# Ventromedial Prefrontal Cortex Does Not Play a Selective Role in Pattern Separation

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## Abstract

■ Humans have the capacity to form new memories of events that are, at times, highly similar to events experienced in the past, as well as the capacity to integrate and associate new information within existing knowledge structures. The former process relies on mnemonic discrimination and is believed to depend on hippocampal pattern separation, whereas the latter is believed to depend on generalization signals and conceptual categorization supported by the neocortex. Here, we examine whether and how the ventromedial prefrontal cortex (vMPFC) supports discrimination and generalization on a widely used task that was primarily designed to tax hippocampal processes. Ten individuals with lesions to the vMPFC and 46 neurotypical control participants were administered an adapted version of the mnemonic similarity task [Stark, S. M., Yassa, M. A., Lacy, J. W., & Stark, C. E. L. A task to assess behavioral pattern separation (BPS) in humans: Data from healthy aging and mild cognitive impairment. *Neuropsychologia*, *51*, 2442–2449, 2013], which assesses the ability to distinguish previously learned images of everyday objects (targets) from unstudied, highly similar images (lures) and dissimilar images (foils). Relative to controls, vMPFC-lesioned individuals showed intact discrimination of lures from targets but a propensity to mistake studied targets and similar lures for dissimilar foils. This pattern was accompanied by inflated confidence despite low accuracy when responding to similar lures. These findings demonstrate a more general role of the vMPFC in memory retrieval, rather than a specific role in supporting pattern separation. ■

## INTRODUCTION

The ability to encode and retrieve distinct memory traces of similar, overlapping items and events—like remembering where you parked your car or which medication you have taken—is essential to everyday life. This memory function critically relies on a neurobiological process known as pattern separation, whereby sparse firing of granule cells in the dentate gyrus (DG) of the hippocampus leads to the encoding of unique traces even for highly similar memories (Rolls, 2016; Neunuebel & Knierim, 2014; Leutgeb, Leutgeb, Moser, & Moser, 2007). Equally important is generalization, the extraction of commonalities or gist across items, events, and their representations to make sense of newly encountered stimuli (Rolls, 2016). Generalization is believed to be facilitated by projections from the CA1 subfield of the hippocampus to the ventromedial prefrontal cortex (vMPFC). This process allows us to recognize congruence among related but nonidentical stimuli (Ngo, Michelmann, Olson, & Newcombe, 2021; Schapiro, Turk-Browne, Botvinick, & Norman, 2017; Rolls, 2016; Deuker, Doeller, Fell, & Axmacher, 2014; Schlichting, Zeithamova, & Preston, 2014) and to make sense of newly encountered items based on prior knowledge of associated, previously encountered items. A causal role in pattern separation and generalization has been established for the hippocampus (De Shetler & Rissman, 2017; Baker et al., 2016; Berron et al., 2016), but not for regions of neocortex. The current study aims to assess if the vMPFC directly contributes to these processes on a task of mnemonic discrimination as part of a broader hippocampal-neocortical circuit.

Behavioral paradigms designed to approximate pattern separation typically assess mnemonic discrimination, or the ability to distinguish between previously studied stimuli and unstudied similar lures. The Mnemonic Similarity Test (MST) was designed as a behavioral approximation of pattern separation and has quickly become ubiquitous in the hippocampal memory literature, having been reported in over 100 published studies since it was first described in 2013 (Stark, Kirwan, & Stark, 2019). The task includes an incidental object encoding phase followed by a surprise recognition task, wherein participants must distinguish among studied images of objects (targets), novel objects unlike those that were studied (foils), and objects that are visually and conceptually similar to studied objects (lures; Stark, Yassa, Lacy, & Stark, 2013). Performance on the MST has been shown to rely on the DG based on

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patient-lesion (Baker et al., 2016), high-resolution functional neuroimaging (Berron et al., 2016), and typical and atypical aging studies (e.g., Reagh et al., 2018; Yassa et al., 2010). Similar studies have also examined the role of CA1 in this process and found a complementary pattern of results: CA1 lesions have been shown to disrupt MST performance (Hanert, Pedersen, & Bartsch, 2019), but closer inspection suggests that this is because of a higher proportion of similar lures being mistaken as "new" rather than "old" (Mitchnick, Marlette, Belchev, & Rosenbaum, 2023), which is opposite to what has been found in an individual with DG lesions (Baker et al., 2016). Consistent with the perspective that the CA1 subfield subserves generalization rather than pattern separation, similar patterns of CA1 activation have been observed during presentation of both lures and targets (De Shetler & Rissman, 2017; Lacy, Yassa, Stark, Muftuler, & Stark, 2011). Although extant research suggests that pattern separation critically depends on the hippocampus, prior work has also demonstrated contributions of extrahippocampal brain regions and nonmnemonic abilities on MST performance (Foster & Giovanello, 2020; Pishdadian, Hoang, Baker, Moscovitch, & Rosenbaum, 2020; Davidson, Vidjen, Trincao-Batra, & Collin, 2019).

The question of whether medial PFC (mPFC)-mediated processes may influence mnemonic discrimination has been addressed in a few studies to date, although results are varied. In a rodent analog of the MST, inhibition of the mPFC was found to impair discrimination of lures from targets (Johnson et al., 2021). By contrast, no difference in vMPFC activation was detected between correct rejection of similar lures, false alarms to lures, and recognition of previously studied targets on a continuous two-choice (old/new) mnemonic discrimination task, suggesting that the vMPFC does not play a distinct role in pattern separation (Nash, Hodges, Muncy, & Kirwan, 2021). It has also been hypothesized that subregions of the mPFC are functionally heterogeneous, with separation supported by processes in the anterior mPFC and integration supported by processes in the mid-mPFC (Schlichting, Mumford, & Preston, 2015).

Despite well-documented evidence of memory impairments following vMPFC lesions (Yu, Kan, & Kable, 2020), the mechanism underlying vMPFC involvement in memory remains uncertain and is a topic of continued debate. Different perspectives highlight a role for the vMPFC in assigning value to personally significant memories (Rolls, 2022), confidence, or feeling of rightness (FOR) supporting mnemonic decision-making and response selection (Hebscher & Gilboa, 2016), and establishing schematic contexts against which memories can be evaluated (Gilboa & Moscovitch, 2017). Recent research has also revealed strong connectivity between neocortex and the basal forebrain (Rolls, 2022), illuminating a possible pathway for vMPFC to modulate cholinergic inputs to the hippocampus, which have been shown to promote pattern separation and inhibit pattern completion (for a review, see Duncan & Schlichting, 2018).

Other research has explored the role of the vMPFC in instantiating and using schemas to organize and understand new information, as well as retrieving the most appropriate information for a given task (Gilboa & Marlatte, 2017). Individuals with vMPFC lesions are impaired in identifying words as schema-congruent (e.g., words associated with bedtime or the doctor's office) compared with controls (Ghosh, Moscovitch, Colella, & Gilbo, 2014), and show impairment on tasks where schema instantiation is known to benefit memory (Spalding, Jones, Duff, Tranel, & Warren, 2015; Ciaramelli, Ghetti, Frattarelli, & Làdavas, 2006). Neuroimaging studies have also demonstrated coupling of anterior hippocampal and vMPFC activity when participants learn paired associates in schema-consistent but not schema-inconsistent conditions (Guo & Yang, 2020), suggesting that involvement of vMPFC at encoding is specific to situations where contextualizing new information against prior knowledge is essential. vMPFC activity at encoding may also vary as a function of knowledge-congruency, where encoding of information congruent with existing knowledge is associated with greater vMPFC activation (Brod & Shing, 2018).

At retrieval, the vMPFC may be involved in selecting the most appropriate response to meet the demands of a given task, and appraising the appropriateness of a chosen response (Gilboa & Moscovitch, 2017; Ciaramelli & Spaniol, 2009; Moscovitch & Winocur, 2002). Evidence for this function is partly based on accounts of individuals with vMPFC damage who confabulate or spontaneously produce false autobiographical memories (Schnider, Nahum, & Ptak, 2017; Gilboa & Verfaellie, 2010) because of a failure to suppress irrelevant memories (Nieuwenhuis & Takashima, 2011; Schnider & Ptak, 1999). Individuals with vMPFC damage have also been shown to exhibit source confusion and a tendency to respond with previously, but not currently relevant information (Gilboa et al., 2006). These findings may reflect vMPFC contributions to an intuitive FOR at retrieval by producing confidence signals in the veracity and appropriateness of retrieved traces informed by prior experience (Hebscher, Barkan-Abramski, Goldsmith, Aharon-Peretz, & Gilboa, 2016; Hebscher & Gilboa, 2016; Ciaramelli & Ghetti, 2007). FOR is thought to emerge from a strong correspondence between retrieval cues and activated memory traces (Hebscher & Gilboa, 2016), signaling that appropriate networks have been activated.

Multiple studies have shown that vMPFC activity is associated with confidence in both memory and decision-making tasks (Shapiro & Grafton, 2020; Spaniol, Di Muro, & Ciaramelli, 2019; Gherman & Philiastides, 2018; De Martino, Fleming, Garrett, & Dolan, 2013) and that functional connectivity between the vMPFC and other frontal regions predicts the relationship between confidence and accuracy (De Martino et al., 2013). Prior research has shown that in individuals with vMPFC lesions, confidence may be disjointed from accuracy, with vMPFC-lesioned individuals typically overestimating their performance (Hebscher & Gilboa, 2016; Ciaramelli & Ghetti, 2007).

In the current study, individuals with relatively selective lesions to the vMPFC were administered a version of the

MST adapted to include confidence judgments: After each test response made, participants were asked to rate their confidence in their answer on a scale from 1–5. We examine if and how vMPFC function is essential to support the hippocampal processes targeted by the MST, including pattern separation, generalization, and general recognition memory, as well as whether these functions are related to vMPFC-generated confidence signals. As described, vMPFC-lesioned cases have been shown to underincorporate relevant information into schemas and to confidently overreport irrelevant information (Hebscher et al., 2016; Ghosh & Gilboa, 2014). Furthermore, prior rodent and neuroimaging studies exploring vMPFC contributions to pattern separation have produced contradictory results (Johnson et al., 2021; Nash et al., 2021). Thus, it is reasonable to predict that the vMPFC contributes to MST performance in a number of ways and for different reasons. Here, we consider three possible outcomes:

1. If vMPFC is necessary for pattern separation, then vMPFC compromise would result in mnemonic discrimination failure. This hypothesis would be supported if our results demonstrate that individuals with vMPFC lesions exhibit behavior consistent with a specific pattern separation deficit: accurate recognition of previously learned targets, but confusion of similar lures for their studied counterparts (i.e., mislabeling lures as old). Consistent with this possibility is research showing that individuals with vMPFC lesion are both mnemonically disorganized and disinhibited, and may spontaneously retrieve contextually irrelevant information (Ghosh et al., 2014; Gilboa et al., 2006).
2. If vMPFC is necessary for facilitating generalization, then vMPFC lesions would result in difficulties recognizing similarities between lures and targets at retrieval. Because the vMPFC plays a well-documented role in the use of conceptual knowledge and schematic structure to link related information and is strongly interconnected with the CA1 subfield of the hippocampus (Hanert et al., 2019; Brod & Shing, 2018), damage to the vMPFC could lead to a failure to identify linkages between similar stimuli. This hypothesis would be supported if vMPFC damage leads to an overdiscrimination of targets from similar lures and a tendency to treat lures as dissimilar foils. Statistical support for this hypothesis would be understood as a reflection of the role of the vMPFC in generalizing across similar stimuli to form schemas with input from CA1.
3. If vMPFC is necessary for overall recognition of previously studied items, then vMPFC lesions would result in a general failure in recognition memory. This hypothesis would be supported by findings that individuals with vMPFC lesions are biased toward responding new to all items, whether targets, lures, or foils. Because the correct identification of a similar lure requires the recall of its previously studied counterpart, generally poor encoding or retrieval would obscure any findings related to mnemonic discrimination.

In addition to these hypotheses, evidence that disproportionate confidence may reflect failures in metamnemonic monitoring following vMPFC dysfunction (Hebscher & Gilboa, 2016) leads to our prediction that individuals with vMPFC lesions will exhibit distorted or overly high confidence relative to actual performance. Findings from this study will contribute to a more complete understanding of hippocampal- vMPFC interactions underlying the representation of unique and shared elements of episodic memories.

## METHODS

### Participants

A total of 10 well-characterized individuals with focal lesions to the vMPFC participated in the present study. The sample size was determined by recruiting all known individuals in our network with such lesions. Five of the individuals (three men) were recruited from the Rotman Research Institute at Baycrest Health Sciences in Toronto, Canada, and the other five (two men) were recruited from the Centre for Studies and Research in Cognitive Neuroscience of the University of Bologna, Cesena campus, Italy. The vMPFC cases, on average, were 67 years old (range: 53–82 years, $SD = 9.73$ years) and had 13.14 years of education (range: 6–18 years, $SD = 4.26$ years). Lesions to the vMPFC followed the rupture of anterior communicating artery (ACoA) aneurysm in all but one case (R.L.) who experienced vMPFC lesions following an anterior cerebral artery stroke. Participants were tested between 2021 and 2022, and at least 6 years post-injury (range: 6–15 years).

MRI scans were obtained for research purposes, and individual lesions were manually drawn on each slice of a normalized T1-weighted template using MRIcro software, combining manual segmentation and registration to a standard template into a single step (Rorden & Brett, 2000). Figure 1 shows the location, extent, and overlap of the vMPFC lesions. Lesions largely affected Brodmann areas' (BAs) 10, 11, 32, 24, and 25, and were bilateral in all but two cases (A.M.O. and A.G.I.). Two cases had minimal damage to lateral pFC (BAs 9, 46, 47), constituting ~5% of their lesion volume, roughly one-tenth the size of their vMPFC lesions, whereas one case (A.G.I.) had more extensive damage to BAs 44 and 45, comprising ~31% of his lesion volume. Two patients had damage to the visual cortex (BAs 17, 18, 19, 37) that constituted ~41% and ~32% of their lesion volume. These patients did not have visual problems precluding their participation in the study and attained normal scores on the copy of the Rey-Osterrieth Complex Figure (percentile scores: 66 and 68; Spreen & Strauss, 1998) and on the Wechsler Test of Adult Reading (percentile scores: 55 and 47;

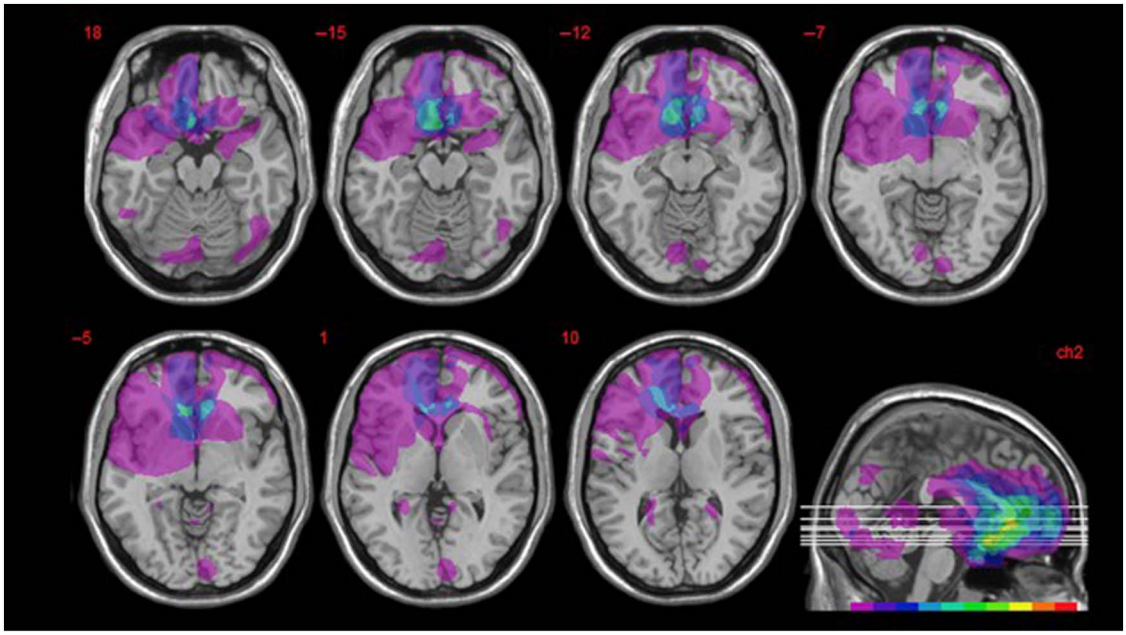


**Figure 1.** Lesion location and extent in vMPFC patients. Axial slice template illustrating lesion overlap across vMPFC patients. Slices are at $z = -18$, $-15$, $-12$, $-7$, $-5$, $+1$, and $+10$, with level of slice depicted in the sagittal reference image. The color bar indicates the number of patients with damage to a particular area, with purple representing regions damaged in only one patient and red representing regions damaged in all six patients. The image was created using MRIcro software (Chris Rorden; www.psychology.nottingham.ac.uk/staff/cr1/mricro.html). Neurological convention is followed (left hemisphere presented on the left). Details of lesion location and size are provided in the main text, and etiology, demographic information, and neuropsychological profiles are presented in Table 1.

Holdnack, 2001). It was determined that removal of each of the aforementioned participants did not affect the results, so they were retained in the final analyses. Additional neuropsychological and demographic information is presented in Table 1. Although some variability in performance on neuropsychological measures is present and to be expected when participants have sustained lesions (Irish & van Kesteren, 2018), we believe that our sample provides a valid and strong foundation for investigating the role of vMPFC in memory.

Performance of the vMPFC group was compared with that of 49 age-matched healthy adults, including 29 controls recruited in Toronto through the community and the Rotman Research Institute, and 20 controls recruited through the University of Bologna. This sample size was chosen based on precedence in prior work (Mok et al., 2021). Control participants were screened for history of psychiatric and neurological illness, and for risk of mild cognitive impairment using the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005). The MoCA was administered virtually through video call, which has been validated as a reliable administration method (Chapman et al., 2021; DeYoung & Shenal, 2019). Three control participants scored lower than 26/30 and were excluded from the study, resulting in a final comparison group of 46 healthy controls (19 men), with an average age of 64.67 years (range: 54–82 years, $SD = 7.8$ years), and 14.29 years of education (range: 8–20 years, $SD = 3.37$ years). Chi-square tests of independence showed no significant difference in age, $X^2$ $(23, n = 56) = 16.2$, $p = .85$, or education level, $X^2$ $(10, n = 56) = 9.8$, $p = 0.46$, between lesion and control groups. All participants were fluent in English or Italian depending on the testing site. Participants provided informed consent in accordance with the Human Research Ethics Committees of York University, Baycrest Health Sciences, and the Regional Health Service of Emilia Romagna, Italy.

## Experimental Tasks

### *Mnemonic Similarity Task*

All testing materials and instructions were provided in English for Canadian participants and in Italian for Italian participants. The task was administered by study personnel using PsychoPy (Peirce et al., 2019) and shared remotely with participants using the videoconferencing platform Zoom. One vMPFC-lesioned participant (C.R.) was tested in person because of barriers to virtual testing. The MST included an incidental encoding phase followed by a surprise recognition memory test (Stark et al., 2013). During the encoding phase, participants viewed 128 images of everyday objects and verbally identified each as an "indoor" or "outdoor" item. Images were presented for 2000 msec with an ISI of at least 500 msec or until the participant made a response.

Participants received instructions for the test phase immediately after the conclusion of the study phase. In the test phase, participants viewed a series of 192 images:

**Table 1.** Demographic and Neuropsychological Data for Participants with vMPFC Lesions

| | | | | | | | | Word Learning Task | | | Complex Figure Task | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Case* | *Etiology* | *Age* | *Sex* | *Edu* | *IQ/PF* | *WCST* | *LF* | *AQ* | *LDFR* | *Recog* | *Copy* | *DR* |
| Canadians | | | | | | | | | | | | |
| C.R. | ACoA | 63 | M | 17 | 99 | – | – | 1% | < 0.7% | < 0.7% | 68–70% | 1–2% |
| M.T. | ACoA | 58 | M | 12 | 98 | > 16% | 20% | 4% | < 0.7% | – | 84–86% | 13% |
| R.L. | ACA | 82 | F | 16 | 102 | – | 40% | 81% | 50% | – | 66–68% | 61–63% |
| M.M. | ACoA | 72 | M | 18 | 98 | > 16% | < 2% | 8% | 6–7% | < 0.7% | 22–23% | 18–19% |
| J.W. | ACoA | 66 | F | 15 | 99 | > 16% | 30–40% | 1% | < 0.02% | 30–32% | 1–2% | 13% |
| Italians | | | | | | | | | | | | |
| A.M.O. | ACoA | 73 | F | 6 | – | 30% | 3 | 2 | 0 | – | 4 | 0 |
| A.G.I. | ACoA | 53 | M | 10 | – | 90% | 1 | 0 | 1 | – | 4 | 2 |
| E.M.E. | ACoA | 50 | F | 5 | – | 1% | 1 | 2 | 1 | – | 0 | 2 |
| M.G.R. | ACoA | 65 | F | 13 | – | 30% | 2 | 4 | 4 | – | 4 | 4 |
| G.T.I. | ACoA | 54 | M | 13 | – | 1% | 4 | 0 | 0 | – | 4 | 0 |

Data from Canadian patients are presented in percentiles compared with normative samples, and data from Italian patients are presented in equivalent scores (0 = "impaired," 1 = "borderline," 2 = "low-end average," 3–4 = "average"), in line with respective regional reporting standards. Word list learning was based on the California Verbal Learning Test–II in Canadians and the Bushke-Fuld Test in Italians. Taylor Complex Figure Test was reported for A.G.I., M.G.R., and G.T.I.; Rey-Osterrieth Complex Figure Test was reported for all others. Canadian data were adapted from (Mok et al., 2021). Age = age in years; Edu = education in years; IQ = full-scale IQ; ACA = anterior cerebral artery; P. F. = premorbid functioning, based on the National Adult Reading Test for M. T. and M. M.; Wechsler Test of Adult Reading for R. L.; WCST = Wisconsin Card Sorting Task; LF = Letter Fluency; AQ = acquisition; LDFR = long delay free recall; DR = delay recall.

64 each of previously studied targets, novel foils, and similar lures, although they were not informed of the proportions of each stimulus type. Similar lures are binned according to their level of similarity, allowing for analyses of response variability to high and low similarity lures (Stark et al., 2019). Participants were instructed to verbally identify each image as an exact repeat of a previously studied image (old), a novel image unlike anything studied previously (new), or a conceptually and visually similar image to one from the study phase ("similar"). After each response, participants rated how confident they were that they responded correctly using a 5-point Likert scale, with 1 representing *very unconfident* and 5 representing *very confident*. Test images were presented for 2000 msec, followed by an ISI of least 500 msec, or until a response was made. Next, the confidence scale was presented until a response was made, followed by an additional 250-msec ISI. A schematic of the task is presented in Figure 2.

## Statistical Analyses

### *Mnemonic Discrimination and Recognition Memory*

On the MST, mnemonic discrimination, or pattern separation ability, was inferred from the lure discrimination index (LDI), calculated as p("Similar"|Lure) – p("Similar"|Foil). Recognition memory of studied items (REC) was calculated as p("Old"|Target) – p("Old"|Foil). Both LDI and REC were compared between lesion and control groups using Welch's two-sample *t* tests. By comparing lesion against control groups using both LDI and REC, we can explore whether any apparent differences in lure discrimination ability are more likely driven by a specific pattern separation deficit or general recognition memory

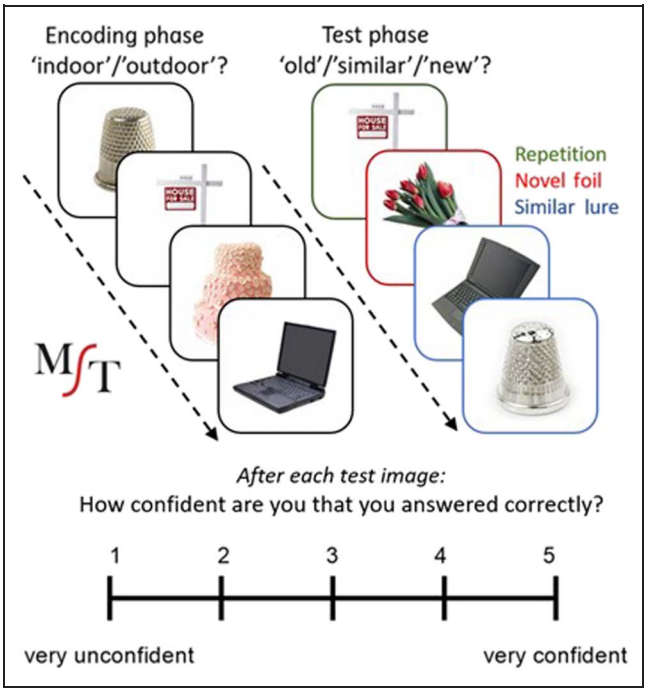


**Figure 2.** Schematic of the adapted mnemonic similarity task with confidence.

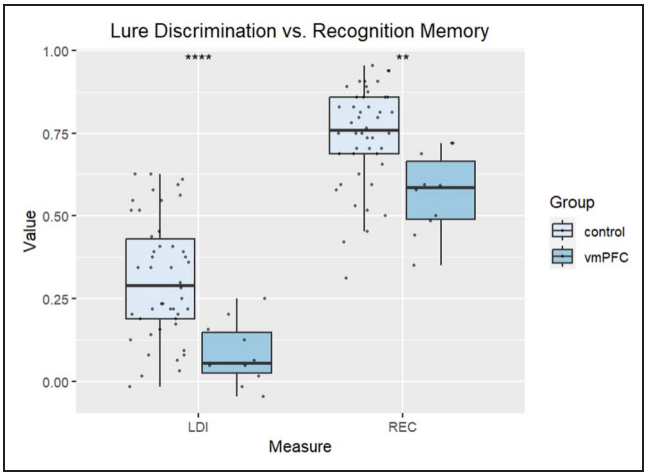


**Figure 3.** Recognition memory and lure discrimination. LDI (calculated by subtracting the proportion of similar responses given to lures from the proportion of similar responses given to foils) and recognition memory (REC; calculated by subtracting the proportion of old responses given to foils from the proportion of old responses given to targets) are compared between patient and control groups. Welch's *t* tests found the group means to be significantly different on both metrics (LDI: $p < .0001$; REC: $p < .001$).

impairment. Because errors in target and lure identification can be driven by two different response patterns (i.e., mislabeling targets as either similar or new instead of old and mislabeling lures as either old or new instead of similar), proportions of old, similar, and new responses given to each stimulus type were compared between groups using Welch's two-sample *t* tests.

### *Confidence*

Hypothesized distortions in confidence signals by individuals with vMPFC lesions were assessed using confidence-accuracy calibration (*C*) statistics and over/underconfidence (*O*/*U*) metrics (Weber & Brewer, 2004). *C* was computed as the weighted mean of the squared difference between confidence and proportion correct for each confidence level, and is a measure of deviation from perfect calibration ranging from 0 (perfect calibration) to 1 (worst possible calibration). *C* was calculated for each participant to assess any group differences in the relationship between confidence and accuracy across each stimulus type.

*O*/*U* is a gross measure of each participant's tendency to report more or less confidence than warranted by the accuracy of their response (Weber & Brewer, 2004). *O*/*U* ranges from −1 (complete underconfidence) to +1 (complete overconfidence) and was calculated as the difference between mean confidence and mean accuracy. Whereas *C* provides a general calibration measure based on accuracy at each confidence level, *O*/*U* provides more information about the overall direction of miscalibration. As with *C*, *O*/*U* was compared between groups within each stimulus type using Welch's two-sample *t* tests.

To assess whether any observed confidence differences between the vMPFC cases and controls were unique to vMPFC functioning rather than simply a consequence of low or high performance, confidence was specifically compared between the vMPFC cases and low-performing controls. Controls were divided into equally sized groups of high and low performers based on LDI. Those with an above-average LDI were considered "high performers," and controls with a below-average LDI were considered "low performers."

## RESULTS

### Mnemonic Discrimination and Recognition Memory

The LDI was significantly lower in the vMPFC cases ($M = 0.08$, $SD = 0.10$) than in healthy controls ($M = 0.31$, $SD = 0.18$), with vMPFC cases scoring an average of 1.3 *SD*s below controls, $t(25.17) = 5.55$, $p < .001$, Hedge's $g = 1.31$, 95% CI [0.57, 2.04]. REC followed a similar pattern and was approximately 1.2 *SD*s lower in vMPFC cases

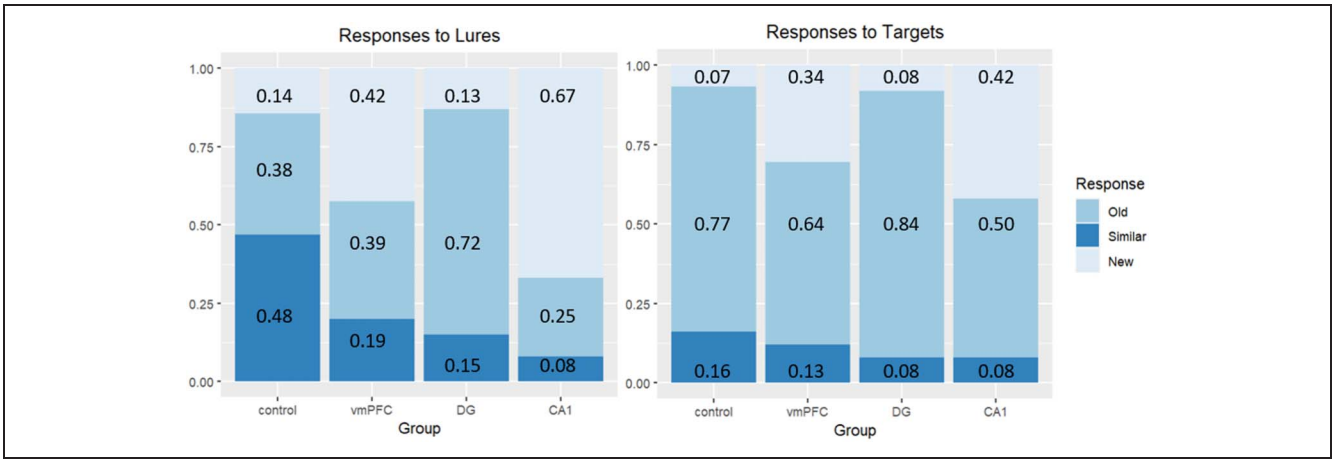


**Figure 4.** Proportion of lure and target responses between groups. Proportion of responses given to lures and targets compared between vMPFC patients, controls, an individual with selective lesions to the DG (Patient B.L.), and an individual with selective lesions to CA1 (Patient B.R.).

($M = 0.5$, $SD = 0.12$) than controls ($M = 0.74$, $SD = 0.15$), $t(15.31) = 3.93$, $p = .001$, Hedge's $g = 1.20$, 95% CI [0.47, 1.92]. Taken together, these findings suggest a general recognition memory impairment that is not specific to mnemonic discrimination (Figure 3).

The differences in LDI were driven by a significantly lower proportion of accurately identified lures by the vMPFC group ($M = 0.20$, $SD = 0.13$) than by controls ($M = 0.47$, $SD = 0.17$), $t(16.52) = 5.48$, $p < .001$, $g = 1.58$, 95% CI [0.83, 2.33]). However, the proportion of lures miscategorized as previously studied targets did not differ between vMPFC cases ($M = 0.38$, $SD = 0.20$) and controls ($M = 0.39$, $SD = 0.15$), $t(11.23) = -0.17$, $p = .87$, $g = 0.07$, 95% CI [−0.62, 0.76], indicating that they were equally likely to misremember lures as being previously studied. Group differences in lure discrimination were instead driven by a higher proportion of lures misidentified as novel foils by vMPFC cases ($M = 0.42$, $SD = 0.25$) compared with controls ($M = 0.14$, $SD = 0.09$), $t(8.42) = -3.19$, $p = .01$, $g = -2.07$, 95% CI [−2.89, −1.25] (Figure 4).

Relatedly, correct identification of previously studied targets was significantly lower in the vMPFC group ($M = 0.64$, $SD = 0.13$) than controls ($M = 0.77$, $SD = 0.14$), $t(14.39) = 2.83$, $p = .01$, $g = 0.90$, 95% CI [0.19, 1.61]. As with the similar lures, the target errors were driven by a higher proportion of targets being misidentified as novel foils by the vMPFC group ($M = 0.34$, $SD = 0.35$) than controls ($M = 0.07$, $SD = 0.07$), $t(9.34) = -3.48$, $p = .007$, $g = -2.24$, 95% CI [−3.04, −1.43]. There were no group differences in the proportion of targets falsely labeled as similar (vMPFC, $M = 0.13$, $SD = 0.10$; control, $M = 0.16$, $SD = 0.11$; $t(14.16) = 0.73$, $p = .48$, $g = 0.24$, 95% CI [−0.46, 0.93]). Overall, errors made by the vMPFC cases on this task were driven by a general tendency to identify all items as new. Proportions of each response type given to lures and targets are depicted in Figure 5.

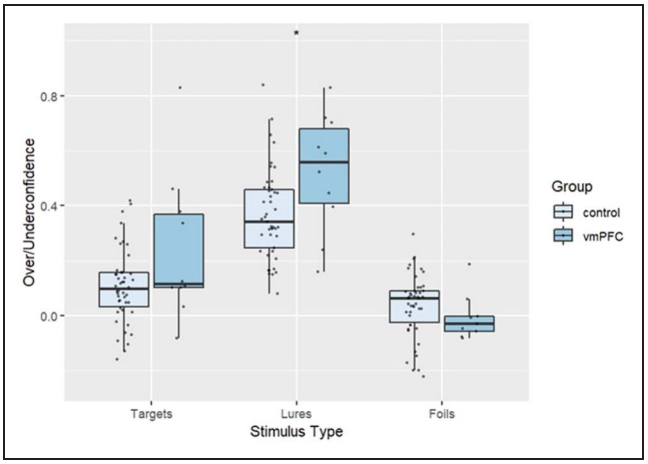


**Figure 5.** Over/underconfidence by stimulus type. Over/underconfidence (O/U) ranges from −1 (complete underconfidence) to +1 (complete overconfidence) and is calculated as the difference between mean confidence and mean accuracy. Welch's $t$ tests found that vMPFC patients were significantly more overconfident than controls when responding to lures ($p = .04$), but not to targets ($p = .16$) or foils ($p = .11$).

## Confidence

Between-groups comparisons were calculated for both $C$ and $O/U$ within each stimulus type. Large differences were found between groups in the confidence calibration for lures using both metrics. $C$ was significantly higher in patients ($M = 0.45$, $SD = 0.19$) than controls ($M = 0.26$, $SD = 0.16$; $t(12.15) = -3.07$, $p = .009$, $g = -1.15$, 95% CI [−1.88, −0.43]), suggesting worse calibration overall in response to lures. vMPFC patients ($M = 0.52$, $SD = 0.21$) were significantly overconfident relative to controls ($M = 0.35$, $SD = 0.18$) when responding to lures as indicated by $O/U$ levels, $t(12.08) = -2.30$, $p = .04$, $g = -.87$, 95% CI [−1.58, −0.16]. $O/U$ metrics are reported in Figure 5.

**Table 2.** Comparisons of Confidence between vMPFC Patients and Healthy Controls

| | *vMPFC* | | *Controls* | | | | | |
|---|---|---|---|---|---|---|---|---|
| | *M* | *SD* | *M* | *SD* | *df* | *t* | *p* | *Hedge's g, [95% CI]* |
| Confidence statistic | | | | | | | | |
| Targets | 0.16 | 0.24 | 0.04 | 0.05 | 9.16 | −1.62 | .14 | −0.52, [−1.47, 0.68] |
| Lures | 0.45 | 0.19 | 0.26 | 0.16 | 12.15 | −3.07 | .009 | −1.15, [−1.88, −0.43] |
| Foils | 0.03 | 0.03 | 0.03 | 0.03 | 11.33 | 0.07 | .13 | 0.03, [−0.66, 0.72] |
| Over/underconfidence | | | | | | | | |
| Targets | 0.24 | 0.27 | 0.11 | 0.13 | 10.00 | −1.54 | .16 | −0.80, [−1.51, −0.10] |
| Lures | 0.52 | 0.21 | 0.35 | 0.18 | 12.08 | −2.30 | .04 | −0.87 [−1.58, −0.16] |
| Foils | −0.04 | 0.12 | 0.04 | 0.11 | 12.56 | 1.72 | .11 | 0.62 [−0.08, 1.32] |

The confidence statistic ($C$) is computed as the weighted mean of the squared difference between confidence and proportion correct at each confidence level. $C$ ranges from 0 (perfect calibration) to 1 (worst possible calibration). Over/underconfidence ($O/U$) ranges from −1 (complete underconfidence) to +1 (complete overconfidence) and is calculated as the difference between mean confidence and mean accuracy.

**Table 3.** Individual Patient and Country Performance

| *vMPFC Patients* | *LDI* | *REC* | *Confidence Calibration (C)* | | *Over/Underconfidence* | | | |
|---|---|---|---|---|---|---|---|---|
| | | | *Targets* | *Lures* | *Foils* | *Targets* | *Lures* | *Foils* |
| Canadian | | | | | | | | |
| M.M. | −0.05 | 0.48 | 0.12 | 0.71 | 0.01 | 0.34 | 0.83 | 0.00 |
| M.T. | 0.12 | 0.59 | 0.03 | 0.46 | 0.03 | 0.11 | 0.61 | −0.08 |
| R.L. | 0.20 | 0.68 | 0.01 | 0.26 | 0.01 | 0.10 | 0.45 | 0.06 |
| J.W. | 0.02 | 0.59 | 0.02 | 0.54 | 0.01 | −0.08 | 0.72 | −0.03 |
| C.R. | 0.06 | 0.14 | 0.19 | 0.51 | 0.00 | 0.38 | 0.24 | −0.06 |
| Italian | | | | | | | | |
| A.M.O. | 0.05 | 0.50 | 0.77 | 0.68 | 0.01 | 0.83 | 0.70 | −0.01 |
| A.G.I. | 0.25 | 0.72 | 0.02 | 0.38 | 0.04 | 0.03 | 0.39 | −0.08 |
| E.M.E. | 0.05 | 0.35 | 0.34 | 0.55 | 0.01 | 0.46 | 0.59 | −0.05 |
| M.G.R. | −0.02 | 0.72 | 0.03 | 0.31 | 0.05 | 0.10 | 0.52 | 0.19 |
| G.T.I. | 0.16 | 0.59 | 0.12 | 0.11 | 0.11 | 0.12 | 0.16 | −0.30 |
| Controls *M* (*SD*) | 0.31 (0.18) | 0.74 (0.15) | 0.04 (0.05) | 0.26 (0.16) | 0.03 (0.03) | 0.11 (0.13) | 0.35 (0.18) | 0.04 (0.11) |
| Canadians | 0.31 (0.18) | 0.79 (0.12) | 0.03 (0.04) | 0.24 (0.15) | 0.03 (0.02) | 0.09 (0.12) | 0.36 (0.16) | 0.05 (0.11) |
| Italians | 0.31 (0.19) | 0.68 (0.17) | 0.06 (0.06) | 0.28 (0.17) | 0.03 (0.03) | 0.12 (0.15) | 0.35 (0.22) | 0.01 (0.11) |

Confidence calibration is a measure of the association between confidence and accuracy ranging from 0 to 1, where a score of 0 would indicate perfect calibration and a score of 1 would indicate complete dissociation. Over/underconfidence ranges from −1 to 1, with −1 indicating complete underconfidence and +1 indicating complete overconfidence. Welch's *t* tests found no significant differences between Canadian and Italian control groups on any measures. LDI, computed by subtracting the proportion of similar responses given to novel foils from the proportion of similar responses given to lures. REC, computed by subtracting the proportion of old responses given to novel foils from the proportion of old responses given to targets.

Importantly, these group differences in confidence disappeared when high-performing controls were removed from the data set. Low-performing controls were not significantly different from vMPFC cases on either $C\,CM = 0.$ $(SD = 0.1, M = t(14.0.351), SD = p = .0, g = -16; t(95\%\,\text{CI})$ $[-1.14.67) = -1.5, pO/U = .15, M = 0.43, SD = 0.16;$ $t(14.58) = -1.23, p = .24, g = -, g = 49,$ 95% CI $[-1.25, 0.27])-0.59,$ 95% CI $[-1.35, 0.45])$ or $O/U$ $(M = 0.43, SD = 0.16; t(14.58) = -1.23, p = .24, g = -0.49,$ 95% CI $[-1.25, 0.27])$. No significant group differences were found in either confidence measure in response to targets or foils (see Table 2). Individual data from vMPFC-lesioned participants on all mnemonic discrimination and confidence measures are available in Table 3, along with controls' performance separated by country.

## DISCUSSION

The present study provides evidence of impaired performance in individuals with vMPFC lesions on a test of mnemonic discrimination, suggesting that brain regions outside of the hippocampus/medial temporal lobe critically influence performance on these tasks. Individuals with vMPFC lesions exhibited deficits in both lure discrimination and overall recognition memory, suggesting that the role of the vMPFC does not appear to be specific to mnemonic discrimination (Nash et al., 2021). These results are consistent with our third hypothesis that vMPFC is necessary for overall recognition of previously studied information. However, because a general recognition memory deficit precludes more granular interpretations of mnemonic discrimination, our first and second hypotheses (that vMPFC may specifically support pattern separation or generalization, respectively) cannot be conclusively accepted or rejected. Closer inspection of the results indicates that, compared with controls, individuals with vMPFC lesions showed a bias toward mistaking both lures and targets for dissimilar novel foils. This performance pattern is opposite to what would be expected if mnemonic discrimination difficulties had been central (i.e., confusing lures for targets). It is, however, difficult to draw conclusive interpretations about the potential role of vMPFC in supporting pattern separation from these data; pattern separation deficits will not emerge if recognition memory is significantly impaired, because a new memory trace will always be formed when there is no similar memory retrieved. When a participant views a lure image, they must recall the previously studied target to

compare it to the lure, regardless of whether they eventually reject or accept it (Lacy et al., 2011; Kirwan & Stark, 2007). This phenomenon also poses a challenge for neuroimaging studies, because any region involved in recall will likely show similar activation in response to lures and targets, whether the participant makes a correct response (Racsmány, Bencze, Pajkossy, Szőllősi, & Marián, 2021). If the role of the vMPFC in mnemonic discrimination is theorized to be referencing prior knowledge to choose the most appropriate response (Gilboa & Moscovitch, 2017), activation consistent with recall does not preclude vMPFC involvement in this process in individuals without lesion. To answer the question of vMPFC involvement in mnemonic discrimination more fully, one may consider less demanding tasks designed to ensure proper encoding (through repeated study, slower image presentation, or fewer images overall) and/or ease of retrieval (through cueing or multiple-choice prompts). Furthermore, different results might emerge had our task featured schematic stimuli or unfamiliar objects, which are assumed to be respectively more or less likely to benefit from vMPFC-mediated memory organization than everyday objects.

Given the general hypothesis that the vMPFC supports hippocampal functioning at both encoding and retrieval (Rolls, 2022; Hebscher et al., 2016), it is worthwhile to compare the performance of our sample to that of two individuals with selective lesions to DG and CA1, respectively (see Figure 5). B.R., an individual with bilateral CA1 lesions (Mitchnick et al., 2023), showed a similar pattern of responses to individuals with vMPFC lesions: a tendency toward responding new to all stimulus types. This pattern is opposite to that of B.L., an individual with DG lesions, who misidentified lures as previously studied targets (reported in Baker et al., 2016) in the context of relatively intact overall recognition. These findings are theoretically consistent with prior research examining the effects of CA1 impairment on mnemonic discrimination (Mitchnick et al., 2022; Hanert et al., 2019), which showed a general bias in recognition memory, with a tendency toward labeling similar lures as new. The finding that lesions to CA1 and vMPFC produce markedly similar performance patterns on the MST suggests that vMPFC may work together to support integration across similar stimuli to extract a gist or schema. It has also been suggested that CA1 is responsible for combining information from CA3 into effective retrieval cues (sometimes by generalizing to conceptually related information), which are then backprojected to the neocortex (Rolls, 2022). It is possible that the role of the vMPFC in this process is to aid in the selection of the most appropriate response to satisfy the demands of the retrieval cue received from CA1 (Hebscher & Gilboa, 2016).

Based on prior literature, we hypothesized that the failure to retrieve previously learned information would be uniquely accompanied by a distorted confidence signal in individuals with vMPFC lesions, suggesting a lack of congruence between their perceived and actual retrieval abilities (Hebscher et al., 2016; Hebscher & Gilboa, 2016). Notably, vMPFC cases were not generally overconfident: In this group, confidence was only dissociated from accuracy while processing similar lures, when it was more critical to discern whether incoming information was congruent with encoded information (based on FOR). However, this dissociation of confidence and accuracy was also present in low-scoring controls, suggesting that the skewed confidence was not specific to vMPFC lesions, but perhaps a correlate of poor performance on this task. Nonetheless, it is worth noting that the mechanisms supporting high confidence despite poor mnemonic discrimination (i.e., confusing lures for targets, as was typical in low-performing controls) may differ from the mechanisms supporting high confidence despite poor overall recognition and generalization (i.e., identifying both studied and unstudied items as new, which includes confusing similar lures for foils, as was typical in the vMPFC group). Thus, the inflated and uninformative confidence signals could be indicative of disruption of vMPFC-based FOR monitoring mechanisms when there is a weak memory trace to begin with, but may also be inherent in a task designed to confuse participants between multiple iterations of highly similar images.

To our knowledge, this study is the first to directly assess the role of the vMPFC in mnemonic discrimination in humans. We did not find that individuals with vMPFC lesions exhibit the same mnemonic discrimination deficit indicative of faulty pattern separation that is observed in individuals with lesions to the hippocampus and, in particular, the DG (Stark et al., 2019; Baker et al., 2016; Berron et al., 2016). Rather, damage to the vMPFC results in impaired overall recognition of images. Any specific consequence to performance in the vMPFC group may be considered a paradoxical improvement in identifying lures as "unstudied," reflecting an inability to integrate or generalize across targets and lures. This pattern of error is opposite to that of controls, who more frequently confused lures with conceptually and visually similar targets.

A challenge of lesion studies is the lack of control over exact lesion boundaries, especially given prior research demonstrating functional specificity within the mPFC. This is a particular issue given neuroimaging findings of a role of anterior regions in pattern separation and middle regions in memory integration (Schlichting et al., 2015). It is possible that, in the current study, behaviors consistent with more specific pattern separation, completion, or generalization deficits were obscured by the inclusion of individuals with extensive vMPFC lesions spanning anterior–posterior axis. Nonetheless, by working with individuals with lesions predominantly to the vMPFC, we were able to draw conclusions about the causal role of this region in episodic memory and develop a richer understanding of behavior than could be obtained from functional neuroimaging studies alone (Irish & van Kesteren,

2018; Rosenbaum, Gilboa, & Moscovitch, 2014). A strength of this study is the use of the three-choice version of the MST, which allows for old, similar, and new responses, rather than the two-choice version, which only allows for old/new discrimination (Stark et al., 2019). Use of the two-choice task in the current study would have precluded detection of a potentially critical nuance in our findings: the tendency of individuals with vMPFC lesions to respond new instead of similar to lures, which would have been interpreted as accurate performance in a two-choice version.

Overall, the current findings highlight the role of vMPFC as an essential node in the set of regions supporting episodic memory abilities. Whereas the DG of the hippocampus supports pattern separation, the vMPFC may play a complementary role in supporting the overall retrieval and possibly a more specific role in the integration of similar or overlapping incoming information to form new knowledge structures (schemas) in conjunction with CA1. These results support the view that recognition memory depends on projections from CA1 to the vMPFC, such that damage to either region will affect performance in a similar way (see Figure 5). Findings from this study encourage further work to better understand the flexible interplay between the hippocampus and vMPFC in balancing pattern separation and generalization during memory tasks.

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### Data Availability Statement

Please email C. L. (cdlauzon@yorku.ca) to request access to study data and materials.

### Author Contributions

Claire Lauzon: Conceptualization; Data curation; Investigation; Methodology; Writing—Original draft. Daniel Chiasso: Investigation. Jennifer S. Rabin: Funding acquisition; Supervision; Writing—Review & editing. Elisa Ciaramelli: Conceptualization; Supervision; Writing—Review & editing. R. Shayna Rosenbaum: Conceptualization; Funding aquisition; Methodology; Supervision; Writing—Original draft; Writing—Review & editing.

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### Diversity in Citation Practices

Retrospective analysis of the citations in every article published in this journal from 2010 to 2021 reveals a persistent pattern of gender imbalance: Although the proportions of authorship teams (categorized by estimated gender identification of first author/last author) publishing in the *Journal of Cognitive Neuroscience* (*JoCN*) during this period were M(an)/M = .407, W(oman)/M = .32, M/W = .115, and W/W = .159, the comparable proportions for the articles that these authorship teams cited were M/M = .549, W/M = .257, M/W = .109, and W/W = .085 (Postle and Fulvio, *JoCN*, 34:1, pp. 1–3). Consequently, *JoCN* encourages all authors to consider gender balance explicitly when selecting which articles to cite and gives them the opportunity to report their article's gender citation balance.

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