34	0.008
L/R sLOC	Male > Female	+16	-70	+58	6994	-7.99	<0.001
L SPL		-16	-46	+52	377	-5.91	0.003
R Precuneus		+10	-40	+48	297	-5.50	0.015
R PreCG		+50	-02	+14	269	-5.88	0.028

Note: Results from SBC analysis for source voxel (-44 -40 10) Females > Males, controlling for MoCA score. Coordinates are in MNI space. Abbreviations: sLOC = superior lateral occipital cortex, MidFG = middle frontal gyrus, pMTG = posterior middle temporal gyrus, SPL = superior parietal lobule, PreCG = precentral gyrus.

L Cerebellum 4 5

The SBC analysis using the left cerebellar ROI as a seed for whole brain connectivity incorporating both Females > Males and Encoded > Novel contrasts identified 9 regions with significantly different connectivity patterns. Females had greater connectivity between the left cerebellum 4 5 ROI to the left and right frontal pole and left and right sLOC, PCC and a cluster

in the right cerebellum crus 2. Males had greater connectivity from the cerebellar seed to bilateral PostCG, and the left POpC and central operculum cortex. The clusters associated with this SBC are presented in Table 7.

Table 7

Seed-Based Connectivity for Cerebellum 4 5

Cluster Location	Contrast	Max Voxel Coordinates (x, y, z)			Cluster Size	t-value	Size p- FWE
L Frontal Pole	Female > Male	-24	+48	+06	905	5.69	<0.001
R Cerebellum Crus 2		+28	-66	-30	750	5.60	<0.001
L sLOC		-46	-70	+46	745	4.93	<0.001
R sLOC		+40	-58	+44	651	4.68	<0.001
PCC		+04	-36	+40	456	5.90	<0.001
R Frontal Pole		+20	+66	-08	451	5.43	<0.001
L/R PostCG	Male > Female	-36	-34	+56	5993	-9.45	<0.001
L POpC		-46	-24	+24	542	-5.54	<0.001
L Central Operculum		-54	+02	+02	297	-5.25	0.015

Note: Results from SBC analysis for source voxel (-14 -44 -32) Females > Males, controlling for MoCA score. Coordinates are in MNI space. Abbreviations: sLOC = superior lateral occipital cortex, PCC = posterior cingulate cortex, PostCG = post central gyrus, POpC = parietal operculum cortex.

R Posterior Middle Temporal Gyrus

The SBC analysis using the right pMTG ROI as a seed for whole brain connectivity incorporating both Females > Males and Encoded > Novel contrasts identified 8 regions with

significantly different connectivity patterns. Females had greater connectivity between the pMTG ROI and the precuneus/PCC as well as the ACC/PaCiG. Males had greater connectivity between the pMTG ROI and the bilateral inferior frontal gyrus, right temporal occipital fusiform cortex, right middle frontal gyrus, left MTG, right inferior lateral occipital cortex, and left inferior temporal gyrus. The clusters associated with this SBC are presented in Table 8.

Table 8

Seed-Based Connectivity for Right Posterior Middle Temporal Gyrus

Cluster Location	Contrast	Max Voxel Coordinates (x, y, z)			Cluster Size	t-value	Size p-FWE
Precuneus/PCC	Female > Male	+04	-20	+46	1963	6.32	<0.001
ACC		-10	+38	+16	935	5.98	<0.001
L/R IFG	Male > Female	-48	+34	+08	1026	-5.63	<0.001
R TOFusC		+36	-60	-22	442	-4.86	0.001
R MidFG		+46	+24	+28	429	-5.19	0.001
L MTG		-62	-62	+10	390	-4.83	0.003
R iLOC		+48	-66	-02	340	-4.35	0.007
L ITG		-46	-58	-14	294	-4.81	0.019

Note: Results from SBC analysis for source voxel (58 -30 -8) Females > Males, controlling for MoCA score. Coordinates are in MNI space. Abbreviations: PCC = posterior cingulate cortex, ACC = anterior cingulate cortex, IFG = inferior frontal gyrus, TOFusC = temporal occipital fusiform cortex, MidFG = middle frontal gyrus, MTG = middle temporal gyrus, iLOC = inferior lateral occipital cortex, ITG = inferior temporal gyrus.

L Paracingulate Gyrus

The SBC analysis using the left PCG ROI as a seed for whole brain connectivity incorporating both Females > Males and Encoded > Novel contrasts identified 16 regions with significantly different connectivity patterns. Females had greater connectivity than males from the left PaCiG to the right and left inferior lateral occipital cortex, left cerebellum crus 8, left temporal occipital fusiform cortex, right temporal pole, right PreCG, right inferior frontal gyrus. Males had greater connectivity between the left PaCiG ROI and the left superior lateral occipital cortex, right AG, right cerebellum crus 2, left middle frontal gyrus, right pMTG, bilateral Frontal pole, and two clusters in the PCC. The clusters associated with this SBC are presented in Table 9.

Table 9

Seed-Based Connectivity for Left Paracingulate Gyrus

Cluster Location	Contrast	Max Voxel Coordinates (x, y, z)			Cluster Size	t- value	Size <i>p</i> - FWE
R iLOC	Female > Male	+48	-66	+18	4897	5.53	<0.001
L iLOC		-46	-84	-16	1296	4.36	<0.001
L Cerebellum Crus 8		-06	-72	-50	610	4.96	<0.001
L TOFusC		-38	-62	-18	442	5.57	0.001
R Temporal Pole		+52	-14	-10	432	5.34	0.001
R PreCG		+46	+06	+54	405	4.93	0.002
R IFG		+52	+28	-12	328	4.54	0.010
L Frontal Pole	Male > Female	-02	+42	+08	2257	-7.20	0.003
L sLOC		-54	-44	+48	788	-5.00	<0.001
PCC		+04	-30	+34	517	-5.19	<0.001
PCC		-22	-38	+00	514	-5.73	<0.001
R AG		+50	-56	+46	395	-4.28	<0.001
R Cerebellum crus 2		+46	-66	-40	371	-4.41	0.004

L MidFG	-34	+12	+58	297	-4.35	0.019
R Frontal Pole	+40	+36	+22	260	-4.42	0.040
R pMTG	+68	-18	-20	251	-4.61	0.049

Note: Results from SBC analysis for source voxel (-10 +50 +14) Females > Males, controlling for MoCA score. Coordinates are in MNI space. Abbreviations: iLOC = inferior lateral occipital cortex, TOFusC = temporal occipital fusiform cortex, PreCG = precentral gyrus, IFG = inferior frontal gyrus, sLOC = superior lateral occipital cortex, PCC = posterior cingulate cortex, AG = angular gyrus, MidFG = middle frontal gyrus, pMTG = posterior middle temporal gyrus.

L Superior Frontal Gyrus

The SBC analysis using the left SFG ROI as a seed for whole brain connectivity incorporating both Females > Males and Encoded > Novel contrasts identified 6 regions with significantly different connectivity patterns. Females had greater connectivity between the left SFG ROI and the right MTG and right temporal pole, whereas males had greater connectivity to the left SFG, right cerebellum crus 2, left inferior temporal gyrus, and left superior lateral occipital cortex. The clusters associated with this SBC are presented in Table 10.

Table 10

Seed-Based Connectivity for Left Superior Frontal Gyrus

Cluster Location	Contrast	Max Voxel Coordinates (x, y, z)			Cluster Size	t-value	Size p-FWE
R MTG	Female > Male	+62	-34	+24	466	4.65	<0.001
R Temporal Pole		+46	+06	-30	344	5.69	0.008
L SFG	Male > Female	-04	+22	+46	547	-5.57	<0.001
R Cerebellum crus 2		+36	-76	-42	461	-4.32	<0.001

L ITG	-52	-56	-08	351	-5.37	0.007
L sLOC	-34	-66	+36	329	-5.24	0.010

Note: Results from SBC analysis for source voxel (-22 +50 +44) Females > Males, controlling for MoCA score. Coordinates are in MNI space. Abbreviations: MTG = posterior middle temporal gyrus, SFG = superior frontal gyrus, ITG = inferior temporal gyrus, sLOC = superior lateral occipital cortex.

3.4 NETWORK VISUALIZATION RESULTS

Most DMN seeds (PCC, HC, PaCiG) showed greater connectivity for males to DMN subnetworks. Greater connectivity to DMN A and B was observed for males from the left PostCG, Precuneus/PCC, left HC, left PaCiG, whereas for the left SFG and the right pMTG males had greater connectivity to subnetworks A and B respectively, but not both. In contrast, females had greater DMN A and B connectivity for the left POpC and left Cereb 4 5. Additionally, females had greater connectivity to DMN A from the right pMTG and to DMN B from the left SFG.

Con B had the same overall pattern of connectivity for females versus males for each seed as DMN A. Other prominent network level differences included greater connectivity with Vis A for females from the left PostCG, PCC, left Cereb 4 5, left PaCiG, and left SFG. Oppositely Vis A had greater connectivity from males to the L POpC and the R MTG. DAN A and VAN A also showed large differences in connectivity between females and males, with females having greater connectivity to both networks from the left PostCG, Precuneus, HC, left PaCiG and left SFG. Males showed greater connectivity to the DAN A from left POpC, left cereb 4 5, R MTG and greater connectivity to VAN A from cereb 4 5. Lastly, the females

showed greater connectivity with SomMot A from the hippocampus whereas males showed greater connectivity with SomMot A from cereb 4 5. Full visualization of voxels classified into one of the seventeen functionally connected networks from the Yeo 17 Network Parcellation for each source voxel is presented in Figure 9.

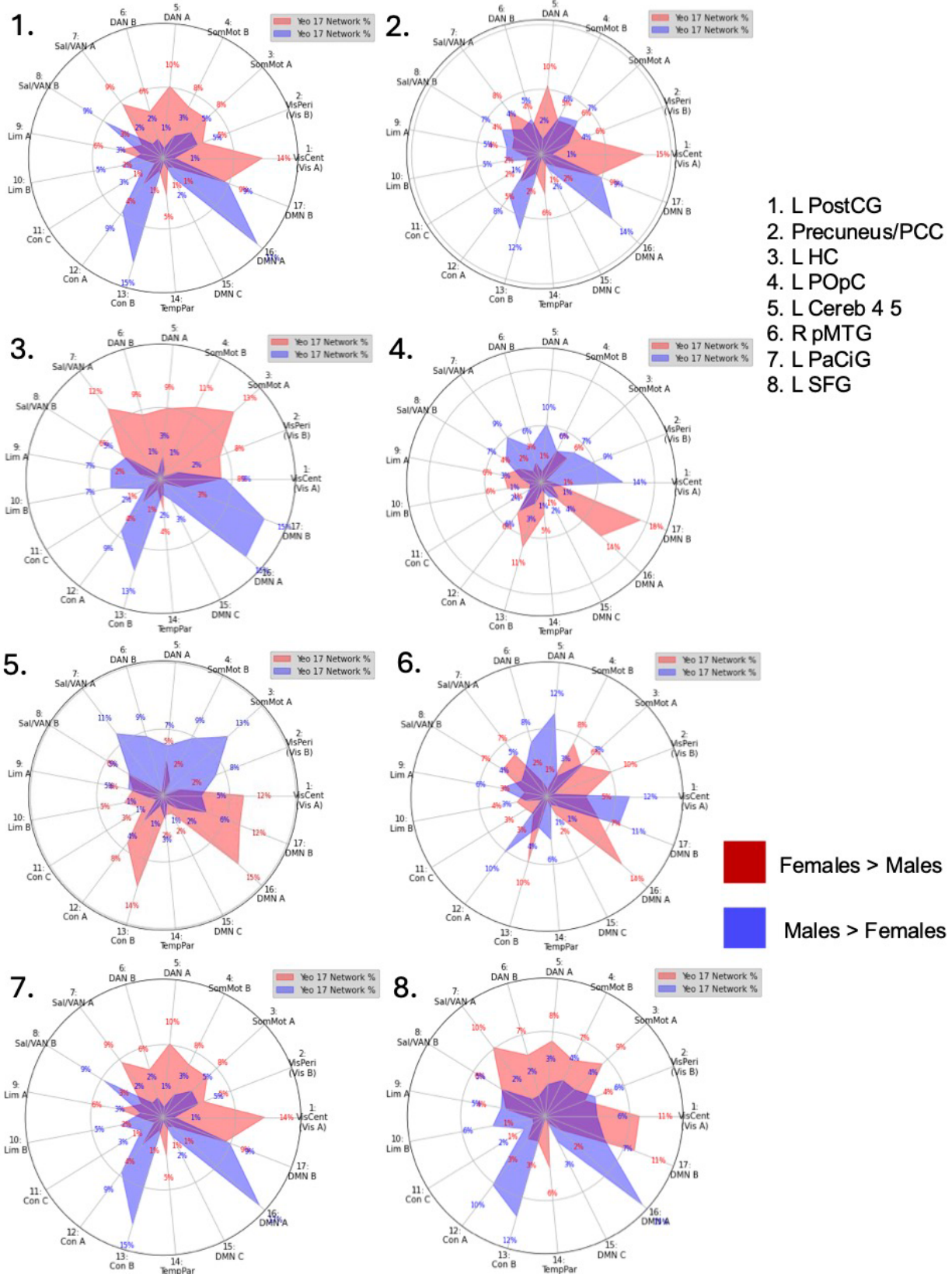


Figure 9: Radar Plot Network Visualization of SBC Results using Yeo 17 Classification

Note: Radar plot of unthresholded SBC results classified into Yeo-17 cortical networks (Thomas Yeo et al., 2011b) for each fc-MVPA ROI. *Female > Male (Red)*, *Male > Female (Blue)*.

Networks counter-clockwise from 1. Central Visual (Vis A), 2. Peripheral Visual (Vis B), 3. Somatomotor A (SomMat A), 4. Somatomotor B (SomMat B), 5. Dorsal Attention A (DAN A), 6. Dorsal Attention B (DAN B), 7. Ventral Attention A (VAN A), 8. Ventral Attention B (VAN B), 9. Limbic A (Lim A), 10. Limbic B (Lim B), 11. Control C (Con C), 12. Control A (Con A), 13. Control B (Con B), 14. Temporoparietal (TempPar), 15. Default C (DMN C), 16. Default A (DMN A), 17. Default B (DMN B).

CHAPTER 4: DISCUSSION

4.1 MAIN FINDINGS

In this study, we sought to identify sex-specific patterns of functional connectivity associated with recognition of previously encoded naturalistic scenes. To do so, we contrasted previously viewed scenes with novel scenes during fMRI and analyzed the functional connectivity patterns for the patterns that explained the most variance between females and males using fc-MVPA. We also measured delayed recall of the previously viewed scenes with a free recall paradigm. Behaviourally, we hypothesized that females would perform better on the delayed free recall task. Neurally, we hypothesized that females and males would show different patterns of functional connectivity in the HC and DMN. In line with our hypothesis, results from this study show that females and males have different patterns of functional connectivity within and beyond the DMN and HC. Interestingly, there was no observed sex differences in episodic recall of the stimuli. In summary, our results show that older females and males showed similar behavioural memory performance, but different patterns of functional connectivity during recognition of previously encoded scenes. This suggests that similar episodic memory processes may be maintained by different configurations of connectivity networks.

4.2 MEMORY PERFORMANCE VS. CONNECTIVITY DIFFERENCES

In contrast to our behavioural hypothesis, our results do not show a female advantage in episodic memory recall, suggesting that this advantage may be specific to some tests and may not extend to more naturalistic episodic memory paradigms. We hypothesized that females would perform better on the recall task based on previously reported episodic memory advantages for women (Herlitz et al., 1997) including performance on narrative recall (Hultsch et al., 1991). In our study, females did perform better on one of the traditional behavioural episodic

memory tests, the Picture Sequence Memory Test (Weintraub et al., 2013). During the Picture Sequence Memory Test, participants view a series of animated pictures depicting events in a larger story and later arrange the pictures in the correct chronological order. Although this task shares some features with the episodic recall task used in the present study, including event-based content and memory for temporally structured information, the two tasks also differ in several important ways. The Picture Sequence Memory task uses animated images, no dialogue, immediate recall, explicit event cues, and short stimulus duration. In contrast, the present task used live-action audiovisual vignettes with dialogue, delayed free recall, minimal retrieval cues, and a longer encoding period. Although the present study cannot isolate which task features account for these differing behavioural outcomes, this comparison highlights important distinctions between traditional laboratory measures and more naturalistic assessments of episodic memory. Overall, these findings suggest that older females may continue to show an episodic memory advantage in some domains, but that this advantage may not extend to delayed free recall of complex, real-world experiences.

Notably, we shed light on whether females and males use different memory networks to achieve the same performance. Given that we used the same stimuli for our recall task and our fMRI recognition task, we can observe both behavioural and neural memory findings from the same population of older females and males. At delayed recall there were no sex differences in performance, but during viewing of previously encoded scenes, females and males showed different patterns of whole brain connectivity. This disconnect between behavioural and neural differences suggests different memory networks may be implicated in females and males for relatively similar performance. This complements previous research by Subramaniapillai et al. (2019) who used a face-location memory association task to investigate if there are sex

differences in the effect of age and memory performance on brain activity during retrieval. Their behavioural analysis indicated no significant sex differences in retrieval accuracy but found sex differences in brain regions that supported memory at retrieval, including the PFC, PHG and inferior parietal cortex. They attributed these differences to aging and concluded that females and males may differ in regions used for age related successful retrieval. Given our older sample, future analyses that look for an age by sex interaction would be warranted.

4.3 DMN AND HC SEX SPECIFIC ORGANIZATION

Our results show sex specific DMN and HC connectivity, which may suggest specific functional memory networks differ between females and males. Specifically, the fc-MVPA results revealed differences in whole brain connectivity between females and males from the 8 including the hippocampus and four other regions identified as DMN (PaCiG, Precuneus/PCC, SFG, pMTG). These findings extend previous evidence of sex differences in PCC connectivity to different regions of the DMN across adulthood (Ficek-Tani et al., 2023) by demonstrating that differences in DMN connectivity are also evident in older adulthood. Our seed overlapped with the PCC and precuneus, which has been associated with visual imagery and rich episodic contextual episodic memory associations (Lundstrom et al., 2005), and should be particularly relevant for recognizing previously viewed naturalistic scenes. The PCC has also been implicated in episodic memory, with research from Natu et al., (2019) finding that functional connectivity between the PCC and HC modulated the strength to which deep brain stimulation of the PCC could impair memory recall. This directly implicates the connection between the PCC and HC as an essential component for memory performance. Additionally, connectivity between PCC and other DMN regions, as well as connectivity between HC and other DMN regions, is associated with successful memory encoding (Li et al., 2015).

Our SBC results further characterize sex specific connectivity profiles by revealing different hippocampal to DMN and PCC to DMN profiles for males and females. Females showed greater connectivity than males from the PCC to the right precuneus and from the HC to the left precuneus. Males, on the other hand, showed greater connectivity from the PCC to the left precuneus, left pMTG, left frontal pole and left SFG, as well as greater connectivity from the HC to the left and right pMTG and left frontal pole. This is consistent with Ficek et al. (2021), who found that males had greater connectivity in anterior nodes of the DMN (including the frontal pole). Despite these differences in connectivity profiles, females and males showed comparable recall, suggesting that different patterns of hippocampal and DMN organization may support recognition differently in older men and women.

4.4 WITHIN-NETWORK VERSUS BETWEEN NETWORKS

To provide insight into how these differences are distributed across large scale functional networks, we used the SBC results and radar plot visualizations. Specifically, the radar plot visualization results in Figure 5 show stronger DMN connectivity for males compared to females. Salami et al. reported that the level of within DMN network connectivity is positively associated with episodic memory scores and that within DMN connectivity for both anterior and posterior DMN components decline as a function of increasing age. Of the seeds determined to belong to the default mode (PaCiG, SFG, HC, pMTG, Precuneus/PCC) all but one (right pMTG) showed greater connectivity for males to the DMN. Research by Ficek-Tani et al., (2023) indicated males have higher relative connectivity from the PCC and other DMN nodes to the anterior DMN, which is consistent with our SBC results for males > females that showed greater connectivity from the left PCC, left HC, and left PaCiG to the frontal pole (which has a large degree of overlap in the anterior DMN). Additionally, the left SFG showed within anterior DMN

connectivity that was greater for males than females, specifically showing greater connectivity to another cluster of voxels in the left SFG. This supports previous findings that suggest males have more modular connectivity (Ingallhalikar et al., 2014).

In our unthresholded SBC results, we saw a pattern where males had greater PCC to DMN connectivity specifically to regions associated with DMN A in the Yeo 17 network parcellation. These results conflict in part with Ficek-Tani (2023), who reported females to have greater posterior DMN connectivity and greater overall within DMN connectivity than males for the bilateral PCC during resting state. Consequently, less within DMN connectivity observed in our study of older females may reflect age-related changes in network connectivity rather than a general sex difference. Additionally, we had significant clusters with greater connectivity to the precuneus for both males > females and females > males that were similar size (491 voxels, 422 voxels). These may represent different subregions, demonstrating within DMN-network connectivity sex difference to relatively adjacent regions of the DMN. Previous research (e.g., Ficek et al. 2021) used resting state to study sex differences that may not reflect the same within or between network patterns as memory tasks. It is possible that this discrepancy comes from our use of a naturalistic task that engaged the DMN in different ways and this task aligns more with DMN segregation seen in older females (Ballard et al., 2023).

Our SBC also demonstrated greater connectivity for females than males from DMN regions to the dorsal and ventral attention networks. This is inconsistent with literature that suggests that females have higher segregation of networks (e.g., Sidhu et al., 2025), which report that whole-brain, associative, DMN, VAN, and FPN segregation is greater in females compared to males during resting state, irrespective of age. However, higher segregation has also been negatively associated with memory performance. Spalek et al. (2023) compared sex dependent

differences in connectivity patterns to recall. Their results showed that females had less network segregation, which was associated with better performance on picture free recall. Taken together with our findings, reduced connectivity between DMN regions might reflect reduced DMN segregation, which was observed in female networks and is consistent with task-based memory studies that report females having reduced segregation. Collectively, these findings demonstrate sex differences in network level whole brain connectivity within the DMN and between the DMN and other networks, indicative of sex specific patterns of functional memory architecture.

4.5 AGING, MENOPAUSE, AND DISEASES OF EPISODIC MEMORY

There are widespread sex differences in the prevalence and mechanisms of age-related diseases, including diseases of episodic memory, making their discussion a crucial topic in women's health research (Sampathkumar et al., 2020). For example, women have an increased risk for memory disorders relative to men later in life (Jacobs et al., 2016). The sex differences we observed may be linked to age-related DMN functioning. The DMN supports recall performance in elderly individuals (Huo et al., 2018) and both impaired and unimpaired aging are associated with changes in the DMN (Nyberg, 2017). Specifically, decline in DMN connectivity has been linked to AD (Brier et al., 2012) and connectivity between HC-DMN is targeted by AD.

In females, postmenopausal women showed enhanced bilateral hippocampal connectivity relative to premenopausal and perimenopausal women and behaviourally it has also been shown that post-menopausal women have worse verbal memory than premenopausal women (Jacobs et al., 2016). We observed connectivity differences that may interact with age related changes in older females and males and may reflect neural processes relevant to disease vulnerability. Papma et al. (2017) found evidence that functional network changes are a predictor of PCC

functioning in MCI and that PCC functioning during episodic memory relates to hippocampal function in MCI. Additional attention should be paid to similarities between MCI and AD progression of functional connectivity and the functional connectivity patterns in females that may help to identify predictors of disease. Together with our findings, this suggests sex specific patterns of HC to DMN connectivity may represent an important avenue for longitudinal studies investigating how functional connectivity differences precede or accompany behavioural performance and experience. Determining whether these connectivity profiles are associated with resilience or increased disease susceptibility to MCI or AD may improve our understanding of sex differences in disease progression.

4.6 LIMITATIONS AND FUTURE DIRECTIONS

There are several limitations and future directions for this study. First, our sample of participants comes from a WEIRD (Henrich et al., 2010) society and is predominantly western, educated, industrialized, rich, and democratic. The average education level in the sample is 14.83 years and our participants were predominantly white. Future research should extend the current task to a more diverse population of participants. A second limitation relates to the use of naturalistic movie stimuli to elicit episodic memories. Although the stimuli were designed to engage episodic retrieval, previously viewed scenes and novel foils inevitably differed in characteristics such as visual content, emotional salience, language, and other cognitive processes associated with movie viewing. As a result, some observed differences may reflect factors beyond episodic memory alone. Nevertheless, the complexity of naturalistic stimuli is also a major strength as it more closely approximates real world memory experiences than highly controlled lab tasks. Several design features were incorporated to reduce potential confounds, including contrasting previously viewed and novel scenes, randomizing stimulus presentation,

and administering a free recall task before scanning, which allowed us to later verify that participants encoded the scenes. Additionally, the experimental design was constrained by practicality and resources. Because we designed the scenes and had them performed by hired actors, we were required to coordinate schedules with multiple actor sets for different scenes (as well as some replacements). There are also limitations to fMRI, such as participants' individual experience including anxiety or claustrophobia, discomfort with the loudness of the MRI, and potential disengagement from the task. Functional connectivity in MRI also has limitations in that it is based on correlation between voxels and cannot predict or signify causal directionality of observed effects.

4.7 CONCLUSIONS

In conclusion, to the best of our knowledge, this is the first study to use naturalistic stimuli to examine sex differences in whole-brain functional connectivity during an episodic recognition memory task in older adults. This is an important contribution because older adults, particularly post-menopausal women, remain understudied at the intersection of sex differences, neuroimaging, and memory, despite their heightened vulnerability to diseases that affect episodic memory. Our results support the existence of sex-specific memory network organization that includes distinct connectivity patterns from the HC and the DMN to the rest of the brain in older females and males. More specifically we observed within network DMN connectivity to be greater for males during viewing of previously encoded scenes. Although our findings do not demonstrate a female episodic memory advantage in episodic memory performance, they do reveal sex-specific patterns of connectivity that differ from those reported in younger adults. More importantly, the lack of memory advantage in females for our naturalistic task is notable considering females had distinct memory network organization. This thesis therefore

contributes to memory and sex difference research by finding that during viewing of previously encoded scenes females and males have unique patterns of functional connectivity within and beyond the DMN that contribute to equal memory performance between groups.

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SUPPLEMENTARY MATERIALS

APPENDIX A: DRAM 4850 CREATING A SCENE ASSIGNMENT

Creating a Scene for Scientific Research

DRAM 4850: Theatre Production for Scientific Purposes

Assignment guidelines and requirements:

You are being tasked with creating or adapting a short vignette to be used as experimental stimuli for a neuroscience experiment studying memory. This vignette must meet very specific criteria to be used in scientific research looking at episodic memory encoding. From this class we intend to create and perform 6-10 scenes that will be completely refined by the end of the class.

Follow these two checklists:

Scene Logistics	Plot Requirements
Scene logistic criteria: • Have a plot • Include a series of events • Have 2-3 characters • Be reproducible • Simple set • Simple costuming	The plot should be: • Entertaining • Common • Elicit Emotion • Current Setting (2024 era) • Safe

Scene Logistics:

- Plot: Each scene should have segments of beginning, middle and end that can be easily identified for statements such as, "in the beginning..."
- Events: The scene should have a series of events. Favour a structure that encourages "and then.." statements during free recall based on the series of events, and how they might be arranged in a distinct manner. "She took a dog for a walk, and then she ran into a friend, and then she got a phone call.."
- Characters: the scene should include 2 characters who have distinct personalities. The audience should be able to observe emotional moments for the characters as well as a gist of their personality and features. The character can include distinct items of costuming but these do not need to be noteworthy for all characters.
- Reproducible: The vignette will need to be a scene that can be acted in a near identical way every time it is performed. Avoid actions that may cause unnecessary variation (ex. the reliance on someone making a buzzer beater shot in a game)

- Simple set: each scene will have to be performed in one room and will have an identical sized set that all actions must take place in. All props and acting must fit within the space given. The set and props should be simple and easy to change quickly. This stand size will be determined with the class based on the space.
- Simple Costuming: The costumes should be easy to change quickly and be relatively distinct from one another.

Plot features:

- Entertaining: Keep the audience engaged and interested.
- Common: These scenes should be something you may observe in your day to day activities. (Examples: coffee shop conversations, date or break-up in a public place, interaction in a workplace)
- Elicit Emotion: The audience should have feelings towards the characters
- Current Setting: These scenes do not need to be non-fiction but should include events that would happen within our current setting (Lethbridge AB, 2025). They should not include elements of fantasy or science fiction. No out of context features (No magic, time-travel, knights, cave-men et.)
- Safe: Scenes being used in research must pass ethical guidelines and not sway our results based on content or emotion. Topics that cause psychological distress or have strong emotional responses and associations with possible trauma must be avoided. DO NOT include mention of self harm, suicide, sexual assault, trauma, abortion etc. If you are unsure, consult your instructor.

APPENDIX B: fMRI Prep Boiler Plate

This appendix is the boilerplate text of our fMRIPrep preprocessing steps, automatically generated by NiReports that is suggested to be copied and pasted into manuscripts unchanged.

Results included in this manuscript come from preprocessing performed using *fMRIPrep* 25.1.4 (Esteban et al. (2019); Esteban et al. (2018); RRID:SCR_016216), which is based on *Nipype* 1.10.0 (K. Gorgolewski et al. (2011); K. J. Gorgolewski et al. (2018); RRID:SCR_002502).

Anatomical data preprocessing

A total of 1 T1-weighted (T1w) images were found within the input BIDS dataset. The T1w image was corrected for intensity non-uniformity (INU) with `N4BiasFieldCorrection` (Tustison et al. 2010), distributed with ANTs 2.6.2 (Avants et al. 2008, RRID:SCR_004757), and used as T1w-reference throughout the workflow. The T1w-reference was then skull-stripped with a *Nipype* implementation of the `antsBrainExtraction.sh` workflow (from ANTs), using OASIS30ANTs as target template. Brain tissue segmentation of cerebrospinal fluid (CSF), white-matter (WM) and gray-matter (GM) was performed on the brain-extracted T1w using `fast` (FSL (version unknown), RRID:SCR_002823, Zhang, Brady, and Smith 2001). Volume-based spatial normalization to one standard space (MNI152NLin2009cAsym) was performed through nonlinear registration with `antsRegistration` (ANTs 2.6.2), using brain-extracted versions of both T1w reference and the T1w template. The following template was selected for spatial normalization and accessed with *TemplateFlow* (24.2.2, Ciric et al. 2022): *ICBM 152 Nonlinear Asymmetrical template version 2009c* [Fonov et al. (2009), RRID:SCR_008796; TemplateFlow ID: MNI152NLin2009cAsym].

Functional data preprocessing

For each of the 3 BOLD runs found per subject (across all tasks and sessions), the following preprocessing was performed. First, a reference volume was generated, using a custom methodology of *fMRIPrep*, for use in head motion correction. Head-motion parameters with respect to the BOLD reference (transformation matrices, and six corresponding rotation and translation parameters) are estimated before any spatiotemporal filtering using `mcflirt` (FSL, Jenkinson et al. 2002). The BOLD reference was then co-registered to the T1w reference using `mri_coreg` (FreeSurfer) followed by `flirt` (FSL, Jenkinson and Smith 2001) with the boundary-based registration (Greve and Fischl 2009) cost-function. Co-registration was configured with six degrees of freedom. Several confounding time-series were calculated based on the *preprocessed BOLD*: framewise displacement (FD), DVARS and three region-wise global signals. FD was computed using two formulations following Power (absolute sum of relative motions, Power et al. (2014)) and Jenkinson (relative root mean square displacement between affines, Jenkinson et al. (2002)). FD and DVARS are calculated for each functional run, both using their implementations in *Nipype* (following the definitions by Power et al. 2014). The three global signals are extracted within the CSF, the WM, and the whole-brain masks. Additionally, a set of physiological regressors were extracted to allow for component-based noise

correction (*CompCor*, Behzadi et al. 2007). Principal components are estimated after high-pass filtering the *preprocessed BOLD* time-series (using a discrete cosine filter with 128s cut-off) for the two *CompCor* variants: temporal (tCompCor) and anatomical (aCompCor). tCompCor components are then calculated from the top 2% variable voxels within the brain mask. For aCompCor, three probabilistic masks (CSF, WM and combined CSF+WM) are generated in anatomical space. The implementation differs from that of Behzadi et al. in that instead of eroding the masks by 2 pixels on BOLD space, a mask of pixels that likely contain a volume fraction of GM is subtracted from the aCompCor masks. This mask is obtained by thresholding the corresponding partial volume map at 0.05, and it ensures components are not extracted from voxels containing a minimal fraction of GM. Finally, these masks are resampled into BOLD space and binarized by thresholding at 0.99 (as in the original implementation). Components are also calculated separately within the WM and CSF masks. For each *CompCor* decomposition, the k components with the largest singular values are retained, such that the retained components' time series are sufficient to explain 50 percent of variance across the nuisance mask (CSF, WM, combined, or temporal). The remaining components are dropped from consideration. The head-motion estimates calculated in the correction step were also placed within the corresponding confounds file. The confound time series derived from head motion estimates and global signals were expanded with the inclusion of temporal derivatives and quadratic terms for each (Satterthwaite et al. 2013). Frames that exceeded a threshold of 0.5 mm FD or 1.5 standardized DVARS were annotated as motion outliers. Additional nuisance timeseries are calculated by means of principal components analysis of the signal found within a thin band (*crown*) of voxels around the edge of the brain, as proposed by (Patriat, Reynolds, and Birn 2017). All resamplings can be performed with a *single interpolation step* by composing all the pertinent transformations (i.e. head-motion transform matrices, susceptibility distortion correction when available, and co-registrations to anatomical and output spaces). Gridded (volumetric) resamplings were performed using `nitransforms`, configured with cubic B-spline interpolation.

Many internal operations of *fMRIPrep* use *Nilearn* 0.11.1 (Abraham et al. 2014, RRID:SCR_001362), mostly within the functional processing workflow. For more details of the pipeline, see [the section corresponding to workflows in *fMRIPrep*'s documentation](#).

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APPENDIX C: CONN fc-MVPA BOILER PLATE

Methods

Results included in this manuscript come from analyses performed using CONN^[1] (RRID:SCR_009550) release 22.a^[2] and SPM^[3] (RRID:SCR_007037) release 12.7771.

Preprocessing: Functional data were smoothed using spatial convolution with a Gaussian kernel of 6 mm full width half maximum (FWHM).

Denoising: In addition, functional data were denoised using a standard denoising pipeline^[4] including the regression of potential confounding effects characterized by white matter timeseries (5 CompCor noise components), CSF timeseries (5 CompCor noise components), motion parameters and their first order derivatives (12 factors)^[5], session and task effects and their first order derivatives (4 factors), QC_white_matter regressors (1 components), QC_a_comp_cor regressors (262 components), QC_cosine regressors (29 components), QC_csf regressors (1 components), QC_rot regressors and their first order derivatives (6 components), QC_trans regressors and their first order derivatives (6 components), QC_t_comp_cor regressors (27 components), outlier scans (below 494 factors)^[6], and linear trends (2 factors) within each functional run, followed by bandpass frequency filtering of the BOLD timeseries^[7] between 0.008 Hz and 0.09 Hz. CompCor^[8,9] noise components within white matter and CSF were estimated by computing the average BOLD signal as well as the largest principal components orthogonal to the BOLD average, motion parameters, and outlier scans within each subject's eroded segmentation masks. From the number of noise terms

included in this denoising strategy, the effective degrees of freedom of the BOLD signal after denoising were estimated to range from 133.6 to 283.6 (average 239.3) across all subjects^[10].

First-level analysis fcMVPAN included: Functional connectivity multivariate pattern analyses (fc-MVPA^[11]) were performed to estimate the first 10 eigenpatterns characterizing the principal axes of heterogeneity in functional connectivity across subjects and conditions. From these eigenpatterns, 10 associated eigenpattern-score images were derived for each individual subject and condition characterizing their brain-wide functional connectome state. Eigenpatterns and eigenpattern-scores were computed separately for each individual seed voxel as the left- and right- singular vectors, respectively, from a singular value decomposition (group-level SVD) of the matrix of functional connectivity values between this seed voxel and the rest of the brain (a matrix with one row per target voxel, and one column per subject and condition). Individual functional connectivity values were computed from the matrices of bivariate correlation coefficients between the BOLD timeseries from each pair of voxels, estimated using a singular value decomposition of the z-score normalized BOLD signal (subject-level SVD) with 64 components separately for each subject and condition^[1].

Group-level analyses were performed using a General Linear Model (GLM^[12]). For each individual voxel a separate GLM was estimated, with first-level connectivity measures at this voxel as dependent variables (one independent sample per subject and one measurement per task or experimental condition, if applicable), and groups or other subject-level identifiers as independent variables. Voxel-level hypotheses were

evaluated using multivariate parametric statistics with random-effects across subjects and sample covariance estimation across multiple measurements. Inferences were performed at the level of individual clusters (groups of contiguous voxels). Cluster-level inferences were based on parametric statistics from Gaussian Random Field theory^[13,14]. Results were thresholded using a combination of a cluster-forming $p < 0.001$ voxel-level threshold, and a familywise corrected $p\text{-FDR} < 0.05$ cluster-size threshold^[15].

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APPENDIX D: CONN SBC BOILER PLATE

Methods

Results included in this manuscript come from analyses performed using CONN^[1] (RRID:SCR_009550) release 22.a^[2] and SPM^[3] (RRID:SCR_007037) release 12.7771.

Preprocessing: Functional data were smoothed using spatial convolution with a Gaussian kernel of 6 mm full width half maximum (FWHM).

Denoising: In addition, functional data were denoised using a standard denoising pipeline^[4] including the regression of potential confounding effects characterized by white matter timeseries (5 CompCor noise components), CSF timeseries (5 CompCor noise components), motion parameters and their first order derivatives (12 factors)^[5], session and task effects and their first order derivatives (4 factors), QC_white_matter regressors (1 components), QC_a_comp_cor regressors (262 components), QC_cosine regressors (29 components), QC_csf regressors (1 components), QC_rot regressors and their first order derivatives (6 components), QC_trans regressors and their first order derivatives (6 components), QC_t_comp_cor regressors (27 components), outlier scans (below 494 factors)^[6], and linear trends (2 factors) within each functional run, followed by bandpass frequency filtering of the BOLD timeseries^[7] between 0.008 Hz and 0.09 Hz. CompCor^[8,9] noise components within white matter and CSF were estimated by computing the average BOLD signal as well as the largest principal components orthogonal to the BOLD average, motion parameters, and outlier scans within each subject's eroded segmentation masks. From the number of noise terms

included in this denoising strategy, the effective degrees of freedom of the BOLD signal after denoising were estimated to range from 133.6 to 283.6 (average 239.3) across all subjects^[10].

First-level analysis SBC_f1m1_recvnov: Seed-based connectivity maps (SBC) and ROI-to-ROI connectivity matrices (RRC) were estimated characterizing the patterns of functional connectivity with 8 ROIs. Functional connectivity strength was represented by Fisher-transformed bivariate correlation coefficients from a weighted general linear model (weighted-GLM^[11]), defined separately for each pair of seed and target areas, modeling the association between their BOLD signal timeseries. Individual scans were weighted by a boxcar signal characterizing each individual task or experimental condition convolved with an SPM canonical hemodynamic response function and rectified.

Group-level analyses were performed using a General Linear Model (GLM^[12]). For each individual voxel a separate GLM was estimated, with first-level connectivity measures at this voxel as dependent variables (one independent sample per subject and one measurement per task or experimental condition, if applicable), and groups or other subject-level identifiers as independent variables. Voxel-level hypotheses were evaluated using multivariate parametric statistics with random-effects across subjects and sample covariance estimation across multiple measurements. Inferences were performed at the level of individual clusters (groups of contiguous voxels). Cluster-level inferences were based on parametric statistics from Gaussian Random Field theory^[13,14]. Results were thresholded using a combination of a cluster-forming $p <$

0.001 voxel-level threshold, and a familywise corrected p-FDR < 0.05 cluster-size threshold^[15].

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APPENDIX E: UNTHRESHOLDED SBC MASKS

