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**KNOWING WHAT IS NEW: THE EFFECTS OF ITEM-RELATEDNESS  
ON THE NEURAL CORRELATES OF NOVELTY DETECTION**

A Thesis in

Psychology

by

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## ABSTRACT

Accurate memory depends both on the ability to correctly endorse previously encountered information as old and correctly identify novel information as new. Behavioral memory research has shown that similarity between old and new information makes novelty detection more difficult, leading to a greater number of novel items misidentified as old. However, the cognitive and neural processes subserving *successful* novelty detection are not well understood and have yet to be examined in the context of relatedness to old items. The present study used fMRI to investigate the neural basis of novelty detection when items were either related or unrelated to items presented at study. Results showed general novelty regions that included right anterior medial temporal lobe, left middle temporal gyrus, and right early visual cortex, suggesting increased encoding processes for novel items independent of item-relatedness. Related novelty was associated with a vast set of regions including bilateral early and late visual cortex, bilateral ventrolateral prefrontal cortex (VLPFC), and bilateral superior parietal cortex, indicating engagement of visual details, cognitive control, and top-down attention to support successful related novelty detection. Finally, unrelated novelty was associated with regions including bilateral inferior and middle temporal gyrus, right superior temporal gyrus, and bilateral inferior parietal cortex, indicating engagement of semantic and categorical processing and bottom-up attention to support unrelated novelty detection.

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## **Chapter 1**

### **Introduction**

When thinking about what it means to have a good memory, we typically think about correctly retrieving information with which you have previous experience. For example, you might correctly recognize someone you met briefly at a party or recall the date of your anniversary. However, successful memory also depends on correctly identifying new or novel information with which you have no previous experience. In this case, you might be introduced to someone new who asks you, ‘Have we met before?’ – to which you could correctly reply, ‘No, I don’t believe so.’ In order to identify novelty, one must reference previously stored information in memory and determine the degree of overlap between the current item and those stored in memory (M. W. Brown & Bashir, 2002; Kumaran & Maguire, 2007a, 2007b). As such, when new information is distinct from what we have experienced previously it may be relatively easy to dissociate new information from old information. However, when new information closely resembles previous information, it may become much more difficult to identify novelty. The present study sought to elucidate the neural correlates of correctly identifying novel information and examine the role perceptual and semantic relatedness plays in novelty detection.

Previous behavioral research has suggested a key role for perceptual and/or semantic similarity in novelty detection (Deese, 1959) such that correctly identifying novelty becomes more difficult when similar items are presented at study (e.g. Hancock, Hicks, Marsh, & Ritschel, 2003; Seamon, Luo, Shulman, Toner, & Caglar, 2002). For example, in the classic Deese Roediger-McDermott (DRM) paradigm, participants view a list of words (e.g. dream, pillow,

tired) that all converge on a single word (e.g. sleep) that is not presented during study. In tests of both recall (Roediger, Watson, McDermott, & Gallo, 2001; Seamon, Luo, Kopecky, et al., 2002; Seamon, Luo, Shulman, et al., 2002) and recognition (Gallo, Roediger, & McDermott, 2001; Meade, Watson, Balota, & Roediger, 2007), participants are highly likely to remember the associated but unrepresented word (Roediger & McDermott, 1995). Accounts of false memory attribute the effect of relatedness to memory traces that are not able to separate general similarity from more fine-grained semantic or perceptual distinctions between related items. For example, according to Fuzzy Trace Theory, related items share ‘gist’ – abstract categorical and semantic information – which can preempt the use of ‘verbatim’ traces – detailed perceptual and contextual information that distinguishes between closely related but non-identical items (Brainerd & Reyna, 1990). Despite this growing literature on the effect of item-relatedness on novelty detection, the cognitive processes supporting *successful* novelty detection for related items have yet to be determined. That is, how do we identify novelty when it strongly resembles aspects of our past experience as opposed to when it is more distinct?

One way to investigate cognitive processes associated with varying types of novelty detection is through neuroimaging tools such as fMRI. While in behavioral research false memory and novelty detection are usually inverses of one another, neuroimaging allows us to investigate cognitive processes associated with each separately. The proposed study seeks to use information about neural processing obtained through fMRI to better understand novelty detection for related and unrelated items.

### **Novelty detection and the Medial Temporal Lobes**

Two sources of information about novelty processing have come from neuropsychological and neuroimaging studies of episodic memory. Knight (1996) found that

patients who had damage to posterior medial temporal lobe (MTL) regions showed a reduced ERP signal (P3a component) and a reduced sympathetic skin response to novelty. Another patient study found that the hippocampus proper contributes to detecting items that are situationally novel (that is, novel within the context of the experiment) and does so more than MTL regions outside the hippocampus (Grunwald, Lehnertz, Heinze, Helmstaedter, & Elger, 1998). These findings suggest that the MTL – a structure whose importance to long term memory has been well established (e.g. Eichenbaum, Yonelinas, & Ranganath, 2007; Gabrieli, Stebbins, Singh, Willingham, & et al., 1997; Scoville & Milner, 1957; Squire & Zola-Morgan, 1991) – also plays a role in identifying novelty.

Neuroimaging studies have also supported the role of the MTL in novelty detection with both PET and fMRI studies showing the hippocampus to be more active for both novel compared to familiar items (Daselaar, Fleck, & Cabeza, 2006; Henson, Cansino, Herron, Robb, & Rugg, 2003; Kirchoff, Wagner, Maril, & Stern, 2000; Schott et al., 2004) and for novel associations compared to individual novel items (Honey, Watt, & Good, 1998; Kohler, Danckert, Gati, & Menon, 2005). For example, Daselaar et al., (2006) measured novelty responses to individually presented words and found that activity in anterior hippocampus as well as cortical MTL regions increased as items were rated as more subjectively old, while Schott et al. (2004) measured novelty responses for face–tool pairings and their spatial configurations and found greater activity in anterior hippocampus for novel as compared to old items.

This enhanced MTL activity for novel compared to familiar items has been posited to reflect an increase in encoding-related activity (Bogacz, Brown, & Giraud-Carrier, 2001; Kumaran & Maguire, 2007b; Tulving & Kroll, 1995; Tulving, Markowitsch, Kapur, Habib, & Houle, 1994). In particular, novelty-related activations in anterior MTL regions (Daselaar, Fleck, & Cabeza, 2006; Schott et al., 2004) are consistent with a wide array of studies that find anterior MTL regions to be involved in memory encoding (for metaanalysis see Lepage, Habib, & Tulving,

1998; S.E. Prince, Daselaar, & Cabeza, 2005). In fact, when Kirchoff et al., (2000) measured activity within regions that responded to novelty, they found that many of the regions were also associated with successful encoding, including bilateral MTL, bilateral inferior prefrontal cortex, and bilateral anterior fusiform gyrus, suggesting that these regions actively contribute to the encoding process. Previous research has also shown that this anterior MTL region is associated with perceived novelty regardless of whether the item has been previously studied (Daselaar, Fleck, Prince, & Cabeza, 2006), which suggests that enhanced novelty-encoding is greatest when novelty is consciously experienced.

One theory suggests that MTL novelty detection operates via a familiarity signal in which an item is assessed for global similarity to items stored in memory (M. W. Brown & Bashir, 2002; Norman & O'Reilly, 2003). That is, newly presented items that are more similar to items stored in memory have a greater familiarity signal and are more likely to be endorsed as old. Conversely, items that are more dissimilar to items in memory have a weaker familiarity signal and will be more likely perceived as novel. Another theory posits a role for recollection processes in novelty detection such that specific recalled details of an encoding episode can be compared to the current item and assessed for match or mismatch (Kumaran & Maguire, 2007b). Previous behavioral research suggests that related novel items are associated with a greater sense of familiarity (Brainerd & Reyna, 2002; N. R. Brown, Buchanan, & Cabeza, 2000; Roediger & McDermott, 1995) compared to unrelated novel items. Despite this behavioral finding, to our knowledge, no study has used information about item-relatedness to determine the extent to which familiarity and recollection contribute to novelty detection in the MTL.

Based on previous findings that the MTL shows enhanced activity for successful novelty detection, we predict that the MTL will show greater responses to items correctly identified as novel compared to items incorrectly identified as old, for both related and unrelated items. In addition, we expect that unrelated items, which are typically more easily identified as novel, will

show increased anterior MTL activity when compared directly to related items, given the greater level of familiarity associated with related items.

### **Perceptual processing in related novelty detection**

Previous research shows that reactivation of previously encoded sensory information is a key factor in determining retrieval success, particularly activity in primary sensory regions (Cabeza, Rao, Wagner, Mayer, & Schacter, 2001; Dennis, Bowman, & Vandekar, 2012; Okado & Stark, 2003; Slotnick & Schacter, 2004; Stark, Okado, & Loftus, 2010). For example, Slotnick and Schacter (2004) found that early visual cortex showed greater activity for true recognition compared to false recognition of related items; however, late visual cortex did not differentiate between true and false recognition. Activation in early visual cortex during retrieval has also been associated with true recollection more so than false recollection (Dennis et al., 2012), which suggests that early visual activity reflects reactivation of veridical details associated with true memories that can distinguish between related items (Vaidya, Zhao, Desmond, & Gabrieli, 2002; Wheeler, Petersen, & Buckner, 2000). However, this reactivation signal has thus far only been shown to distinguish between correct and incorrect memory responses, either by comparing true and false memories (e.g. Slotnick & Schacter, 2004) or hits and misses (e.g. S. E. Prince, Dennis, & Cabeza, 2009). However, the extent to which sensory reactivation may support correct memory responses based on differences in the items context has not yet been explored. Specifically, sensory reactivation may also support novelty detection by allowing for comparison between specific features of new and old items, particularly when items are related.

Greater activation in visual cortex has also been associated with successful encoding of visually presented stimuli (e.g. Otten, Henson, & Rugg, 2001; Summerfield et al., 2006). Given that brain areas subserving novelty detection are also those that subserve encoding processes, it is

likely that increases in visual activity correspond both to reactivation of competing perceptual details to support retrieval success (Dennis et al., 2012; Slotnick & Schacter, 2004), and also increased attention to perceptual details to promote further encoding of these details (Buckner, Wheeler, & Sheridan, 2001; Kirchoff et al., 2000; Summerfield et al., 2006). Specifically, visual cortex has been shown to be more active at encoding for items that are subsequently remembered in a recognition test compared to items that are subsequently forgotten, particularly when rich images are used as stimuli (e.g. Gutchess et al., 2005).

In addition, studies examining subsequent memory for novel items presented during a retrieval task (i.e. studies that include a second memory test for the lures presented in an initial recognition task) have suggested that retrieval itself can function as a deep encoding task. Studies have found that behavioral performance on the second recognition test is very similar to both intentional and deep encoding tasks and greater than shallow encoding tasks (Buckner et al., 2001; Kirchoff et al., 2000). Buckner et al. (2001) also found that activity in the left fusiform gyrus showed greater activation for subsequently remembered items than subsequently forgotten during this recognition-encoding task. Therefore, increased activity in visual cortex is an important indicator of both encoding and retrieval success.

If related items are more perceptually similar and therefore require greater emphasis on specific perceptual details, we predict that, in the case of perceptually and semantically related novel items, increasing attention to perceptual details will contribute to successful novelty detection. Increased perceptual similarity between related items will require more detailed inspection and reactivation of specific details from old items to support successful novelty detection and be reflected in greater activity in early visual cortex.

### **Cognitive control in related novelty detection**

In addition to bottom-up sensory processes, top-down control processes have been shown to play an important role in episodic memory. Evidence suggests that the prefrontal cortex (PFC) is important for monitoring and regulating memory traces during both encoding and retrieval (Fuster, 2001; Murray & Ranganath, 2007). Considerable evidence from fMRI, PET, patient and electrophysiological studies suggests that the PFC, particularly the right PFC, is involved in memory retrieval (Henson, Shallice, & Dolan, 1999; Lepage, Ghaffar, Nyberg, & Tulving, 2000; Rugg, Fletcher, Frith, Frackowiak, & Dolan, 1996; Tomita, Ohbayashi, Nakahara, Hasegawa, & Miyashita, 1999). Some researchers have suggested that this region may be responsible for inducing a 'retrieval mode' [i.e. "processes related to thinking back in subjective time" (Nyberg et al., 1995, p. 249)] (Lepage et al., 2000; Nyberg et al., 1995) to support episodic memory. Other accounts have posited that this consistent right PFC activity indicates top-down control (Miller & Cohen, 2001; Tomita et al., 1999) or monitoring processes (Henson et al., 1999; Rugg et al., 1996) that serve to evaluate and regulate the products of other cognitive processes and overt behaviors (Ridderinkhof, van den Wildenberg, Segalowitz, & Carter, 2004). For example, Gehring and Knight (2000) found that patients with lateral prefrontal damage were able to monitor their performance (supported by intact anterior cingulate function) but could not correct their errors and regulate their behavior. This suggests that while more medial PFC regions may be responsible for monitoring the results of memory processes, lateral PFC regions are responsible for executing cognitive control (Cohen, Botvinick, & Carter, 2000; Gehring & Knight, 2000; MacDonald, Cohen, Stenger, & Carter, 2000). When the demands of the task are higher (Barch et al., 1997) or there is greater conflict between response options (Botvinick, Braver, Barch, Carter, & Cohen, 2001), right PFC is recruited to support additional cognitive control in order to increase performance on the task.

As such, related novel items may present a greater task demand as well as greater competition between response options compared to unrelated items. Given greater similarity in the sensory signal associated with related novel and old items, increased monitoring and cognitive control processes may be necessary to lead to successful novelty detection for these items, resulting in greater PFC activity in both medial and lateral regions.

Specifically regarding the role of item-relatedness in the PFC, research has shown that right anterior PFC shows greater activity for strongly related semantic associates compared to weakly related semantic associates during retrieval (Fletcher, Shallice, Frith, Frackowiak, & Dolan, 1996), which provides evidence that this region is sensitive to similarities between items and that negotiating these similarities engages control processes. Other neuroimaging studies have confirmed a role of the PFC in negotiating memory tasks with high levels of semantic or perceptual interference between items during both encoding and retrieval (Dolan & Fletcher, 1997; Fletcher, Shallice, & Dolan, 2000; Henson, Shallice, Josephs, & Dolan, 2002; Lepage, Blondin, Achim, Menear, & Brodeur, 2005; Uhl, Podreka, & Deecke, 1994). For example Fletcher et al. (1996) used retrieval of paired associates that varied in degree of semantic relatedness (e.g. King – Queen or Puppy – Hurricane) and found decreasing right anterior PFC activity with decreasing semantic relatedness. Consistent with Botvinick et al.'s (2001) theory that increased competition leads to the deployment of cognitive control, this work suggests that greater semantic and perceptual interference leads to activation in regions associated with top-down control processes.

### **Semantic and categorical processing in unrelated novelty detection**

While related items vary mostly in terms of specific perceptual or detailed semantic information, unrelated items also vary in terms of general categorical information. Previous

research suggests that regions in the lateral temporal lobes support decisions based on general categorical information (Martin & Chao, 2001; Simons et al., 2005) with inferior regions representing visual recognition of object form (Gonsalves & Paller, 2000; Lueschow, Miller, & Desimone, 1994; Slotnick & Schacter, 2004) and middle and superior regions representing abstract semantic information (Friederici, Ruschemeyer, Hahne, & Fiebach, 2003; Vandenberghe, Price, Wise, Josephs, & Frackowiak, 1996). Patient work has also shown that damage to these regions can produce impairments to semantic memory that do not necessarily affect new learning (Levy, Bayley, & Squire, 2004), which suggests that these regions are crucial to forming abstract, time invariant representations of conceptual information.

Previous researchers have also suggested that superior and inferior lateral temporal regions support semantic (Dennis, Kim, & Cabeza, 2007; Simons, Koutstaal, Prince, Wagner, & Schacter, 2003) and perceptual (Garoff, Slotnick, & Schacter, 2005; Gutchess & Schacter, 2012; Slotnick & Schacter, 2004) gist processes, respectively. For related items, these regions show increased activity for false memories, indicating that they support memory decisions based on general item familiarity and not item-specific details. These regions have also been associated with language processing (for reviews see Price, 2000, 2010) and may support memories (including false memories) based on verbal tags. For example, Garoff-Eaton, Slotnick and Schacter (2006) reported that many subjects remembered novel geometric shapes by associating them with a verbal label such as 'bird' or 'flower'. This research suggests that semantic or categorical information may support memory decisions when items are unrelated.

Previous studies have explored the role of categorical or gist information in producing false memories but have not considered the functional role of gist in successful novelty detection. In the present study, we predicted that successful novelty detection for unrelated items would be supported by semantic and perceptual gist processes. That is, given relatively little overlap between unrelated novel and old items, gist information is sufficient to correctly identify

unrelated novelty. We therefore predicted that unrelated novelty detection will elicit increased activity in lateral temporal regions.

### **Attentional processes in related and unrelated novelty detection**

Another key brain region involved in retrieval processes and novelty detection is the parietal cortex. Evidence from patient and neuroimaging studies of episodic memory have suggested that the parietal cortex crucially, but subtly, contributes to retrieval processes in memory (Berryhill, Phuong, Picasso, Cabeza, & Olson, 2007; Cabeza, 2008; Wagner, Shannon, Kahn, & Buckner, 2005). In particular, there seems to be a functional dissociation between superior and inferior regions of posterior parietal cortex supporting distinct forms of attentional control in memory.

The Attention to Memory (AtoM) theory posits that these two parietal regions are differentially employed to guide attention during episodic retrieval (for reviews see Cabeza, 2008; Cabeza, Ciaramelli, Olson, & Moscovitch, 2008). According to this account, activity in superior parietal cortex reflects top-down search processes, working to retrieve details and access memorial information when that information does not come immediately to mind. This interpretation is consistent with evidence from attention literature suggesting that superior parietal regions maintain attention during a search task while more inferior regions are involved in target detection (Corbetta, Kincade, Ollinger, McAvoy, & Shulman, 2000). For example, in memory superior parietal activity has been associated with familiarity more than recollection as well as low confidence responses more than high confidence responses (Kim & Cabeza, 2007; Moritz, Glascher, Sommer, Buchel, & Braus, 2006). Such evidence suggests a role for superior parietal cortex in finding confirmatory evidence for a feeling of oldness when a bottom-up sensory reactivation signal is not immediately available.

The other side of this parietal dissociation is the inferior parietal cortex, which the AtoM theory posits captures memorial attention in a bottom-up fashion. That is, information from episodic memory ‘springs’ into consciousness without need for effortful retrieval. Evidence in support of this interpretation of inferior parietal activity comes from studies showing activity in this region for memory responses of the highest confidence, regardless of whether the item is old or new (i.e. ‘definitely new’ responses as well as ‘definitely old’ responses) (Daselaar, Fleck, & Cabeza, 2006; Yonelinas, Otten, Shaw, & Rugg, 2005). In this case, inferior parietal cortex works to reallocate attention based on relevant retrieved details (Cabeza et al., 2008).

Although previous studies have examined the role of parietal cortex in attention and episodic memory, we would like to extend this theoretical model to take into account the relatedness of novel items. Given the increased demand for retrieval of specific perceptual information for related items, we expected greater engagement of the superior parietal cortex for related compared to unrelated novelty detection. Because more detailed comparison to old items is necessary to identify related novelty, we expected that a greater top-down search process would be initiated for these trials. However, we predicted that unrelated novelty would show increased engagement of the inferior parietal cortex. We hypothesized that categorical information associated with unrelated novelty would capture memorial attention in a bottom-up fashion to prevent further retrieval processing that would require unnecessary effort. Together, the difference in inferior and superior parietal cortex activity would reflect a difference in the cognitive control processes necessary for successful memory responses when novel items are related.

### **The present study**

Overall, the present study sought to elucidate the cognitive and neural mechanisms involved in correctly identifying novelty in the context of item relatedness. To do so, we:

(1) Examined neural activity that was common to both related and unrelated novelty detection to determine regions associated with general novelty detection. We expected that both related and unrelated novelty would show common activity in regions supporting encoding success consistent with previous associations between encoding and novelty detection (Kirchhoff et al., 2000).

(2) Directly compared novelty detection for related and unrelated items to assess the neural correlates supporting successful novelty detection for items that vary in their associations with previously presented information. We expected to find that related novelty detection is characterized by increased visual activity associated with attention to perceptual detail, greater prefrontal activity associated with increased monitoring and cognitive control, and greater superior parietal activity associated with top-down attention in episodic memory. We expected that unrelated novelty detection would be characterized by activity in lateral temporal regions associated with perceptual and semantic gist as well as greater engagement of inferior parietal cortex associated with bottom-up attention in episodic memory. For predicted BOLD contrast results, see Figure 1-1.

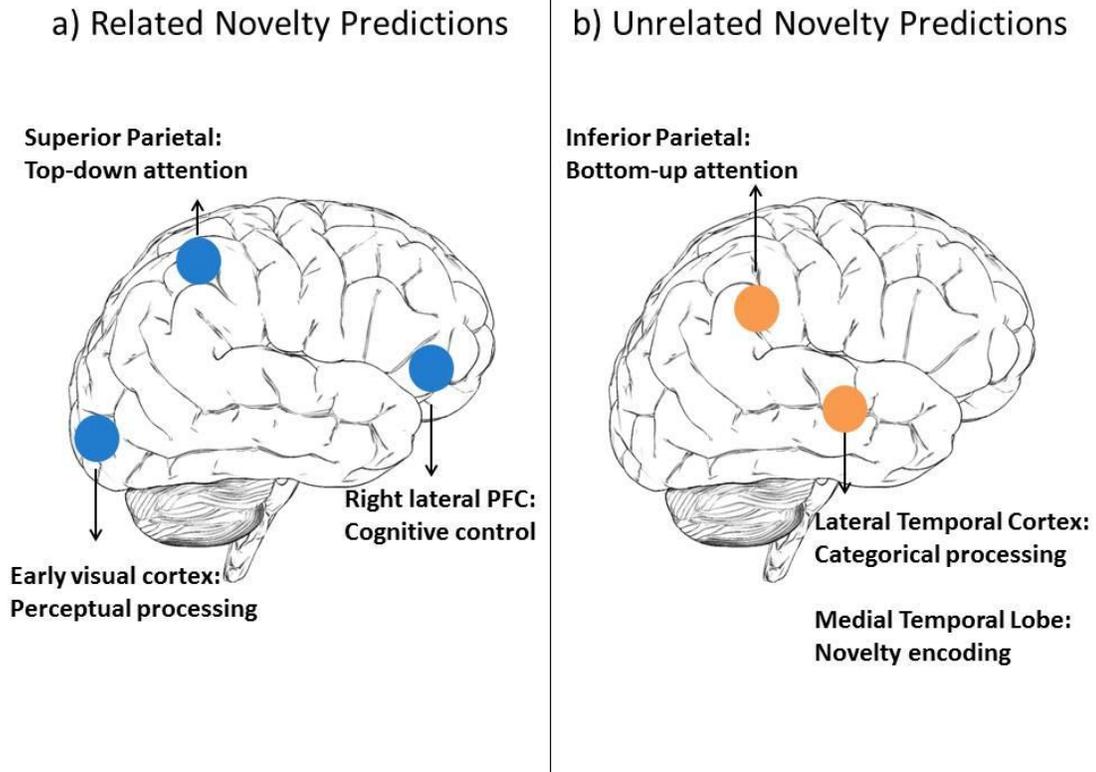


Figure 1-1. Predicted results for BOLD contrasts.

Schematic representation of predicted brain regions for (a) related novelty BOLD contrasts and (b) unrelated novelty BOLD contrasts.

## **Chapter 2**

### **Method**

#### **Participants**

Twenty right-handed native English speakers were recruited from the Penn State University community. Participants were screened for history of neurological disorders and psychiatric illness, alcoholism, drug abuse, and learning disabilities. Two participants were excluded from the analysis due to head motion in excess of 4 mm and one was excluded for performing below chance, leaving data from 17 participant reported in all analyses [11 females; mean age = 21.28 yrs (SD=1.79)]. All participants provided written informed consent and received financial compensation for their participation. All experimental procedures were approved by Penn State University's Institutional Review Board for the ethical treatment of human participants.

#### **Stimuli**

Stimuli consisted of 1092 color pictures of common objects. Images were obtained from an internet image search. All backgrounds were removed and pictures were cropped and resized to an approximate size of 480 x 480 pixels. Images were presented focally and equated for resolution. Seven hundred and twenty images were presented during encoding, including 90 categories of stimuli with 8 exemplars per category (see Figure 1 for example stimuli). Six hundred and forty two images were presented at retrieval including (a) 270 targets (3 of the 8 exemplars from each category) (b) 270 related lures (3 novel images associated with each encoding category) and (c) 102 unrelated lures (including 3 novel images from each of 34

unrelated categories). For examples, see Figure 2-1. Items selected as targets were counterbalanced between participants.

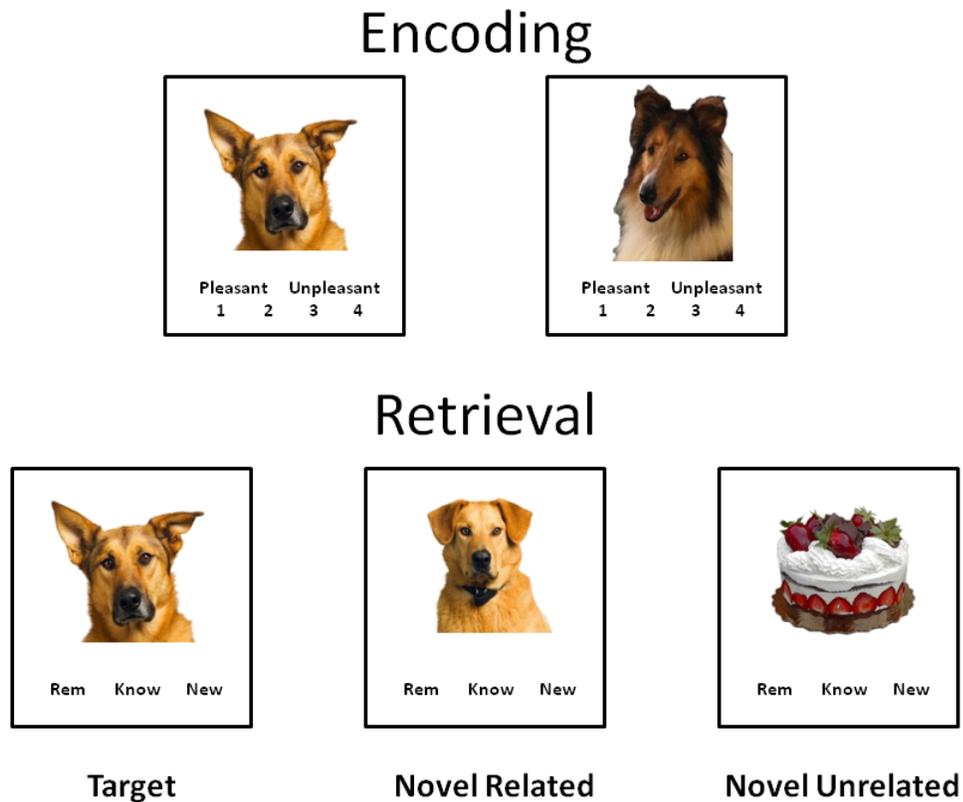


Figure 2-1. Stimuli presentation.

During encoding, participants were presented with exemplars of a category (e.g. dogs) and asked to make pleasantness ratings for each exemplar. At retrieval, participants were presented with items and asked to make memory judgments in the Remember-Know-New paradigm. Items included targets, novel related items, and novel unrelated items.

## Procedure

Encoding and retrieval both took place in the scanner with approximately 24 hours separating the two memory phases. Encoding was incidental and participants were instructed to make subjective pleasantness ratings of objects as they were presented. Encoding images were presented for 1 second and participants were given 2 seconds to make their pleasantness rating, followed by a variable interstimulus interval.

Images were projected onto a screen that participants viewed through a mirror attached to the head coil. All images were presented in the center of the screen with response options (i.e., Remember/Know/New) displayed below each image. Behavioral responses were recorded using a 4 button response box. Images were displayed by COGENT in MATLAB (Mathworks). Scanner noise was reduced with headphones and earplugs, and cushioning was used in the head coil to minimize head motion.

During retrieval, participants completed 6 runs each approximately 8 minutes in length. Each image was displayed for 2.5 seconds while participants made memory responses using the 'Remember-Know-New' paradigm. In accord with typical task instructions, participants were told to respond 'Remember' if they could recollect specific details about the object such as its shape, color, or their thoughts or feelings during its initial presentation. Participants were told to respond 'Know' if the picture looked familiar, but they could not recollect any specific details of its prior presentation. They were told to respond 'New' if they believed the picture was not presented during the encoding session. The images were pseudorandomly sorted, ensuring that no more than 3 images from any one category appeared in a row.

## Image Acquisition

Images were acquired using a Siemens 3T scanner equipped with a 12-channel head coil. A T1-weighted sagittal localizer was acquired to locate the anterior (AC) and posterior (PC) commissures. Images were then prescribed parallel to the AC-PC plane. An MPRAGE was acquired with a 2300 ms TR, 3.41 ms TE, 230 mm field of view (FOV),  $256^2$  matrix, 160 axial slices, and 0.9 mm slice thickness for using an interleaved acquisition, 2000 ms TR, 30 ms TE, 240 mm FOV, a  $64^2$  matrix, 34 axial slices with 3.8 mm slice thickness resulting in 3.8 mm isotropic voxels.

Functional data was preprocessed and analyzed with SPM8 (Statistical Parametric Mapping; Wellcome Department of Cognitive Neurology, <http://www.fil.ion.ucl.ac.uk/spm>). Time-series data were corrected for differences in slice acquisition times and realigned. Images were checked for movement artifacts using a time series diagnostic function TSDiffAna (Freiburg Brain Imaging) in MATLAB (Mathworks). Functional images were spatially normalized to a standard stereotaxic space using the Montreal Neurological Institute (MNI) templates implemented in SPM8 and resliced to a resolution of  $3.8 \text{ mm}^3$ . Finally, the volumes were spatially smoothed using an 8-mm isotropic Gaussian kernel.

## fMRI analyses

Trial-related activity was modeled in the General Linear Model (GLM) with a stick function corresponding to trial onsets convolved with a canonical hemodynamic response function (hrf). Statistical Parametric Maps (SPMs) were identified for each participant by applying linear contrasts to the beta weights for the events of interest. Regressors associated with 'remember' and 'new' responses to related and unrelated lures were used in defining contrasts of

interest (see below). Regressors for ‘no response’ trials as well as those for motion parameters were included in the model and treated as regressors of no interest. All individual SPMs were subjected to a random effects analysis for group analysis.

In order to obtain results that are corrected for multiple comparisons, we used Monte Carlo simulations (<http://www2.bc.edu/slotnics/scripts.htm>) to define individual voxel and cluster extent thresholds (e.g. Forman et al., 1995; Garoff-Eaton, Kensinger, & Schacter, 2007; Slotnick & Schacter, 2004). In this study, an individual voxel threshold of  $p < 0.005$  was used in combination with a cluster extent threshold of 13 resampled voxels ( $713 \text{ mm}^3$ ), which yields results corrected for multiple comparisons at  $p < 0.05$ . In addition, we used the aal pickatlas (Maldjian, Laurienti, Burdette, & Kraft, 2003; Tzourio-Mazoyer et al., 2002) to restrict all analyses to cortical and subcortical regions.

In order to identify neural correlates associated with successful novelty detection of related items, we compared activity associated with ‘New’ responses to related lures (related correct rejection or ‘RCR’) to activity associated with ‘Remember’ responses to related lures (related false alarm or ‘RFA’). A similar comparison was made to compare ‘New’ responses to unrelated lures (unrelated correct rejection or ‘UCR’) to ‘Remember’ responses to related lures (i.e. RFA). These contrasts allowed us to control for the true novelty of an item while isolating regions that support novelty detection for both related and unrelated items. We also performed a direct comparison between ‘New’ responses to related and unrelated items in order to determine the unique neural correlates of each.

## Chapter 3

### Results

#### Behavioral

Participants 'New' (Novelty) and 'Remember' (Recollection) response rates for target, related novel, and unrelated novel items are presented in Table 3-1. Participant more often identified related novel items as novel compared to target items [ $t(16) = 10.20, p < 0.001$ ]. Participants also more often identified unrelated novel items as novel compared to target items [ $t(16) = 17.08, p < 0.001$ ]. This suggests that participants were successful in labeling novelty for both related and unrelated items. Participants were also more likely to correctly identify unrelated novel items as novel compared to related novel items [ $t(16) = 13.73, p < 0.001$ ]. This suggests that novelty detection for unrelated items was much less demanding task than related novelty detection. With regard to reaction times, participants were significantly faster in responding 'new' to unrelated novel items than both responding 'new' to related novel items [ $t(16) = 8.41, p < 0.001$ ] and 'old' to related novel items [ $t(16) = 5.08, p < 0.001$ ]. However, participants were faster in responding 'old' to related novel items than 'new' to related novel items [ $t(16) = 2.15, p < 0.05$ ].

Table 3-1. Behavioral accuracy and reaction times for 'Remember' and 'New' responses.

	Targets	Related Novel	Unrelated Novel
<i>Accuracy</i>			
New	0.19(0.03)	0.49(0.03)	0.99(< 0.001)
Remember	0.47(0.02)	0.19(0.03)	0.04(0.01)
<i>Reaction Times (ms)</i>			
New	1523(40)	1462(26)	1176(37)
Remember	1323(37)	1383(38)	1502(76)

## Imaging

Table 3-2 presents activity associated with successful related and unrelated novelty detection (i.e. RCR > RFA and UCR > RFA) individually as well as activity common to related and unrelated novelty success (i.e. a general novelty). Related novelty success was associated with activity in bilateral medial temporal regions including anterior hippocampus and anterior parahippocampal gyrus. Related novelty success was also characterized by activity in early and late visual regions including cuneus (BA17/18) and fusiform gyrus (BA 19) as well frontal activity in bilateral superior frontal gyrus (BA 6) and cingulate gyrus (BA 24). Unrelated novelty success was associated with activity in bilateral medial temporal regions including anterior hippocampus and anterior parahippocampal gyrus. Unrelated novelty success was also associated with activity in early and late visual regions including right lingual gyrus (BA17) and cuneus (BA 19) as well as right inferior parietal (BA 40), bilateral superior and middle temporal gyrus (BA 22/21), and anterior cingulate (BA 32). Activity in the right anterior hippocampus and parahippocampal gyrus (BA 36), left middle temporal gyrus (BA 21), and right early visual cortex (BA 17/18) was common to both related and unrelated novelty success (see Figure 4-1).

Table 3-2. Brain regions associated with related and unrelated novelty detection and general novelty detection.

Entries in italics are sub-peaks of a larger cluster.

	BA	H	Coordinates (T&T)			t	mm <sup>3</sup>
			x	y	z		
<i>Related novelty &gt; False recollection</i>							
Superior Frontal Gyrus (Premotor)	6	L	-19	11	44	3.94	1482
	6	R	22	7	43	4.35	713
Mid Cingulate	24	M	-7	0	34	3.20	1482
Insula	-	L	-37	6	13	3.72	1152
Middle Temporal Gyrus	21	L	-48	-6	-10	3.85	933
MTL							
<i>Parahippocampal Gyrus</i>	38/28	R	26	-14	-19	4.39	823
	28/34	L	-22	-10	-19	3.70	384
<i>Hippocampus</i>	-	R	30	-14	-19	4.19	658
	-	L	-22	-10	-19	3.92	604
Post Central Gyrus	3/2/1	L	-19	-39	74	4.17	1372
Fusiform/Inferior/Middle Occipital Gyrus	17/18/19	R	22	-79	0	5.01	16736
Cuneus	18/19	M	-7	-81	28	4.26	1482
<i>Unrelated novelty &gt; False recollection</i>							
Anterior Cingulate	32	M	7	45	-9	3.26	1866
Medial Orbitofrontal	11	M	0	26	-21	3.66	1427
Superior/Middle Temporal Gyrus	22/21	R	59	-3	-19	4.87	6146
	22/21	L	-48	-14	-16	5.17	5981
MTL							
<i>Parahippocampal Gyrus</i>	28/35/38	R	26	-14	-19	4.65	1372
	28	L	-19	-11	-22	4.56	713
<i>Hippocampus</i>	-	R	30	-14	-19	6.83	988
	-	L	-22	-11	-22	4.28	439
Inferior Parietal	40	R	48	-51	36	4.19	2524
Lingual Gyrus	17	R	11	-86	4	4.00	3018
Cuneus	19	L	-11	-88	24	5.43	1152
<i>General novelty network</i>							
Hippocampus/Parahippocampal Gyrus	- /36	R	30	-14	-19	6.83	1262
Middle Temporal Gyrus	21	L	-52	-10	-16	4.71	823
Lingual Gyrus	17/18	R	11	-86	4	4.00	2963

Table 3-3 presents brain regions engaged to a greater degree for related compared to unrelated novelty detection (i.e. RCR > UCR). Related novelty detection was associated with activity in early (BA 17/18) and late (BA19/37) visual cortex, frontal regions including superior (BA 6), middle (BA 6), inferior (BA47/45), and cingulate (BA 32) gyrus, as well as left inferior parietal (BA 40) and bilateral superior parietal (BA 7) cortex (see Figure 4-2).

Table 3-3. Brain regions preferentially active for related compared to unrelated novelty detection.

Entries in italics are sub-peaks of a larger cluster.

	BA	H	Coordinates (T&T)			t	mm <sup>3</sup>
			x	y	z		
<i>Inferior Frontal Gyrus (VLPFC)</i>	47/45	L	-30	24	5	6.64	7353
	<b>47/45</b>	<b>R</b>	<b>30</b>	<b>23</b>	<b>-5</b>	<b>7.09</b>	<b>11304</b>
	44/45	R	56	6	20	4.42	4939
<i>Middle Frontal Gyrus</i>	6	L	-30	0	48	3.97	1207
<i>Superior Frontal Gyrus</i>	6	L	-22	-7	58	3.54	1262
<i>Superior Frontal/Cingulate Gyrus</i>	6/32	M	-7	11	51	5.63	11853
<i>Caudate</i>	-	R	19	16	9	4.28	1646
<i>Putamen</i>	-	L	-19	2	10	4.54	2305
<i>Thalamus</i>	-	R	19	-13	7	5.43	3732
	-	L	-11	-20	4	6.11	6201
<i>Precentral Gyrus</i>	4	L	-52	10	26	5.58	7737
<i>Postcentral Gyrus</i>	1/2	L	-45	-33	49	7.81	5103
<i>Inferior Parietal</i>	40	L	-45	-33	46	8.66	8176
<i>Superior Parietal</i>	7	L	-30	-44	46	7.41	6366
	7	R	26	-54	47	5.15	7518
<i>Precuneus</i>	7	L	-15	-66	-56	5.20	1701
<i>Occipitoparietal</i>	19/40	R	26	-58	44	5.00	988
<i>Occipitotemporal</i>	37	R	41	-54	-7	6.63	6146
	37	L	-48	-64	-4	5.18	2305
<i>Fusiform Gyrus</i>	37	L	-37	-43	-21	4.91	3402
	37	R	37	-54	-7	6.42	5488
<i>Inferior Occipital Gyrus</i>	19/18	R	37	-61	-4	5.93	4939
	19/37	L	-48	-71	0	6.65	6366
<i>Cuneus</i>	17/18	R	15	-63	16	6.10	5268
	17/18	L	-15	-71	17	5.13	1811
<i>Middle Occipital Gyrus</i>	19/18	R	41	-82	10	6.90	15914
	19/18	L	-41	-89	4	7.70	10865
<i>Cerebellum</i>	-	L	-33	-43	-24	6.52	8122
	-	R	26	-43	-24	7.32	14871

Table 3-4 presents brain regions that are engaged to a greater degree for unrelated compared to related novelty detection (i.e.  $UCR > RCR$ ). Unrelated novelty detection was associated with activity in anterior cingulate (BA 24/32), bilateral inferior (BA 20/37) and middle (BA 21) temporal gyrus, and bilateral inferior parietal cortex (BA 40, 39) (see Figure 4-3).

Table 3-4. Brain regions preferentially active for unrelated compared to related novelty detection.

	BA	H	Coordinates (T&T)			t	mm <sup>3</sup>
			x	y	z		
Anterior Cingulate	24/32	M	-4	37	-8	5.07	13444
Inferior/Middle Temporal Gyrus	20/21	R	56	-13	-31	6.22	4719
	21	R	56	-34	-8	3.73	1646
	20/37	L	-41	-37	-11	5.05	9328
Superior Temporal Gyrus	22	R	68	-51	13	6.08	9054
Inferior Parietal	40	R	56	-54	47	4.95	2744
	39	L	-56	-65	31	4.69	5871
Cerebellum	-	R	19	-34	-17	3.44	713

## **Chapter 4**

### **Discussion**

The present study sought to elucidate the neural correlates of novelty detection for items that were either related or unrelated to items presented at study. Results showed that although a small set of regions were commonly activated for related and unrelated novelty (including right anterior MTL, left medial temporal gyrus, and right early visual cortex), many more regions showed differential activity for related or unrelated novelty detection. Compared to unrelated novelty detection, related novelty detection was supported by engagement of regions including bilateral VLPFC (BA 47/45), right superior parietal cortex, bilateral fusiform gyrus, bilateral early visual cortex, right occipitoparietal cortex. Finally, compared to related novelty detection, unrelated novelty detection was supported by engagement of regions including the anterior cingulate, bilateral inferior and middle temporal gyrus, right superior temporal gyrus, and bilateral inferior parietal cortex. Each of these findings will be discussed in turn.

#### **General novelty detection**

Common activity for related and unrelated novelty detection revealed a set of brain regions that overlaps greatly with regions associated with episodic memory and semantic and visual processing, including right anterior hippocampus, left middle temporal gyrus, and right early visual cortex. This set of regions distinguished between novel items correctly perceived as new and novel items incorrectly perceived as old, but did not differ based on whether the novel item was related or unrelated to items presented at study. As such, these regions contribute to successful novelty detection independent of the novel item's context.

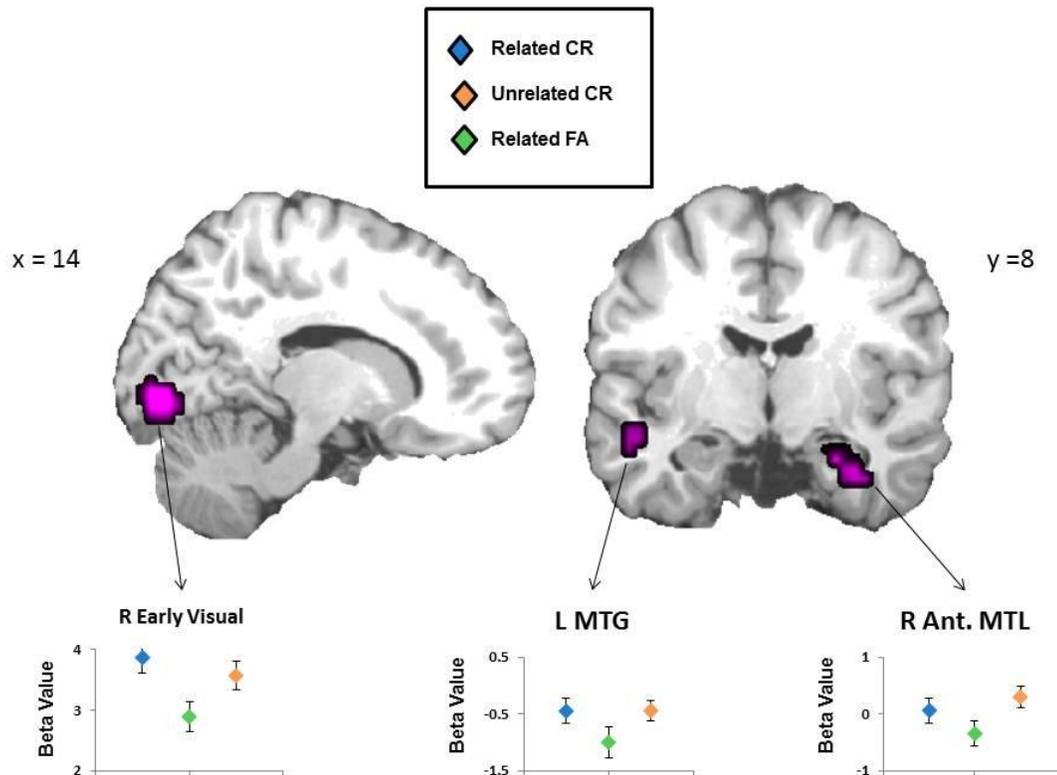


Figure 4-1. Regions associated with novelty regardless of relatedness.

Brain regions exhibiting common activity for related novelty detection and unrelated novelty detection. Graphs represent parameter estimates for related correct rejections, unrelated correct rejections, and ‘remember’ false alarms for the peak voxel within each region. See Table 3-1 for coordinates of peak voxels. R = right, L = left, Ant. MTL = anterior medial temporal lobe, MTG = middle temporal gyrus, CR = correct rejection, FA = false alarm.

Consistent with previous studies of novelty detection, the present results show greater activity in anterior MTL, specifically the perirhinal cortex, for items that were perceived as novel compared to items perceived as old. With regard to novelty detection, activity in this region has been hypothesized to represent encoding-related activity (Bogacz et al., 2001; Kumaran &

Maguire, 2007b; Tulving & Kroll, 1995; Tulving et al., 1994). That is, even in the context of a retrieval task, encoding processes are automatically engaged in order to remember information presented during the episode. In more ecological contexts, episodes are not separated into discrete ‘study’ and ‘test’ phases and thus encoding and retrieval processes occur simultaneously and continuously. Novelty encoding theory suggests that encoding is engaged most strongly for novel items because they have not been previously stored in memory (Tulving et al., 1994). The present results expand upon this theory by showing that this novelty encoding is engaged regardless of the relatedness of the items to items presented during the study phase with no significant differences in the magnitude of the response.

Both related and unrelated novel items showed bilateral MTL activity when compared to subjectively old items, but only one region in the right anterior hippocampus and parahippocampal gyrus showed common activity for both in a conjunction analysis. This common right MTL activity may reflect a similar engagement of visuospatial information for related and unrelated novelty (Golby et al., 2001; Kelley et al., 1998). Overlap in activity in right MTL is consistent with the strong visuospatial nature of the stimuli in the present task.

Theories of novelty detection have predicted that related and unrelated novelty detection would elicit different levels of MTL activity based either on differences in familiarity signals (M. W. Brown & Bashir, 2002; Norman & O'Reilly, 2003) or differences in recollection and mismatch processes (Kumaran et al., 2007; Kumaran & Maguire, 2007a). However, our data showed no differences in MTL activity between related and unrelated novelty detection. Instead, our data suggest that activity in the anterior MTL is driven by the subjective perception of novelty, regardless of item-relatedness or levels of familiarity. That is, anterior MTL activity is driven by conscious percept and not the processing associated with assembling that percept. Such an interpretation is supported by work by previous work showing anterior MTL activity for both old and new items identified as novel (i.e. misses and correct rejections) (Danckert, Gati, Menon,

& Kohler, 2007; Daselaar, Fleck, Prince, et al., 2006) and suggests a role of anterior MTL regions in the conscious perception of novelty. Our findings suggest that activity in anterior MTL activity more strongly reflects encoding processes engaged as the result of the memory decision, not the evidence leading to the memory decision per se. However, further evidence is needed to test this hypothesis including testing of subsequent memory responses to novel items at retrieval.

In addition to common activity in the MTL, right early visual cortex and left middle temporal gyrus – regions supporting perceptual and semantic processing – were also engaged for general novelty detection. Regarding perceptual processing in early visual cortex, it is likely that novel items were correctly identified as new when mismatch was detected between the novel item and items presented at encoding. Therefore, activity in early visual cortex may reflect the reactivation of visual details from the encoding episode for comparison to and evaluation of novel items (Dennis et al., 2012; Slotnick & Schacter, 2004; Stark et al., 2010) or encoding of relevant visual details. Regarding processing in left middle temporal gyrus, previous research has shown that semantic and perceptual representations in lateral temporal regions become increasingly complex as the locus of activation moves from posterior regions to more anterior regions, reflecting greater multimodal integration and subordinate levels of categorization (Bussey & Saksida, 2007; Leveroni et al., 2000; Martin & Chao, 2001; Sergent, Ohta, & Macdonald, 1992). Our results demonstrate that to the extent that related and unrelated novelty detection show semantic overlap, it is in relatively more complex levels of semantic processing compared to regions showing greater engagement for unrelated novelty. One can imagine that individuals use semantic information at relatively higher levels of categorization to make novelty decisions for related items (e.g. ‘collie’ in place of ‘dog’), which in many cases would be a successful retrieval strategy. For unrelated items, although categorization at such a level may not be strictly necessary for distinguishing between novel and old items, some items may be automatically recognized and categorized at such a level (e.g. Johnson & Mervis, 1997). As such, both

perceptual and semantic processing may represent retrieval of relevant information from the encoding phase in order to make a successful memory decision.

However, it is unclear whether common perceptual and semantic signals represent retrieval-related activity, encoding-related activity, or some combination of both. While it is plausible that retrieval of perceptual and semantic details aid successful novelty detection, it is also plausible that such details are encoded as part of a novelty encoding network. In this case, perceptual and semantic information would be encoded to a greater extent for items perceived as novel compared to those perceived as old, consistent with theories of novelty encoding in the MTL. To determine the extent to which novelty encoding processes are involved during retrieval of related and unrelated items, a second retrieval task would be necessary to measure subsequent memory responses for novel items presented during the first retrieval. While others have conducted such analyses (Buckner et al., 2001; Huijbers, Pennartz, Cabeza, & Daselaar, 2009; Kirchoff et al., 2000; Stark & Okado, 2003), none has included a manipulation of item-relatedness. To disentangle encoding and retrieval processes during retrieval tasks, future studies should examine novelty encoding effects as a function of item-relatedness.

### **Related novelty detection**

In addition to determining regions associated with general novelty detection, we were also interested in finding regions that distinguished related from unrelated novelty detection. Results show that regions of bilateral early and late visual cortex, bilateral prefrontal cortex, and superior parietal are engaged for related novelty as compared to unrelated novelty detection.

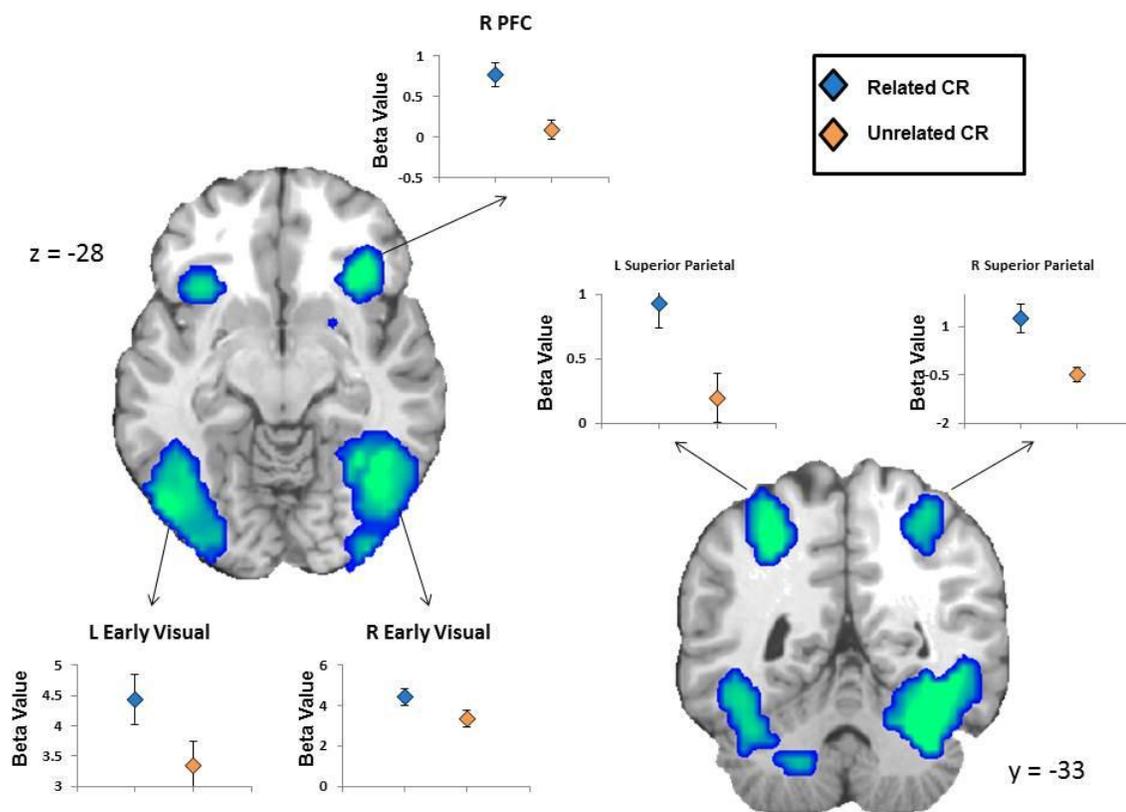


Figure 4-2. Related novelty detection.

Brain regions exhibiting greater activity for related novelty detection compared to unrelated novelty detection. Graphs represent parameter estimates for related correct rejections and unrelated correct rejections for the peak voxel within each region. See Table 3-2 for complete results and coordinates of peak voxels. R = right, L = left, PFC = prefrontal cortex, CR = correct rejection.

As previously noted, activity in early visual cortex has been associated with both the recapitulation of visual details from an encoding episode (Dennis et al., 2012; S. E. Prince et al., 2009; Slotnick & Schacter, 2004; Stark et al., 2010) and increased attention to and encoding of visual details (Gutchess et al., 2005; Kirchoff et al., 2000; Otten et al., 2001). The present

results suggest that processing of visual details contributes to novelty success particularly for related items perhaps because of their stronger perceptual similarity to items from encoding. That is, for related items compared to unrelated items, more detailed perceptual information is necessary in order to create mismatch between the new and old item and generate a successful novelty response. Although we found common activity in an early visual region for related and unrelated novelty detection, the direct comparison between related and unrelated novelty detection showed many visual regions were more engaged for related compared to unrelated novelty. No visual region showed the opposite effect. Therefore, results suggest that while perceptual processing is an important component of novelty detection generally, it is more important when novel items cannot be distinguished from old items based on categorical distinctions alone as is the case with unrelated items.

Visual activity in both early and late regions for successful related novelty detection may also reflect increased encoding of perceptual details. That is, as one attends to perceptual information necessary to make a novelty decision, that information is also encoded in memory. Kirchoff et al.'s (2000) study found that regions of both early and late visual cortex showed both novelty and subsequent memory effects, supporting the notion that novelty detection and encoding processes are inextricably tied. The present findings extend this work by showing that activity in visual regions is also moderated by the extent to which perceptual information is relevant to a retrieval decision. We show that related novelty detection shows greater reliance on processing of visual details necessary to distinguish between perceptually and semantically similar items. Further, activity in early and late visual regions was greater for related novelty detection compared to both unrelated novelty detection and related false alarms. Thus, perceptual processing appears to be greater for processing of related novel items ( $RCR > UCR$ ) for which a successful response is selected ( $RCR > RFA$ ), and does not reflect either a general success effect or a level of categorization effect. Although previous literature has found level of categorization

effects in the ventral visual stream even among non-experts (Gauthier, Anderson, Tarr, Skudlarski, & Gore, 1997), the activity in the fusiform gyrus for related novelty detection compared to related false alarms suggests that the subjective memory decision is also a factor driving activity in this region. That is, the subjective memory response to related novel items shows greater engagement of regions associated with the processing of visual information for recognition (for review see Kanwisher & Dilks, in press).

Taken together, results showing engagement of early and late visual cortex support the notion that perceptual processing is a key factor in determining; however, it is unclear whether this processing represents reactivation of previously encoded perceptual details, encoding of relevant information for later memory decisions, or some combination of encoding and retrieval processes. Further research is necessary to distinguish between these possibilities.

Beyond visual processing regions, we also predicted that related novelty detection would be associated with increases in monitoring processes and cognitive control associated with the ACC and right PFC respectively. Regarding increased monitoring in the ACC, this prediction did not bear out. Instead, a ventral region of the ACC more strongly associated with affective than cognitive tasks (for review see Bush, Luu, & Posner, 2000) was engaged for unrelated novelty detection. This activity may represent the relative “surprise” in seeing an unrelated item in the context of many more difficult memory decisions. The lack of differences between related and unrelated novelty detection in more cognitive regions of ACC may reflect the overall difficulty of the task such that participants were monitoring memory output at relatively high levels throughout retrieval.

Related novelty detection did however show engagement of bilateral VLPFC consistent with our hypothesis that related novelty detection would recruit additional control and monitoring processes to distinguish between items that are semantically and perceptually similar to items presented at encoding. Previous research has suggested that cognitive control processing in right

PFC is an important part of memory retrieval (Henson et al., 1999; Lepage et al., 2000; Rugg et al., 1996; Tomita et al., 1999) with a role in negotiating interference and response selection (Fletcher et al., 1996; Miller & Cohen, 2001; Tomita et al., 1999) particularly when information is semantically or perceptually similar (Dolan & Fletcher, 1997; Henson et al., 2002; Kan & Thompson-Schill, 2004). However, previous research in the domain of novelty detection has not explicitly investigated the role of proactive interference and therefore has not distinguished between the roles of novelty success and interference with regard to the PFC. The present results show that, when success is held constant (i.e.,  $RCR > UCR$ ), bilateral VLPFC activity is greater for related than unrelated items. However, when relatedness is held constant (i.e.,  $RCR > RFA$ ), no lateral PFC region showed increased activity for novelty success compared to false recollection. Thus, the proactive interference itself seems to be driving activity in this region, rather than successful retrieval responses. As such, our data support the notion that bilateral VLPFC activity is engaged in the presence of semantic and perceptual interference and overall activity in this region does not distinguish between successful and unsuccessful responses to related novel items.

In addition to frontal regions, we also found evidence of top-down control processes in bilateral superior parietal cortex for related novelty. Results showed activity in bilateral superior parietal cortex in a direct comparison between related and unrelated novelty detection, suggesting that related novel items engage top-down visual attention. However, like control processes in the PFC, superior parietal cortex did not distinguish between related novelty detection and false recollection, suggesting that related items generally recruit visual attention but that this attention is not a critical determiner of novelty success. Instead, our data suggests that visual attention is engaged whenever items at retrieval resemble those from encoding. Indeed, in a previous paper (Dennis et al., 2012), a region of right superior parietal cortex showed common activity for true and false recollection more so than true and false familiarity. These results are consistent with

the hypothesis that right superior parietal cortex is involved in orienting attention to specific visual details, but does not play a strong role in the memory decision itself. Instead, as previously discussed, the strength of the visual signal itself seems to be the key determiner of success for related novelty detection. That is, the top-down orienting of attention toward visual information is only successful if there is sufficient visual information available (i.e. encoded details from study) to detect the mismatch to the current item.

This interpretation of superior parietal activity is consistent with the AtoM theory of parietal activity during memory retrieval, which suggests that superior parietal cortex orients attention to internally stored mnemonic representations in a top-down fashion (Cabeza, 2008; Cabeza, Ciaramelli, & Moscovitch, 2012; Cabeza et al., 2008). That is, superior parietal cortex may execute an internal search of memory to find evidence to support a memory response. In the present study, increases in task demands for related novelty would require more stored information about previously encountered items in order to come to a conclusion about an item's novelty. This search process may reveal evidence of a novel item's mismatch to old items, but it might also lead to erroneous binding of old details to new items (Dennis et al., 2012; Lampinen, Faries, Neuschatz, & Toggia, 2000; Lampinen, Meier, Arnal, & Leding, 2005; Lampinen, Neuschatz, & Payne, 1999; Odegard & Lampinen, 2004). Thus, mnemonic attention allows for further accumulation of evidence toward a memory decision, but does not ensure that this evidence is associated with the correct item or episode. The present results indicate that such top-down searches are an important component of related novelty, but not related novelty success.

Overall, our results suggest that related novelty involves both an increased sensory signal to detect differences between novel and old items as well as the control and attentional processes necessary to execute this more fine-grained comparison.

## Unrelated novelty detection

Finally, we aimed to determine brain regions associated with successful novelty detection of unrelated items compared to related items. Consistent with our hypothesis that novelty detection for items with a unique categorical label would be based largely on semantic information, unrelated novelty detection was associated with activity in bilateral inferior and middle temporal gyrus, right superior temporal gyrus, and bilateral inferior parietal cortex.

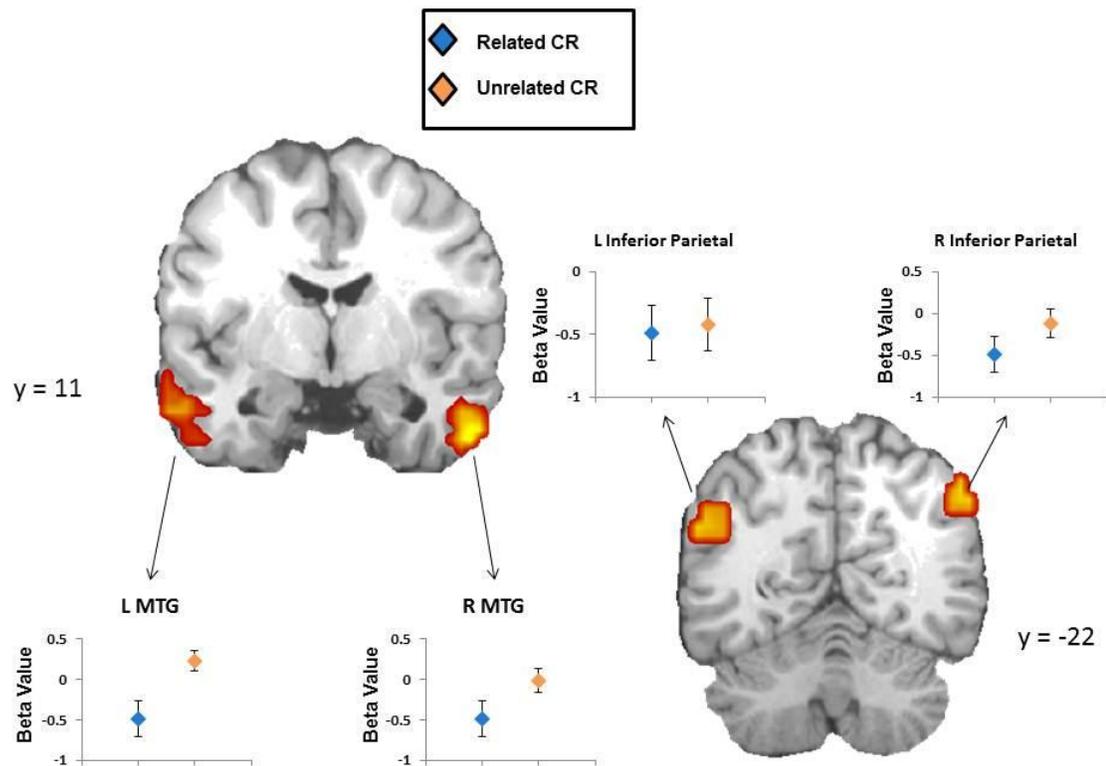


Figure 4-3. Unrelated novelty detection.

Brain regions exhibiting greater activity for unrelated novelty detection compared to related novelty detection. Graphs represent parameter estimates for related correct rejections and

unrelated correct rejections for the peak voxel within each region. See Table 3-3 for complete results and coordinates of peak voxels. R = right, L = left, MTG = middle temporal gyrus, CR = correct rejection.

Although we found that a region of the left middle temporal gyrus showed overlap between related and unrelated novelty, bilateral regions of inferior and middle temporal gyrus and right superior temporal gyrus were shown to support unrelated novelty detection more so than related novelty. No lateral temporal region showed greater activity for related novelty detection. This activity is consistent with the relatively greater semantic and perceptual differences between items that are unrelated to items presented at study and therefore greater emphasis in making memory decisions based on categorical information or semantic labeling. Given their role in categorical and semantic processing (e.g. Galton et al., 2001; Mummery et al., 2000), activity in these regions during memory tasks has often been associated with false memories and categorical or ‘gist’ processing (Dennis et al., 2007; Garoff et al., 2005; Gutchess & Schacter, 2012; Slotnick & Schacter, 2004). When items are related, Fuzzy Trace Theory suggests that reliance on ‘gist’ information can lead to confusion between new and old items if more specific ‘verbatim’ traces are not also retrieved (Brainerd & Reyna, 1990). However, in the case of unrelated novel items, making decisions based on ‘gist’ processing may be sufficient and a highly effective means to support a correct memory decision as these items differ from old items at a categorical level. That is, using semantic when items are unrelated may lead to quicker and less effortful memory decisions without losing accuracy. Our behavioral data support this theoretical account by showing both the highest accuracy and the quickest reaction times for unrelated novel items, suggesting that individuals are able to make unrelated novelty decisions with less effort without losing accuracy. Overall, the present results suggest that when items are unrelated, ‘gist’ processing may be an effective strategy for making novelty decisions.

Supporting the notion that unrelated novelty detection is a less effortful process, unrelated novelty detection was also supported by regions associated with automatic capture of memorial attention, specifically right inferior parietal cortex (Cabeza, 2008; Cabeza et al., 2012; Cabeza et al., 2008). While distinct areas of left inferior parietal cortex showed activity for both related and unrelated novelty, only unrelated novelty engaged right inferior parietal cortex. Although most fMRI studies of episodic memory retrieval find stronger left parietal activations (for metaanalysis see Vilberg & Rugg, 2008), activation in the right inferior parietal cortex has been associated with visuospatial attention (Corbetta et al., 2000; Posner, Walker, Friedrich, & Rafal, 1984). Thus, the present parietal dissociation within the right hemisphere suggests that unrelated novelty detection involves attention to internally stored visuospatial representations of previous items that capture attention in a bottom-up fashion, which is consistent with the strong visuospatial nature of the stimuli in the present study and the uniqueness of the unrelated items. This is in contrast to the previously discussed top-down search of memory traces associated with related novelty detection. Together, the superior-inferior dissociation within right parietal for related and unrelated novelty shows how differences in an item's context can affect attentional demands necessary for successful novelty detection.

Overall, the present results show that unrelated novelty detection engages bottom-up attention to memory as a result of more salient, categorical differences between new and old items. That is, 'gist' information about unrelated items is extracted quickly and automatically, capturing memorial attention and allowing for rapid novelty decisions at high rates of accuracy. Because unrelated novel items are distinct from items at encoding, unrelated novelty detection proceeds with less effortful processing and instead relies on categorical cues and bottom-up capture of attention.

### Exploratory analyses

In addition to BOLD contrasts, we also performed two types of connectivity analyses in order to determine the relationships between regions associated with related and unrelated novelty detection. The first analysis was performed in the GIMME program (Gates & Molenaar, 2012), which measures the effective connectivity between selected ROI time-series and can include information about an event-related task. We selected ROIs based on *a priori* predictions about regions that would be part of the novelty detection network, including anterior MTL, lateral temporal regions, visual cortex, prefrontal cortex, and parietal cortex. To select the specific locus of each ROI, we pulled from BOLD contrasts to ensure that the ROIs we selected were involved in the task of interest at an above-threshold level. We entered 12 ROIs selected from BOLD contrasts and extracted time-series from each participant for each ROI according to the peak coordinate in the group map using an 8mm sphere around that coordinate. ROIs selected from the general novelty activity results included right anterior MTL, left middle temporal gyrus, and right lingual gyrus. See Table 3-2 for peak coordinates. ROIs selected from the contrast  $RCR > RFA$  included left MTL and medial visual cortex. See Table 3-2 for peak coordinates. ROIs selected from the contrast  $UCR > RFA$  included the anterior cingulate, left MTL, right superior temporal gyrus, right inferior parietal cortex, and left visual cortex. See Table 3-2 for peak coordinates. ROIs selected from the contrast  $RCR > UCR$  included two right PFC peaks in BA 44/45 and BA 47/45. See Table 3-3 for peak coordinates.

Although this method returned a valid group model (see Figure 4-4), it did not return any connections that varied with the task demands. That is, there were no connections that were either only present for related or unrelated novelty nor were there connections that were modulated by related or unrelated novelty. This was the case for the group connectivity map as well as for every individual subject's connectivity map. Thus, while the GIMME method of connectivity returned a

valid connectivity map for memory retrieval generally, it did not give any clues about the nature of connectivity during novelty detection specifically. We believe that this was the result of the disparity in power between the overall time series (over 1400 TRs per subject) and the trials associated with novelty detection (approximately 150 trials per subject). Thus, the overall time series accounted for the data so well, we were unable to detect the relatively more subtle differences associated with different types of novelty detection. This account is supported by the excellent fit indices produced by the model (RMSEA = 0.88, NNFI = 0.94, and CFI = 1.00), meaning that much of the variance was accounted for by these general retrieval, task invariant connections. Therefore, the GIMME method produced a model that accounted for the data well, but did not answer our question regarding the network properties of novelty detection.

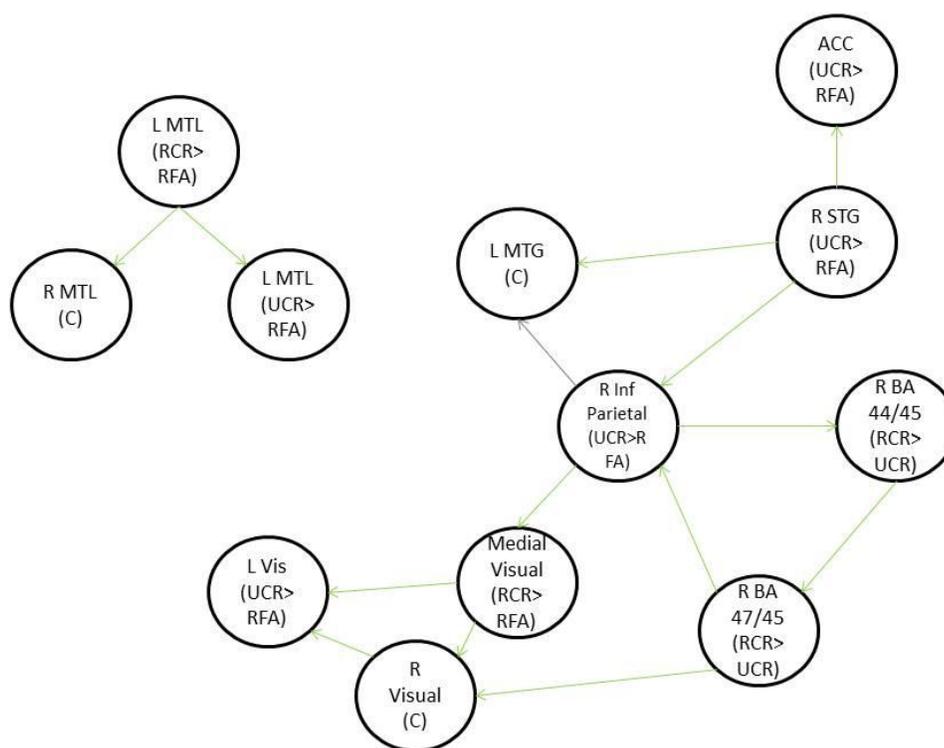


Figure 4-4. GIMME group connectivity map.

GIMME connectivity map for related and unrelated novelty detection. No effect of task was found, so connections represent general connectivity throughout an episodic retrieval task. Only contemporaneous relationships are represented. Green arrows represent connections that were significant in at least 77% of participants. Grey arrows represent connections that were significant in 76% of participants (thus representing marginal significance). All connections were positive on average (i.e. had an average Beta parameter  $> 0$ ). Parenthetical within each ROI indicates which contrast that ROI was drawn from. L = left, R = right, RCR = related correct rejection, UCR = unrelated correct rejection, RFA = related false alarm, C = common activity (i.e. general novelty contrast), vis = visual cortex, MTL = medial temporal lobe, ACC = anterior cingulate, MTG = middle temporal gyrus, STG = superior temporal gyrus, inf = inferior, BA = Brodmann's Area.

Although the GIMME connectivity analysis did not reveal differences in connectivity based on the type of novelty detection, it did reveal a reliable group connectivity map associated with memory retrieval. However, our primary interest was identifying the network properties of novelty detection specifically, and not retrieval generally. To continue pursuing connectivity associated with novelty detection, we used the psychophysiological interactions (PPI) toolbox in SPM8. However, this connectivity method requires identification of a single ROI and calculates whole-brain functional connectivity with that region. Thus, we narrowed our list of ROIs to make this analysis feasible. Thus, we used this connectivity method as a follow-up to the BOLD contrasts associated with related novelty detection and used ROIs in right superior parietal cortex and bilateral inferior frontal gyrus (IFG). In terms of BOLD contrasts, these regions showed greater activity for related as compared to unrelated novelty, but did not distinguish between related novelty detection and related false alarms. We concluded that these regions were engaged when new items resembled items from the study phase, but did not contribute to successful novelty detection decisions. However, it is possible that the magnitude of bilateral IFG is not

itself indicative of successful novelty detection. Instead, the IFG may work as part of a network, specifically with the anterior MTL, to determine successful novelty detection.

For this analysis, we again selected ROIs from BOLD contrasts and drew an 8 mm sphere around each peak coordinate. All ROIs were selected from the contrast  $RCR > UCR$  (i.e. related novelty detection), including right superior parietal cortex (peak: 26, -54, 47), right IFG (peak: 30, 23, -5), and left IFG (peak: -30 24 5). In order to determine how connectivity between each of these regions and the MTL differed for related novelty detection compared to related false alarms, we entered each ROI individually as a seed and  $RCRs$  and  $RFAs$  as the trial types of interest for the interaction. Group analyses were thresholded at an uncorrected threshold of  $p < 0.05$  with an extent of 17 voxels, resulting in a threshold corrected to  $p < 0.05$  (Garoff-Eaton et al., 2007; Slotnick & Schacter, 2004) using an anatomical mask of the MTL (including bilateral hippocampus, parahippocampal gyrus, and amygdala) to restrict analyses to this *a priori* ROI.

Results from the right superior parietal ROI revealed no interactions with the MTL. Related novelty detection and related false alarms did not show differential functional connectivity between the right superior parietal cortex and the MTL. This leads us to conclude either the right superior parietal is indeed engaged for relatedness but does not lead to novelty success or that right superior parietal does not directly contribute to basic memory processing in the MTL. Instead, this region may influence memory through a mediating region. Regarding the bilateral IFG seeds, both showed interactions with the MTL such that the connection was negative for related novelty detection and positive for related false alarms. The right IFG seed showed this interaction with bilateral MTL, including anterior and posterior portions of the hippocampus and parahippocampal gyrus (right MTL peak: 22, 0, -26;  $k = 116$ ; left MTL peak: -26, 0, -26;  $k = 90$ ). The left IFG seed also showed this interaction in bilateral MTL including clusters in anterior and posterior portions of the hippocampus and parahippocampal gyrus (left anterior peak: -15, 0, -13;  $k = 37$ ; left posterior peak: -26, -17, -12;  $k = 26$ ; right

anterior peak: 19, 4, -17;  $k = 18$ ; right posterior peak: 26, -28, -12;  $k = 23$ ). This analysis suggests that the connectivity between bilateral IFG and bilateral MTL relates to the success of the memory decision. Previous research investigating PFC – MTL connectivity during episodic retrieval has found a negative relationship between these regions during true recognition (Kim & Cabeza, 2007) and a positive relationship during false memories (Dennis et al., 2012), suggesting that the connectivity between PFC and MTL is an important factor in determining successful memory responses. Although the present results are correlational in nature and cannot be interpreted strictly in terms of causation, it is consistent with previous work suggesting that the PFC may have a role in regulating the products of episodic memory (e.g. Anderson et al., 2004; Summerfield et al., 2006). In the case of false memory, previous work has interpreted top-down processing to reflect a faulty reconstruction process that allows previously experienced details to be bound to a new item (Dennis et al., 2012). The negative relationship between the PFC and MTL during related novelty detection may reflect the suppression of this process, which would support a successful novelty decision. That is, when the PFC suppresses this reconstructive process for related novel items, there is a higher likelihood that the item will be successfully identified as new. However, further measures of connectivity that can determine directionality will be necessary to support this interpretation. For the time being, we conclude that PFC – MTL connectivity may be an important factor in determining success for related novel items.

### **Conclusions**

The present study sought to elucidate the role of item relatedness in the neural mechanisms of successful novelty detection. While previous research has investigated the role of item relatedness in producing false memories, no study has investigated the cognitive and neural mechanisms involved in successfully negotiating related and unrelated novelty. We first

examined regions that showed overlap between related and unrelated novelty detection to determine regions that contribute to novelty success regardless of an item's context. Such regions included early visual cortex, left middle temporal gyrus, and right parahippocampal gyrus and hippocampus, showing a relationship between novelty detection and encoding processes. Contrary to theories of MTL processing during novelty detection, the MTL did not distinguish between related and unrelated novelty, suggesting that novelty-related activity in the anterior MTL reflects the subjective memory decision and not a graded familiarity or mismatch signal. Regarding related novelty detection, activity in regions such as early and late visual cortex, bilateral VLPFC, and right superior parietal cortex distinguished between related and unrelated novelty, showing regions associated with perceptual processing and top-down control mediate related novelty detection. In contrast, we showed that unrelated novelty success is associated with semantic or categorical distinctions as well as automatic capture of memorial attention, reflected in activity in lateral temporal regions and inferior parietal cortex, respectively.

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