THE ROLE OF THE VENTROMEDIAL PREFRONTAL CORTEX IN MNEMONIC DISCRIMINATION AND GENERALIZATION

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Abstract

The ventromedial prefrontal cortex (vmPFC) is involved in generalizing across similar items and events, working with hippocampally mediated processes that discriminate between those items and events at encoding. These complementary processes may, in turn, contribute to confidence signals regarding the appropriateness or veracity of retrieved memory traces. In this study, mnemonic discrimination and generalization were assessed in individuals with vmPFC lesions using the Mnemonic Similarity Task (MST; Stark et al., 2013), which was designed to assess 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 participants showed intact discrimination of lures from targets but a propensity to mistake similar lures for dissimilar foils, and were overly confident relative to their accuracy. This pattern of performance is suggestive of a failure to develop a conceptual knowledge framework to extract a gist from common items. The findings suggest that mnemonic discrimination requires a balance of hippocampal and vmPFC interactions to facilitate detailed and gist memory of highly similar input.

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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 had not yet taken—is essential to everyday life. This process, known as pattern separation, is reflected in mnemonic discrimination of highly similar items or events and has been shown to critically rely on the sparse firing of granule cells in the dentate gyrus (DG) of the hippocampus (Leutgeb et al., 2007; Neunuebel & Knierim, 2014; Rolls, 2016). Equally important is the ability to extract gist information across similar items and events to organize and make sense of newly encountered information, such as immediately recognizing an apple and knowing that it will likely taste and feel similar to ones that you have experienced before. This process frees up cognitive resources to deal with other potential inputs into memory, and is achieved through a pattern association circuit in the hippocampus involving CA3-mediated pattern completion (retrieval of a memory from a partial cue) and CA1-mediated generalization (the extraction of commonalities or gist across items and events (Deuker et al., 2014; Ngo et al., 2020; Rolls, 2016). Behavioural paradigms designed to approximate pattern separation and completion tend to focus on contributions of specific hippocampal subregions even though these processes also depend on regions of neocortex that provide the necessary input from perception and prior knowledge, and that connect and elaborate its output. The ventromedial prefrontal cortex (vmPFC) is a candidate region due to its known role in gist extraction and schema instantiation via interactions with the hippocampus. The current study investigates whether the vmPFC is critical to mnemonic discrimination and/or complementary generalization by testing individuals with lesions to this region on the widely used Mnemonic Similarity Test (MST).

Pattern separation is purported to occur through a number of interrelated mechanisms in the hippocampus (Rolls, 2016). After receiving input from the entorhinal cortex via the perforant pathway, granule cells of the DG sparsely project onto CA3 pyramidal cells via mossy fibre connections (Rolls, 2016). The sparse firing activity of the DG granule cells in conjunction with the small number of synapses onto each CA3 cell further enables a decorrelation of input signals, allowing for orthogonalized memory traces for similar inputs. Conversely, pattern completion is likely facilitated by recurrent CA3-CA3 collateral connectivity while CA1 is involved in generalization and gist extraction (Guzman et al., 2016; Rolls, 2016). Although hippocampal pattern separation and completion are critical to the way that memories are formed, stored, and accessed, conceptual categorization in the service of generic or schematic representations in neocortex are equally relevant (Rolls, 2016). Categorization occurs when the outputs of similar stimuli are more similar than the inputs, resulting in a recognized congruence among nonidentical stimuli (Rolls, 2016). This process is facilitated by generalization in CA1 and its backprojections to neocortex. Importantly, categorization is unique from pattern completion, the recall of a whole pattern given a partial cue (Neunuebel & Knierim, 2014; Rolls, 2016). A schematic image depicting the interplay of hippocampal and cortical regions during tasks of mnemonic discrimination is depicted in Figure 1.

The MST was designed as a behavioural approximation of pattern separation and has quickly become ubiquitous in the hippocampal memory literature, having been reported in at least 100 published studies since its inception in 2013 (Stark et al., 2019). The MST begins with an implicit encoding phase of object images followed by a surprise recognition task wherein participants must distinguish among previously learned object images (targets), novel images unlike anything shown previously (foils), and images that are visually and conceptually similar

to studied stimuli (lures; Stark et al., 2013). Performance on the MST is a promising index of hippocampal function, and behavioural findings have converged with predictions from computational models of pattern separation (Stark et al., 2019). Individuals with more extensive hippocampal damage exhibit compromise as indicated by the Lure Discrimination Index (LDI), the primary performance index of pattern separation ability (calculated by subtracting the proportion of foils misidentified as lures from the proportion of correctly identified lures; Kirwan et al., 2012). Performance on the MST has also been shown to specifically depend on the DG in both patient lesion and functional neuroimaging studies (Baker et al., 2016; Berron et al., 2016). Age-related deficits on the MST have been associated with hyperactivity of the DG, suggesting a failure in sparse encoding (Reagh et al., 2018), and with smaller CA3/DG volumes in individuals diagnosed with amnestic mild cognitive impairment (MCI; Yassa et al., 2010). Transient dysfunction of CA1 has also been shown to temporarily impair mnemonic discrimination (Hanert et al., 2019). Consistent with the perspective that the CA1 subserves generalization, similar patterns of CA1 activation have been observed during presentation of both lures and targets (De Shetler & Rissman, 2017; Lacy et al., 2011).

Although extant evidence suggests that performance on the MST critically depends on the hippocampus, performance may also be influenced by non-hippocampal regions and even non-mnemonic abilities. It has been demonstrated that general cognitive status as measured by the Montreal Cognitive Assessment (MoCA) is predictive of the LDI above and beyond the contribution of memory ability alone, suggesting possible dependence on non-hippocampal and/or non-mnemonic processes (Davidson et al., 2019; Foster & Giovanello, 2020; Pishdadian et al., 2020). Furthermore, the MST is designed to assess mnemonic discrimination at retrieval, though pattern separation is believed to occur at encoding (Allegra et al., 2020; Rolls, 2016). A

recent study found that a patient with selective DG lesions was impaired in non-mnemonic perceptual discrimination of complex, novel objects, suggesting that the role of the DG in mnemonic discrimination may not be specific to memory per se, but rather that the DG contributes to high-level perception, possibly in the service of memory encoding (Mitchnick et al., 2022). As such, the role of the DG in performance on the MST may be primarily driven by perception and encoding of object differences, while other functions necessary to perform well on the MST may rely more critically on other brain regions. These findings support the view that the MST does not selectively assess neuronal pattern separation within the DG and that mnemonic discrimination is likely influenced by a broader network of interconnected regions.

The vmPFC has been posited as an essential contributor to many aspects of memory, from encoding and consolidation to retrieval (Brod & Shing, 2018; McCormick et al., 2018; Yu et al., 2020). This region is typically defined as the area below the genu of the corpus callosum and the medial region of the orbital surface of the frontal lobes, and includes Broadmann areas 11, 12, 25, and portions of 10 and 32 (Schneider & Koenigs, 2017). The vmPFC may be expected to contribute to MST performance because of its roles in conceptual categorization and schema instantiation, which occur in collaboration with the hippocampus via strong structural and functional interconnectivity (Andrews-Hanna et al., 2010; Catani et al., 2012; Eichenbaum, 2017). Patients with vmPFC lesions are impaired in recognizing schema-congruent information (e.g., words associated with bedtime or the doctor's office) compared to controls (Ghosh et al., 2014), and show no difference in recall of schema-congruent vs. schema-incongruent stimuli on tasks on which schema instantiation is known to benefit memory (Ciaramelli et al., 2006; Spalding et al., 2015). Similar effects have been reported in healthy participants who have undergone transient perturbation of vmPFC function via transcranial magnetic stimulation

(Berkers et al., 2017). Neuroimaging studies have also demonstrated increased vmPFC activation in healthy adults when integrating new information into schemas (van Kesteren et al., 2010) as well as coupling of anterior hippocampal and vmPFC activity when learning paired associates in schema-consistent but not schema-inconsistent conditions (Guo & Yang, 2020). The vmPFC may be more broadly involved in a process of memory transformation, whereby a gist is extracted from commonalities across episodic memories into semantic knowledge or schemas (Hebscher & Gilboa, 2016; Winocur et al., 2010). This idea is bolstered by evidence that that the vmPFC and anterior hippocampus support abstract prototype information during concept generalization, and vmPFC-hippocampal memory integration contributes to knowledge generalization (Bowman & Zeithamova, 2018).

The role of the vmPFC in cognitive organization and schema has been extended to related domains, including associative inference and mnemonic context (Ghosh & Gilboa, 2014). Individuals with damage to the vmPFC exhibit significantly impaired memory for inferred but not studied paired associates (Spalding et al., 2018), and vmPFC damage has been associated with impairment on non-mnemonic transitive inference tasks (Koscik & Tranel, 2012; Wing et al., 2021). The vmPFC is also crucial for remembering the perceptual context of memories (Ciaramelli & Spaniol, 2009), and rodent studies have suggested that the vmPFC is involved in contextualizing memory in order to guide behaviour (Gonzalez & Fanselow, 2020). vmPFC activity at encoding may also vary as a function of knowledge-congruency, where encoding of information congruent with existing knowledge structures is associated with greater vmPFC activation (Brod & Shing, 2018). Recent evidence suggests that the vmPFC may also drive hippocampal processing during retrieval even for newly encoded (autobiographic) episodic memories, not just when a delay is present (McCormick et al., 2020).

The MST requires participants to recognize conceptual similarities between similar lures and studied targets in order to properly classify never-before-seen images as "similar" instead of "new," and the use of such concept categories may depend on the vmPFC (Ghosh & Gilboa, 2014). Thus, while the MST does not specifically test the formation and use of schemas, schema-adjacent conceptual knowledge structures supported by the vmPFC may nevertheless be essential to processing targets and lures as similar to each other and different from unstudied foils. Indeed, inhibition of the medial PFC was found to impair lure discrimination in a rodent analog of the MST (Johnson et al., 2021), though this finding has not yet been replicated in humans.

The vmPFC is also involved in facilitating an appraisal of the veracity and appropriateness of memory traces by producing confidence signals informed by prior experience in both mnemonic and non-mnemonic contexts (Hebscher et al., 2016; Hebscher & Gilboa, 2016). Multiple studies have shown that vmPFC activity is associated with confidence in both memory and decision-making tasks (De Martino et al., 2012; Gherman & Philiastides, 2018; Shapiro & Grafton, 2020) and that functional connectivity between the vmPFC and other frontal regions predicts the relationship between confidence and accuracy (De Martino et al., 2012). This process conceptually links the roles of the vmPFC in decision-making and memory, as meta-mnemonic monitoring implicitly involves judgements about the correctness of information (i.e., "feeling of rightness") and a decision of whether to report or withhold responses based on prior knowledge (Hebscher et al., 2016). It can be argued that confidence and "feeling of rightness" (FOR) are simply different behavioural estimations of the same processes underlying schematic and categorical relatedness: confidence signals are informed by perceived knowledge congruence and may be distorted if congruence is misjudged (Hebscher et al., 2016). If

individuals with vmPFC damage show impairment on the MST, prior research suggests that they may remain highly confident regardless of poor performance.

Taken together, the vmPFC is involved in several interrelated processes that may impact memory and influence performance on the MST, including the incorporation of mnemonic information into existing knowledge structures, the extraction of gist information, and meta-mnemonic appraisal at retrieval. While the vmPFC may not be expected to directly influence pattern separation, it may play a role in the extraction of similarities across items. Because the vmPFC has a well-documented role in the use of conceptual categories and schematic structure to link related information and is strongly interconnected with CA1, vmPFC compromise could lead to a failure to identify such linkages between similar stimuli and a subsequent over-discrimination of related objects. To test these possibilities, individuals with selective lesions to the vmPFC were administered an adapted version of the MST that incorporates confidence judgments. We predict that, relative to controls, individuals with selective lesions to the vmPFC will exhibit impaired lure identification. Recognition of previously studied images, by contrast, is not expected to depend on the instantiation or use of schema or conceptual knowledge structures and is thus predicted to remain intact despite vmPFC compromise. Given evidence that disproportionate confidence may reflect failures in meta-mnemonic monitoring following vmPFC dysfunction (Hebscher & Gilboa, 2016), we expect individuals with vmPFC lesions to exhibit 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 as well as the utility of behavioural paradigms in isolating pattern separation and completion processes.

Methods

Participants

vmPFC Lesion Patients

A total of 10 individuals with focal lesions to the vmPFC participated in the present study. 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 in Cesena, Italy. The vmPFC cases had an average age of 67 (range: 53-82, *SD* = 9.73) and 13.14 years of education (range: 6-18, *SD* = 4.26). All of the cases were in good health and had no additional diagnoses known to affect memory or cognition. Lesions to the vmPFC were sustained following rupture to an anterior communicating artery (ACoA) aneurysm in all but one case (R.L.), who experienced vmPFC lesions following an anterior cerebral artery stroke. All cases were tested between 2021 and 2022, and at least six years post-injury (range: 6-15 years).

MRI scans of the Canadian patients 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 2 shows the location, extent, and overlap of the Canadian vmPFC lesions (previously reported in Mok et al., 2021). Lesions largely affected 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. R. L. had damage to her visual cortex (BAs 17, 18, 19, 37) constituting ∼32% of her lesion volume, though she reported no visual problems during or prior to participation in the study and attained normal scores on the Rey–Osterrieth

Complex Figure test (68th percentile; Spreen & Strauss, 1998). Additional neuropsychological and demographic information is presented in Table 1.

Controls

Performance in the vmPFC group was compared to 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. Control participants were screened for history of psychiatric or neurological illness, and for risk of mild cognitive impairment using the MoCA (Nasreddine et al., 2005). The MoCA was administered virtually though 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, *SD* = 7.8), and 14.29 years of education (range: 8-20, *SD* = 3.37). 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 Centre for Studies and Research in Cognitive Neuroscience at the University of Bologna. Participants received monetary compensation for their participation in the study.

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 patient (C.R.) was tested in person because of barriers to

virtual testing. To ensure consistency with the other participants, he dictated his responses aloud while research personnel controlled the computer task.

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 milliseconds with an interstimulus interval (ISI) of at least 500 milliseconds, 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: 64 each of previously studied targets, novel foils, and similar lures, though they were not informed of the proportions of each stimulus type. 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 milliseconds, followed by an ISI of least 500 milliseconds, or until a response was made. Next, the confidence scale was presented until a response was made, followed by an additional 250 millisecond ISI. A schematic of the task is presented in Figure 3.

Statistical Analyses

Mnemonic Discrimination

On the MST, mnemonic discrimination or pattern separation ability is inferred from the lure discrimination index (LDI), calculated as p("Similar"|Lure) – p("Similar"|Foil). This metric

was calculated for each participant and compared between patient and control groups using a Welch's two-sample t-test. Recognition accuracy of each stimulus type (targets, lures, and foils) was also calculated and compared between groups using Welch's two sample t-tests to contextualize the LDI findings. Impaired recognition across stimulus types would suggest a gross memory impairment not specific to mnemonic discrimination, while impaired recognition of lures but intact recognition of targets and foils would suggest a specific impairment in lure discrimination but intact recognition memory (Stark et al., 2013).

Because errors in lure discrimination can be driven by two different response patterns (i.e., mislabeling lures as either "old" or "new" instead of "similar"), proportions of "old", "similar", and "new" responses given to lures were compared between groups using Welch's two-sample t-tests. Highlighting possible differences in the breakdown of lure responses may better provide insight into the underlying mechanisms of impairment.

Confidence

Hypothesized distortions in confidence signals by individuals with vmPFC lesions were assessed using confidence-accuracy calibration (CAC) curves, calibration (*C*) statistics and over/underconfidence (*O/U*) metrics (Weber & Brewer, 2004). CAC curves are created by plotting average accuracy at each confidence level, and were generated for each group's responses to each stimulus type. Perfect CAC would be reflected by a straight line with a slope of 1 and *y*-intercept of 0; visual inspection of the deviation of actual curves from the theoretically perfect CAC line provides information about the association between confidence and accuracy.

To statistically evaluate differences in CAC, *C* was computed as the weighted mean of the squared difference between confidence and proportion correct for each confidence level. *C* 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 was also calculated as a gross measure of each participant's tendency to respond more or less confidently than warranted by the accuracy of their decision (Weber & Brewer, 2004). *O/U* ranges from -1 (complete underconfidence) to +1 (complete overconfidence) and is calculated as the difference between mean confidence and mean accuracy. While *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.

Results

Mnemonic Discrimination Indices

All analyses were initially conducted separately for each country to ensure consistency across testing sites. Because the pattern of results did not appear to differ across countries, data from the two countries were combined into a single set for the final analyses. A comparison of key variables across countries is displayed in Table 2. All results presented in this section include participants from both sites.

The LDI was significantly lower in the vmPFC patients ($M = 0.08$, $SD = 0.10$) than in healthy controls ($M = 0.31$, $SD = 0.18$), $t(25.172) = 5.55$, $p < .001$, Hedge's $g = 1.31$, 95% CI: [0.57, 2.04]), suggesting impaired mnemonic discrimination in individuals with vmPFC damage (Figure 4). Recognition accuracy was assessed for each stimulus type and is displayed in Figure 5. No significant difference was found between the vmPFC group ($M = 0.52$, $SD = 0.28$) and

controls (M = 0.77, SD = 0.14) on recognition of targets (t(10.26) = 1.92, p = .09, g = 1.14, 95% CI: [0.36, 1.94]). Similarly, no difference was found between the vmPFC group (M = 0.81, SD = 0.09) and controls (M = 0.81, SD = 0.12) on recognition of foils (t(16.52) = 0.03, p = .98, g = 0.01, 95% CI: [-0.68, 0.68]). Consistent with the LDI findings, recognition of lures was significantly lower in the vmPFC group (M = 0.20, SD = 0.13) than in controls (M = 0.47, SD = 0.17), t(16.52) = 5.48, p < .001, g = 1.58, 95% CI: [0.83, 2.33]), suggesting a specific impairment on the component of the task designed to tax pattern separation (identification of lures as different from targets).

Response patterns to lures were more closely inspected to better understand potential mechanisms of impairment. The proportion of lures miscategorized as previously studied targets was not found to differ between patients (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 no difference in the likelihood to misremember lures as being previously studied. Group differences in lure discrimination were instead due to a higher proportion of lures misidentified as novel foils by patients (M = 0.42, SD = 0.25) compared to controls (M = 0.14, SD = 0.09; t(8.42) = -3.19, p =.01, g = -2.07, 95% CI: [-2.89, -1.25]). A breakdown of lure responses between groups is presented in Figure 6**.**

Confidence

Figure 7 displays CAC curves across groups and stimulus types. Visual examination of these plots suggests that confidence and accuracy are better calibrated in both groups when they are responding to targets and foils than to lures. Confidence and accuracy appear to be more poorly calibrated in the vmPFC patients than controls when responding to lures. To statistically evaluate differences in CAC, a calibration statistic (C) was calculated for each participant within

each stimulus type, displayed in Figure 8. *O/U* was also calculated for each participant within each stimulus type and displayed in Figure 9. Between-group comparisons were calculated for both *C* and *O/U* within each stimulus type (see Table 3 for full results). 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]). Individual patient performance on all mnemonic discrimination and confidence measures is available in Table 4, along with controls' performance separated by country.

Discussion

The present study provides evidence of atypical performance in individuals with vmPFC lesions on a test of mnemonic discrimination in a way that is consistent with the known role of the vmPFC in generalizing across exemplars of items to generate schemas as new information is incorporated into memory. The vmPFC-lesioned group exhibited excessive discrimination in the form of misidentifying lures as novel foils, a pattern of performance that differs from that seen in previously studied individuals with hippocampal lesions who primarily misidentify lures as previously studied targets (Kirwan et al., 2012; Baker et al., 2016). This was reflected in the vmPFC patients' subjective judgments of their performance, with confidence and accuracy misaligned only when the patients mistakenly endorsed lures as foils. These findings identify the vmPFC as an important contributor to the hippocampal-neocortical pattern association network and highlight that MST performance is strongly influenced by vmPFC functioning.

Mnemonic function of the vmPFC

The current study confirms previous findings that the vmPFC is involved in mnemonic discrimination, and further clarifies the mechanism of frontal contribution to this ability. Impaired performance in the vmPFC-lesioned cases was selective to the identification of lures; they did not perform differently from controls in identifying previously studied targets or novel foils. It is well-established that the vmPFC supports the use of schemas to organize memory (Ghosh & Gilboa, 2014), and while the MST was not specifically designed to assess the ability to generalize across common inputs, identification of lures as similar (but ultimately unstudied) depends on higher-order brain structures involved in the abstraction and integration of the contents of memory. To perform well on the task, participants must be able to identify two distinct but related objects as being conceptually linked and belonging to the same object category. If participants fail to identify categorical links between lures and targets, they may mislabel similar lures as being novel, which occurred to a significantly greater extent in vmPFC participants than controls. Conversely, if participants overextend object categories such that they cannot discriminate among similar traces, they may falsely identify similar lures as being previously studied—this pattern of failure is more closely in line with most behavioural definitions of pattern separation (Stark et al., 2019). In the present study, rates of mischaracterizing lures as "Old" were indistinguishable between patient and healthy control samples. Instead, the generally worse lure discrimination by vmPFC patients appears to be driven by their failure to recognize the similarities between lures and previously studied targets rather than a failure to discriminate similar information at encoding. That is, while individuals with vmPFC lesions were impaired on the task, they did not exhibit a traditional pattern

separation deficit. Performance in the vmPFC group is in line with findings of impaired lure discrimination in rodents with inhibited medial PFC function (Johnson et al., 2021).

The response pattern observed in our sample of vmPFC-lesioned individuals suggests that the vmPFC may facilitate a process whereby a similar lure triggers a memory of an encoded stimulus belonging to the same conceptual category before a decision can be made about whether the images are identical or merely similar. When the vmPFC is damaged and cannot engage in a process of generalization together with the CA1 subfield, similar lures will not be conceptually linked and, as a result, are more likely to be labelled as "New" instead of "Similar" or "Old." The pattern of misidentifying lures as "New" would also be expected to emerge if vmPFC patients exhibited general encoding and retrieval deficits, but this does not appear to be the case as recognition memory for previously studied targets was intact.

Most models of vmPFC function have focused on its role during retrieval, while models of pattern separation are typically described at encoding. The accurate identification of a lure on the MST, however, likely involves both encoding and retrieval processes. To make sense of how the vmPFC directly interacts with the hippocampus on this task, we combine established models of the role of the vmPFC at retrieval (Moscovitch & Winocur, 2002) with models of hippocampal pattern separation, completion, and generalization (Neunuebel & Knierim, 2014; Rolls, 2016). The working-with-memory (WWM) model described by Moscovitch and Winocur (2002) and extended by Hebscher and Gilboa (2016) suggests that in response to an indirect cue (such as a similar lure), the dorsolateral PFC (dlPFC) formulates a memory search strategy and the ventrolateral PFC (vlPFC) specifies retrieval cues that could potentially satisfy the retrieval task (in this case, the studied target). A memory trace is then activated by the medial temporal lobe (MTL), and a different process ensues depending on whether the stimulus is ultimately

perceived to be old, similar, or new. If the image is perceived to be a previously studied target, then recurrent CA3-CA3 collateral connectivity produces a pattern completion signal, and CA1 produce a generalization signal through backprojections to the vmPFC. A confident FOR signal will be generated by the vmPFC, and the stimulus will be interpreted as "old." Alternatively, if the item is perceived as novel, sparse firing of the DG granule cells and diluted mossy fibre projections to CA3 will occur. No generalization signal is projected by CA1 to the vmPFC, and no conceptual linkage to a previously studied image occurs. The accurate interpretation of a lure requires a combination of the encoding and retrieval processes described above. The MTL is activated by the neocortex, and sparse firing of the DG occurs as the stimulus is encoded as distinct from previously studied images. However, a generalization signal is still produced by the CA1 and backprojected to the vmPFC, where the conceptual congruency between the lure and the associated target is ultimately identified. As such, failures in lure identification driven by undergeneralization may hinge primarily on interrupted CA1-vmPFC connections, which would otherwise enable gist extraction and concept categorization through dilution of competitive networks (Rolls, 2016). A visual depiction of the regions involved in lure identification is depicted in Figure 1.

Confidence signals

As predicted, individuals with vmPFC lesions demonstrated inflated confidence compared to controls, but only when responding to lures. This is evident in the comparison of confidence calibration statistics (Figure 8) and over/underconfidence statistics (Figure 9), but also by a visual examination of the confidence-accuracy plots (Figure 7). Informative and appropriate confidence signals would be expected to result in a straight line, where the highest possible confidence rating (5) would result in 100% accuracy (Weber & Brewer, 2004). This

pattern holds fairly well for both patients and controls in relation to their endorsement of targets and rejection of foils. As depicted in Figure 7, vmPFC patients deviate from perfect calibration to a higher degree than controls only when responding to lures. Nonetheless, both groups appear to have a curvilinear confidence-accuracy relationship when responding to lures, though vmPFC patients deviate to a higher degree than controls, especially at higher confidence levels. This suggests a general confidence-accuracy dissociation during lure identification, heightened by vmPFC compromise.

Though vmPFC patients exhibit uniquely inflated confidence when responding to lures, it is unclear whether inflated confidence is influencing impairment or resulting from it. It could be that confidence levels remain steadily high and only become dissociated from accuracy during the most difficult part of the task (i.e., lure discrimination). This might be taken to suggest that vmPFC compromise is associated with a failure to adjust confidence levels to reflect decreased acuity, though the decrease in acuity itself is driven by other factors (such as failed use of conceptual cognitive structures). Alternatively, and more consistent with the WWM model, the inflated confidence signals may occur upstream of faulty mnemonic decision-making as monitored by the dlPFC, and the inability to produce appropriate FOR may directly lead to faulty responses (Moscovitch & Winocur, 2002). While the present study does not have the sensitivity to determine the exact mechanism by which confidence signals and mnemonic discrimination/generalization interact, we have demonstrated that both depend critically on proper functioning of the vmPFC.

Implications for the MST

The MST is a widely used and well-validated research tool, and its critical index (LDI) has been shown to depend on the hippocampus (Baker et al., 2016; Kirwan et al., 2012; Stark et

al., 2019). The present study identified the vmPFC as another essential node in the set of regions supporting mnemonic discrimination abilities. At a first pass, the vmPFC patients' lure discrimination appears to resemble that described in patients with hippocampal damage (Hanert et al., 2019; Kirwan et al., 2012), including an individual with selective lesions to the DG (Baker et al., 2016). Upon closer inspection, however, the pattern of deficits seen in cases with lesions to the vmPFC vs. hippocampus reveal differential contributions of these regions to task performance. The hippocampus/DG appears to support pattern separation at encoding and the vmPFC appears to support the conceptual linking of information and confidence signals when integrating new information into existing knowledge structures. Though related, the two processes may be dissociated, such that one may be impaired while the other is spared. This study is one of the first to explicitly explore the contributions of non-MTL regions to performance on the MST and highlights the importance of a network-based understanding of performance. Hippocampal pattern separation is likely one of many processes implicated in mnemonic discrimination; dysfunction of other regions may result in similar deficits driven by disparate mechanisms.

In addition to furthering our understanding of the role of the vmPFC in memory processes, these findings provide important context for the MST itself. One important consideration is that the MST can be administered with either three response choices (Old/Similar/New) or with only two choices (Old/New, where targets are categorized as "Old" and lures and foils are both categorized as "New"). The two-choice version is sometimes favored because it is more amenable to signal detection theory modeling and purportedly reduces the task's cognitive load for use in clinical populations (Stark et al., 2019). However, if the two-choice version had been used in the present study, no difference between vmPFC patients and

controls would have been detected. As described, the critical error leading to low LDI in this sample was the misidentification of similar lures as "New," which would not have been captured in the two-choice version, as the correct response to both similar lures and novel foils would have been "New." Thus, while the two-choice version of the MST may be sensitive to failures in pattern separation, the three-choice task is needed to detect failures driven by over-discrimination and poor generalization.

Limitations and Future Directions

There are inherent advantages and disadvantages to the patient-lesion method. Similar to other studies involving focal lesion patients, the current study involved a relatively small sample of vmPFC-lesion patients, though the cognitive and neuroanatomical profiles of most of the patients are well-characterized and have been reported elsewhere (Ciaramelli et al., 2021; Mok et al., 2021). This study did not include measures sensitive to possible compensatory neurocognitive mechanisms, and there are other aspects of vmPFC involvement in tasks of mnemonic discrimination that can be further explored using other methodologies. Nonetheless, human lesion studies continue to offer an unparalleled perspective into the critical role of brain regions in enabling complex cognition and behaviour (Adolphs, 2016; Irish & van Kesteren, 2018).

We have speculated that the vmPFC contributes to linking of similar everyday objects within categorical structures, but we cannot make any certain claims beyond a potential role for the vmPFC in the regulation of FOR and identification of unstudied lures as similar to studied targets. We theorized that the vmPFC may be most critical to the conceptual association of similar lures to their previously studied counterparts, while the hippocampus may be more essential to the formation of discrete traces of similar items at encoding (Baker et al., 2016) and

possibly perception (Mitchnick et al., 2022). While it is now evident that both regions are essential to performance on the MST, a direct comparison of the specific response patterns between individuals with vmPFC vs. hippocampal lesions would clarify their unique contributions to this this task. Likewise, we hypothesized that the disproportionately high confidence in relation to lures would be more prominent in individuals with vmPFC lesions compared to hippocampal or other non-MTL lesions, but this has not been explored directly. Individuals with vmPFC and hippocampal lesions often exhibit similar performance on so-called "hippocampal tasks" despite different theoretical mechanisms of impairment (McCormick et al., 2018). By continuing to examine conditions in which vmPFC and hippocampal compromise lead to similar or dissimilar patterns of impairment (such as when using emotional stimuli), we can deepen our understanding of the neurocognitive basis of mnemonic discrimination, episodic memory, and, more broadly, hippocampal-neocortical interactions.

Conclusion

This study directly assessed the role of the vmPFC in mnemonic discrimination in humans. Our data suggest that the MST critically depends on the vmPFC, though individuals with vmPFC lesions do not exhibit a traditional mnemonic discrimination deficit indicative of faulty pattern separation. Rather, damage to the vmPFC appears to result in over-discrimination of images of similar everyday objects, where lures are misidentified as entirely novel. We also demonstrated that vmPFC impairment is associated with a disconnect between confidence and accuracy during mnemonic discrimination. Although the exact mechanism of vmPFC involvement in mnemonic discrimination and generalization remains to be determined, the current findings suggest that the vmPFC makes a critical contribution to performance on the MST, providing important context for future studies employing this task.

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TABLES

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												
AM.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

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

Table 2

Comparison of Key Variables between Canadian and Italian Samples

	Canadians		Italians					
	M	*SD*	*M*	*SD*	*df*	*t*	*p*	Hedge's *g,* [95% CI]
Accuracy								
Targets	0.78	0.14	0.71	0.15	48.17	1.93	.06	0.52, [-0.02, 1.06]
Lures	0.43	0.20	0.40	0.20	50.91	0.58	.57	0.15, [-0.38, 0.69]
Foils	0.80	0.12	0.81	0.11	51.86	-0.26	.79	-0.07, [-0.60, 0.46]
Confidence statistic								
Targets	0.04	0.16	0.10	0.05	27.43	-1.79	.08	-0.52, [-1.06, 0.02]
Lures	0.28	0.18	0.31	0.18	50.90	-0.59	.56	-0.16, [-0.69, 0.38]
Foils	0.02	0.02	0.04	0.03	42.67	-1.59	.12	-0.44, [-0.97, 0.10]
Over/underconfidence								
Targets	0.11	0.13	0.16	0.21	38.65	-1.10	.28	-0.31, [-0.84, 0.23]
Lures	0.39	0.19	0.37	0.22	47.69	0.33	.75	0.09, [-0.44, 0.62]
Foils	0.04	0.11	0.00	0.13	47.31	1.23	.22	0.33, [-0.20, 0.87]

Note. 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

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]

Note. 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 4

Individual Patient and Country Performance

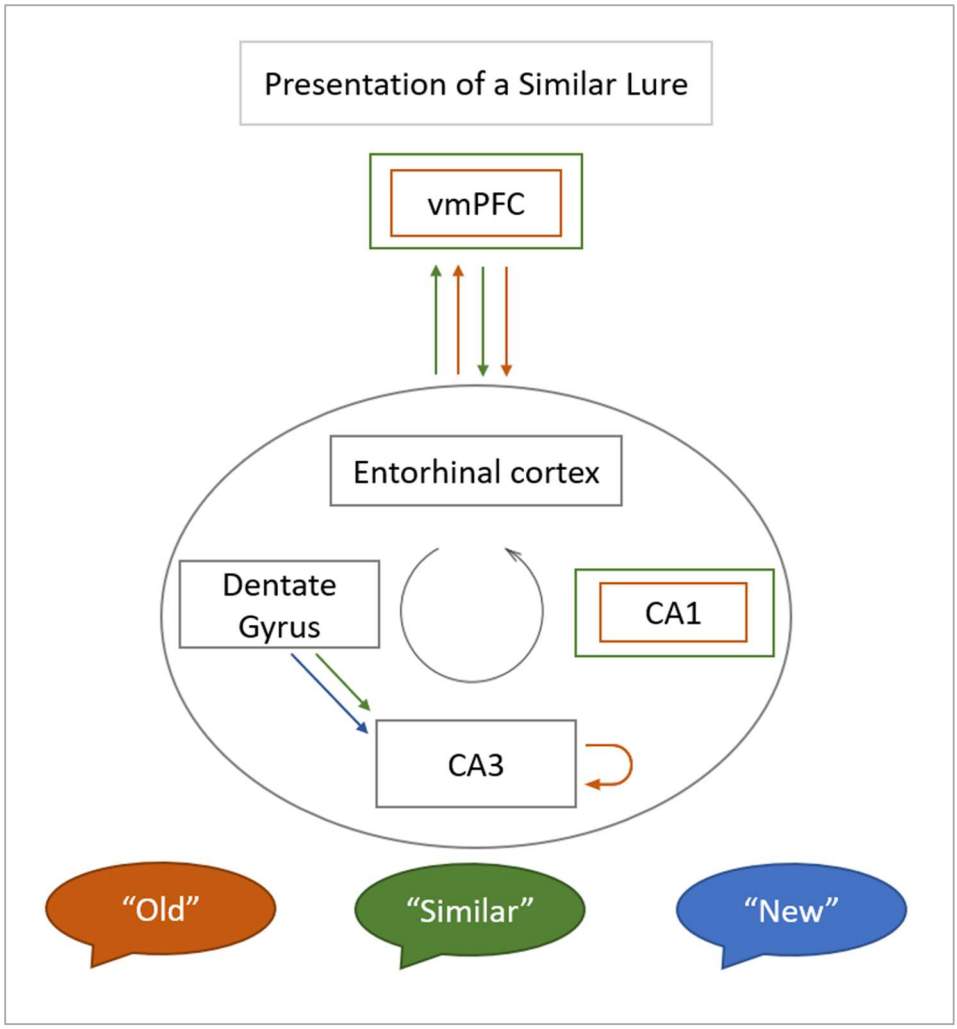
		Proportion Correct			Confidence Calibration (*C*)			Over/Underconfidence		
Patients	LDI	Targets	Lures	Foils	Targets	Lures	Foils	Targets	Lures	Foils
Canadian										
MM	-0.05	0.58	0.00	0.86	0.12	0.71	0.01	0.34	0.83	0.00
MT	0.12	0.64	0.16	0.92	0.03	0.46	0.03	0.11	0.61	-0.08
RL	0.20	0.75	0.34	0.80	0.01	0.26	0.01	0.10	0.45	0.06
JW	0.02	0.78	0.02	0.80	0.02	0.54	0.01	-0.08	0.72	-0.03
CR	0.06	0.50	0.34	0.65	0.19	0.51	0.00	0.38	0.24	-0.06
Italian										
AMO	0.05	0.05	0.12	0.88	0.77	0.68	0.01	0.83	0.70	-0.01
AGI	0.25	0.80	0.31	0.86	0.02	0.38	0.04	0.03	0.39	-0.08
EME	0.05	0.23	0.11	0.84	0.34	0.55	0.01	0.46	0.59	-0.05
MGR	-0.02	0.78	0.28	0.64	0.03	0.31	0.05	0.10	0.52	0.19
GTI	0.16	0.42	0.30	0.83	0.12	0.11	0.11	0.12	0.16	-0.30
Controls *M* (*SD*)	0.31 (0.18)	0.77 (0.14)	0.47 (0.17)	0.81 (0.12)	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)	0.81 (0.13)	0.48 (0.16)	0.8 (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)	0.73 (0.15)	0.45 (0.20)	0.81 (0.12)	0.06 (0.06)	0.28 (0.17)	0.03 (0.03)	0.12 (0.15)	0.35 (0.22)	0.01 (0.11)

Note. LDI = Lure Discrimination Index, and is computed by subtracting the proportion of "similar" responses given to novel foils from the proportion of "similar" responses given to lures. 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.

FIGURES

Figure 1.

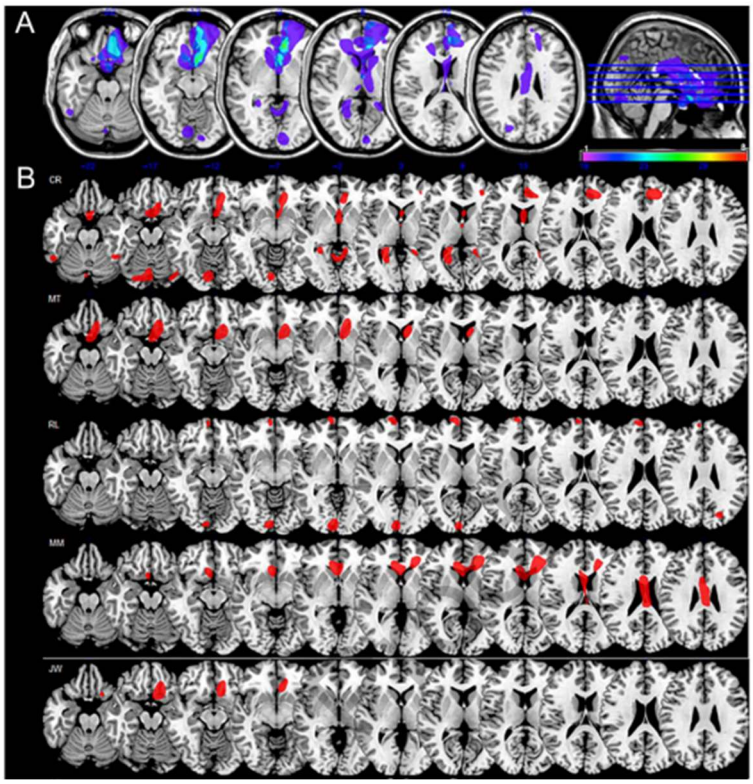
Hippocampal-vmPFC Interactions Supporting Mnemonic Discrimination and Generalization



Note. Graphic depiction of the contributions of the vmPFC and hippocampal subregions to pattern separation, pattern completion, and generalization on the MST. A response of "Old" requires activation of the medial temporal lobe (MTL) by neocortex, followed by recurrent CA3-CA3 collateral connectivity and generalization in CA1, and finally backprojections to the vmPFC where feeling of rightness is generated. A response of "Similar" involves activation of MTL by neocortex, followed by sparse firing of the DG granule cells and mossy fibre projections to CA3, and finally generalization in CA1 and backprojections to the vmPFC where conceptual link to a previously studied item is identified. A response of "New" involves sparse firing of the DG granule cells and diluted mossy fibre projections to CA3, and no involvement of the vmPFC. (This figure excludes other regions of neocortex involved in initial sensory processing and response formulation.)

Figure 2

Lesion Location and Extent in vmPFC Patients.



Note. (A) Axial slice template illustrating lesion overlap across vMPFC patients. Slices are 8 mm apart at $z = -30, -22, -14, -6, +2$, 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). (B) Axial slice templates illustrating the lesion location and extent for each of the vMPFC patients. Slices are 8 mm apart at $z = -22, -17, -12, -7, -2, +3, +8, +13, +18, +23, +28$. 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 (figure previously reported in Mok et al., 2021).

Figure 3

Schematic of the Adapted Mnemonic Similarity Task with Confidence

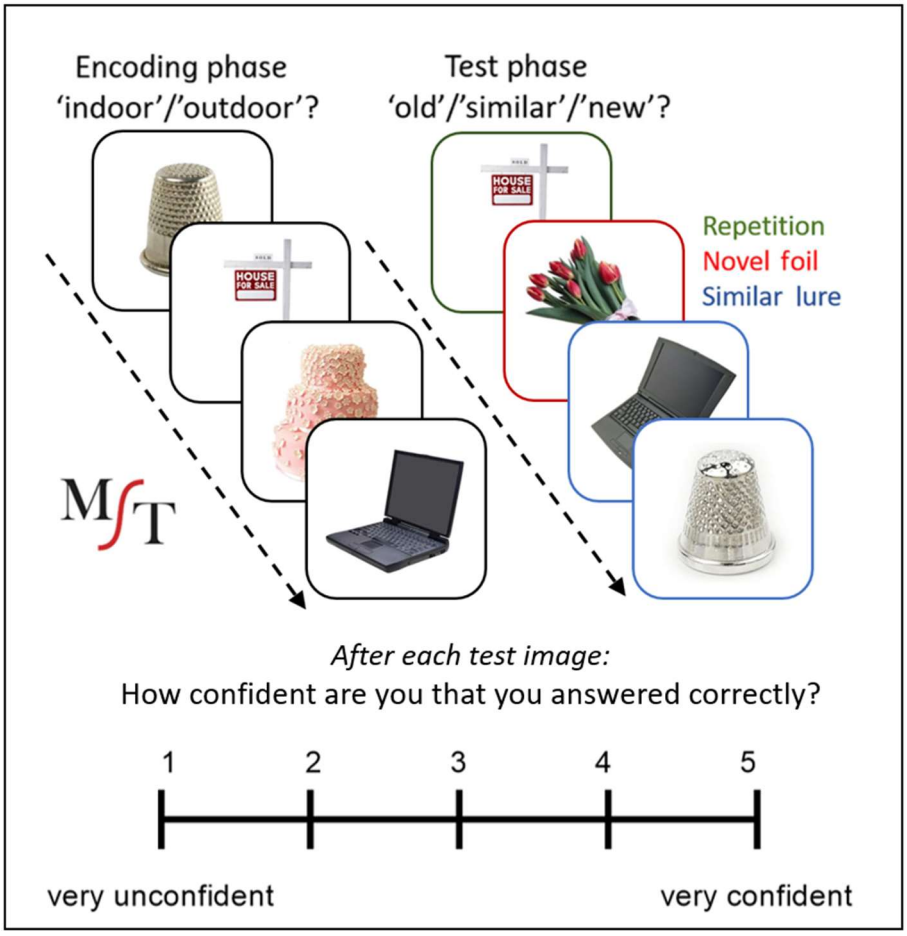
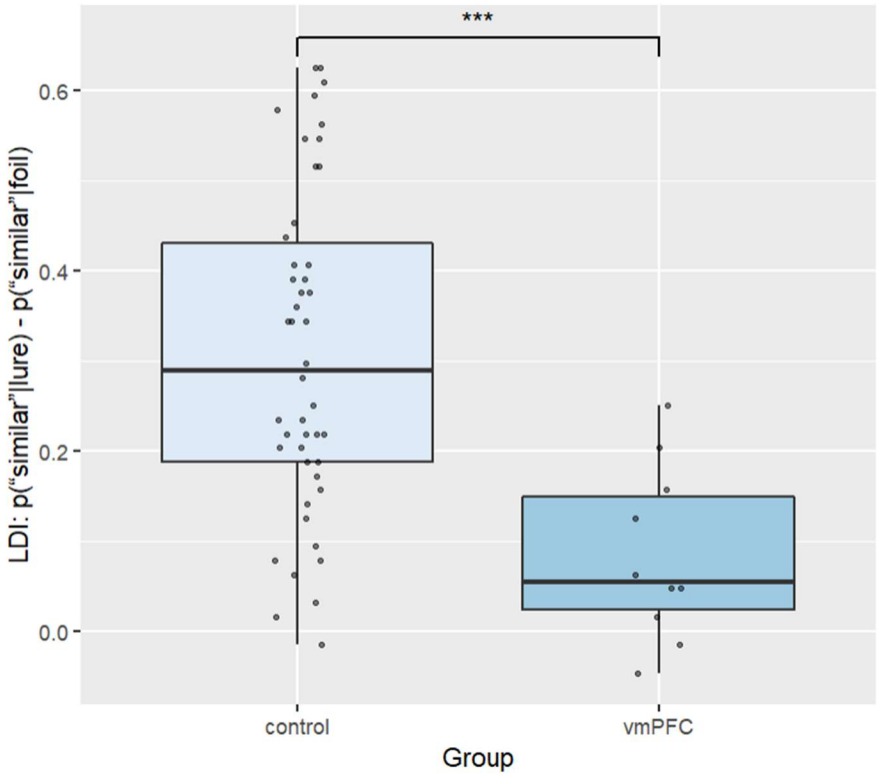


Figure 4

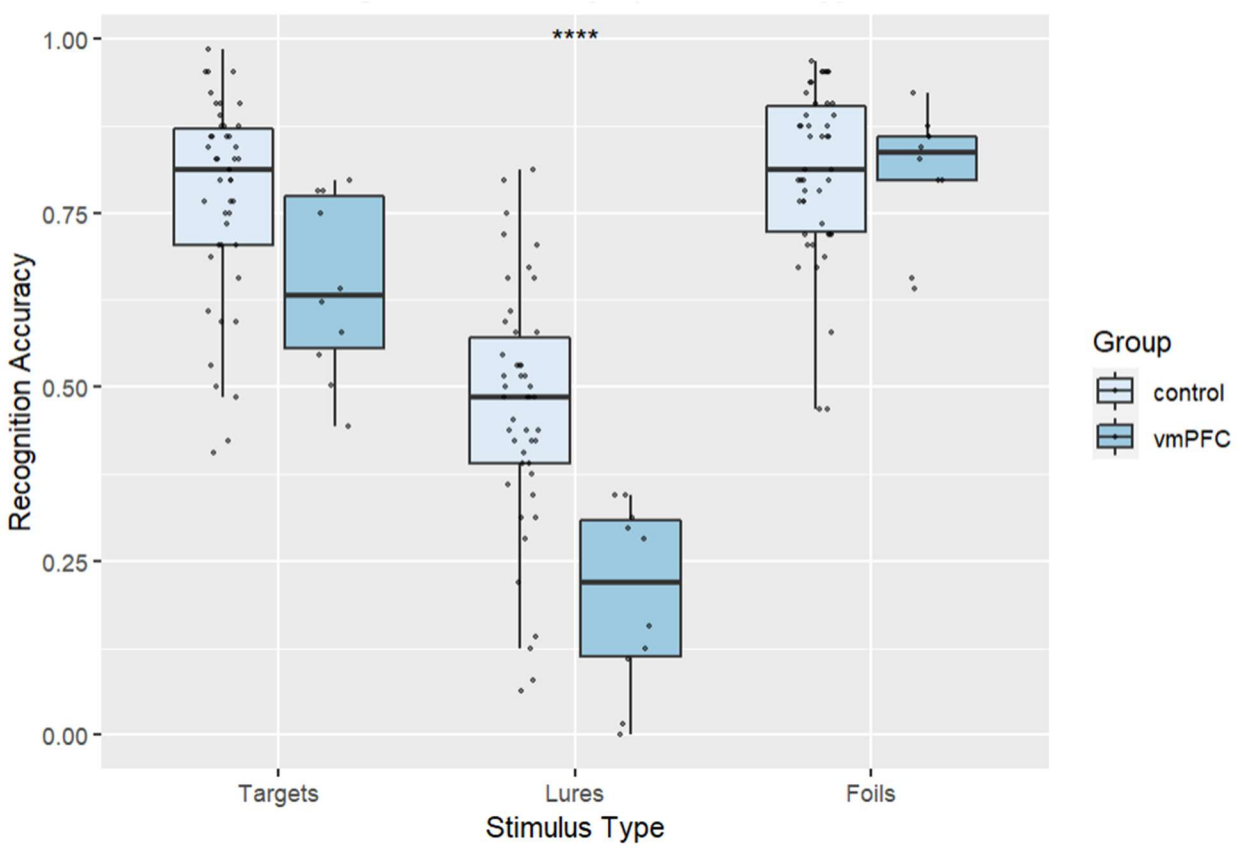
Lure Discrimination by Group



Note. Lure discrimination index (LDI; calculated by subtracting the proportion of similar responses given to lures from the proportion of similar responses given to foils is compared between patient and control groups. A Welch's t-test found the group means to be significantly different ($p < .001$).

Figure 5

Recognition Accuracy by Stimulus Type



Note. Proportion of correct responses to each stimulus type (targets, lures, foils) compared between patient and control groups. Welch's t-tests found a significant group difference on identification of similar lures (p <.0001), but not of previously studied targets (p = .09) or novel foils (p = .98).

Figure 6

Proportion of Lure Response Between Groups

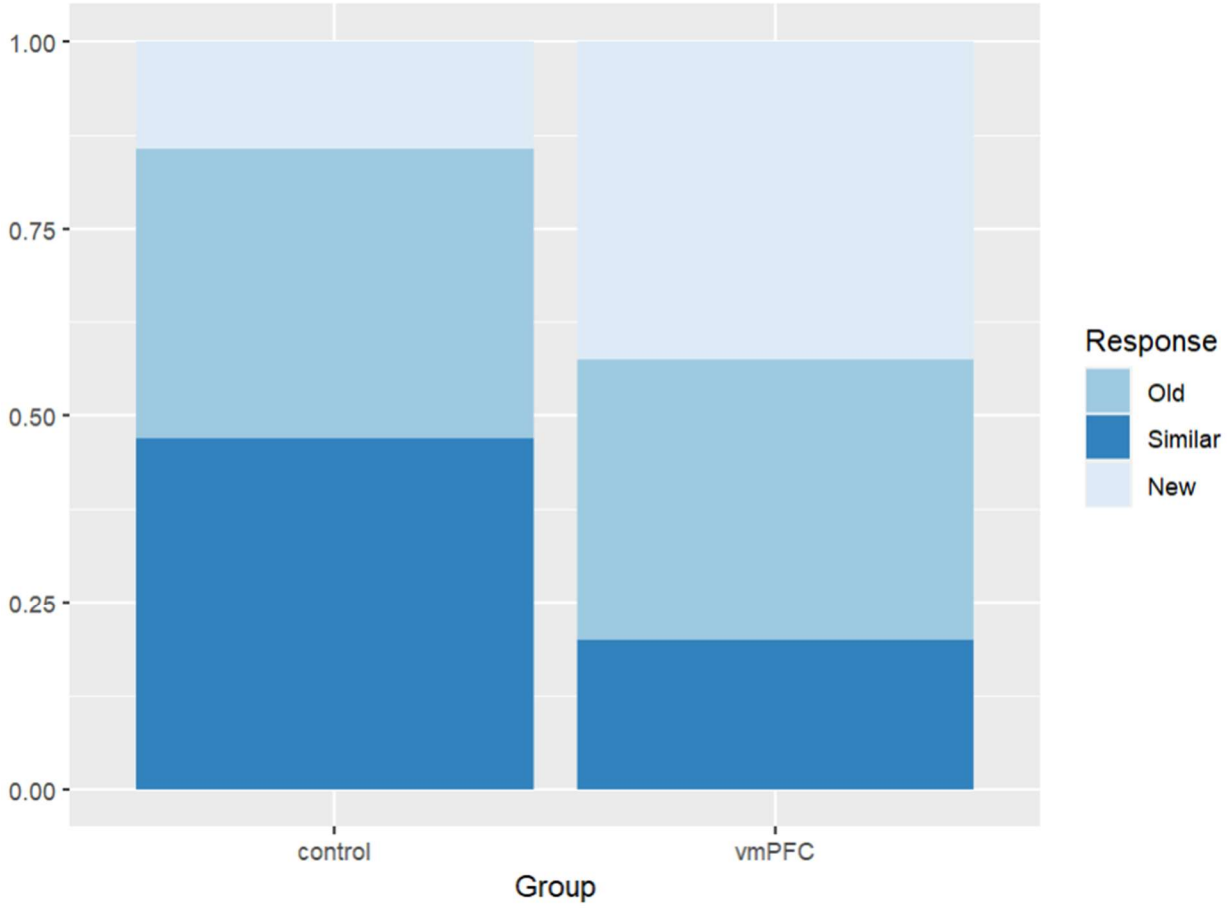
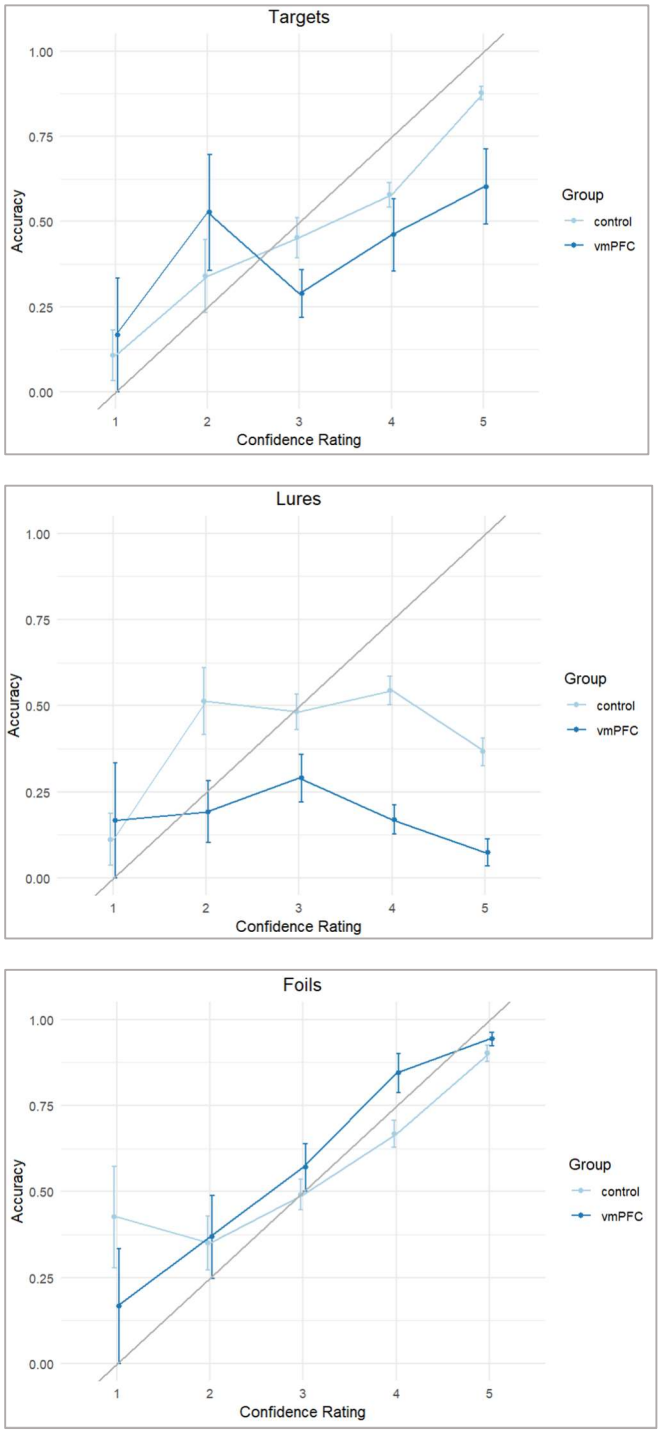


Figure 7

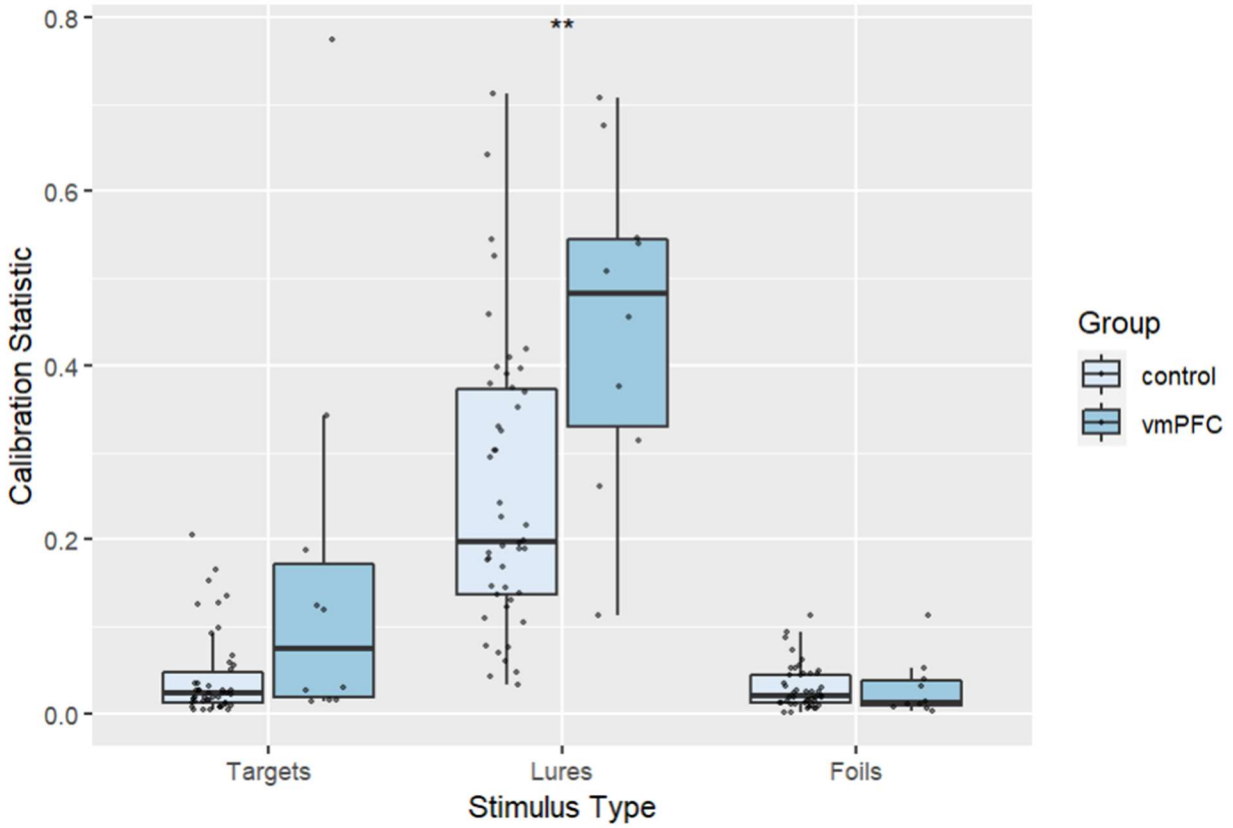
Confidence-Accuracy Calibration Curves



Note. Mean group accuracy at each confidence level (1-5) is plotted for each stimulus type (targets, lures, foils). Error bars depict standard error of the mean at each confidence level. Dashed grey lines depict theoretical perfect confidence-accuracy calibration , where maximum confidence predicts 100% maximum accuracy, 80% confidence predicts 80% accuracy, etc.

Figure 8

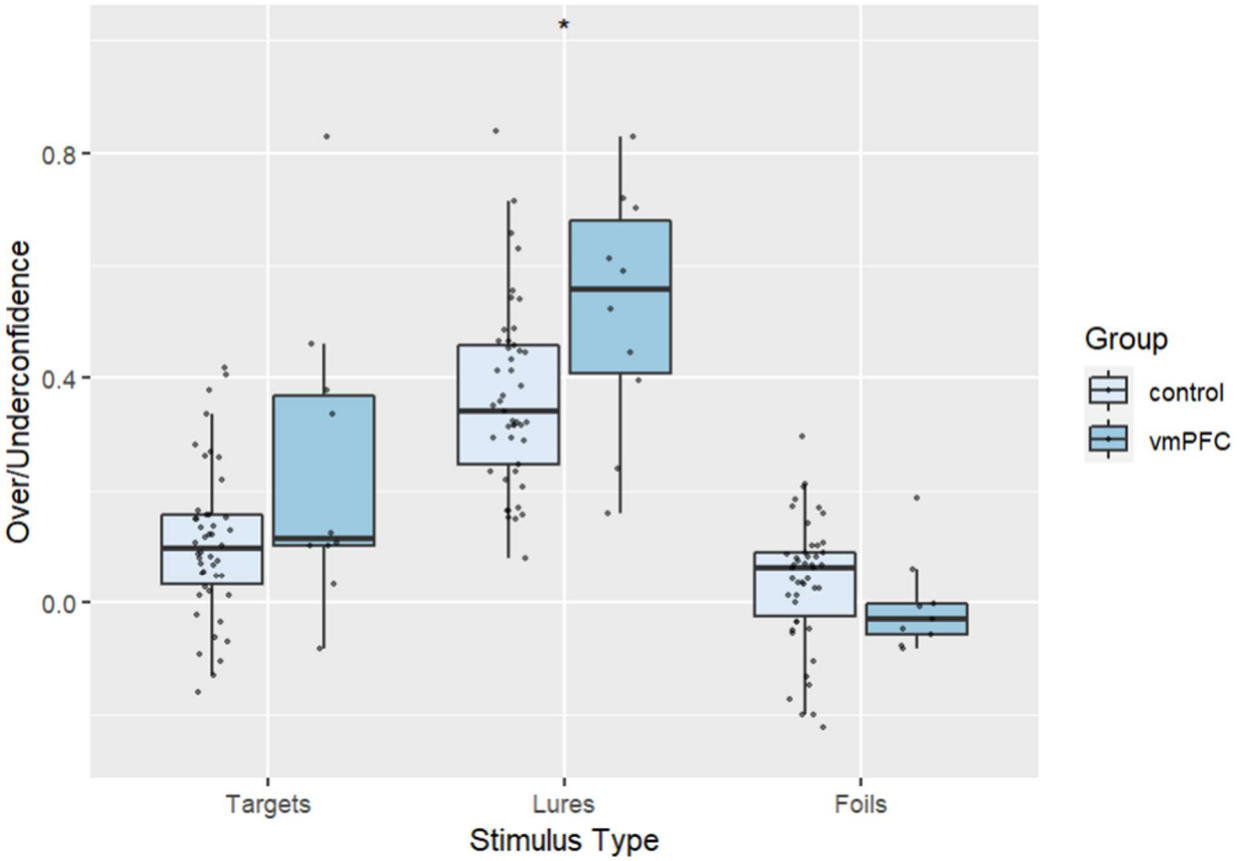
Confidence Calibration by Stimulus Type



Note. The confidence calibration statistic (*C*) was 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). Welch's t-tests found a significant group difference in confidence-accuracy calibration when responding to similar lures (p =.009), but not to previously studied targets (p = .14) or novel foils (p = .13).

Figure 9

Over/Underconfidence by Stimulus Type



Note. 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).