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I *know* I've seen you before: Distinguishing recent-single-exposure-based familiarity from pre-existing familiarity

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Abstract

This study examines how individuals differentiate recent-single-exposure-based familiarity from pre-existing familiarity. If these are two distinct cognitive processes, are they supported by the same neural bases? This study examines how recent-single-exposure-based familiarity and multiple-previous-exposure-based familiarity are supported and represented in the brain using functional MRI. In a novel approach, we first behaviorally show that subjects can divide retrieval of items in pre-existing memory into judgments of recollection and familiarity. Then, using functional magnetic resonance imaging, we examine the differences in blood oxygen level dependent activity and regional connectivity during judgments of recent-single-exposure-based and pre-existing familiarity. Judgments of these two types of familiarity showed distinct regions of activation in a whole-brain analysis, in medial temporal lobe (MTL) substructures, and in MTL substructure functional-correlations with other brain regions. Specifically, within the MTL, perirhinal cortex showed increased activation during recent-single-exposure-based familiarity while parahippocampal cortex showed increased activation during judgments of pre-existing familiarity. We find that recent-single-exposure-based and pre-existing familiarity are represented as distinct neural processes in the brain; this is supported by differing patterns of brain activation and regional correlations. This spatially distinct regional brain involvement suggests that the two separate experiences of familiarity, recent-exposure-based familiarity and pre-existing familiarity, may be cognitively distinct.

Keywords

familiarity; recollection; medial temporal lobe; functional connectivity

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1. Introduction

While riding the bus to work, a woman looks up and sees a man who appears familiar to her. She racks her brain for information about who this person is and how she knows him. Even though she is absolutely sure that she knows this man, she cannot figure out how. This classic example is known as the “butcher on the bus” phenomenon (Mandler, 1980). Had the woman seen this man behind the meat counter at the supermarket, she would have had no problem placing him as her butcher. However, in the absence of this context and additional information, the woman's recognition of the butcher was expressed merely as a sense of familiarity. The problem of recognizing the butcher becomes more complicated with this recent single exposure on the bus. If the woman was to see the same familiar-looking man on the bus the next day, how would she be able to distinguish if the man was familiar from her pre-existing familiarity (the fact that he's the butcher and she has seen him many times throughout her life) or from her single recent exposure to him on the bus the day before?

Taking this situation one step further, the question becomes, is recent-single-exposure-based familiarity cognitively equivalent to (and supported by the same neural bases as) pre-existing familiarity (familiarity due to knowledge accumulated throughout life)? Stimuli, such as frequently seen faces or common words, have a high pre-existing familiarity; with additional exposure, they also have a recent-single-exposure-based familiarity. How are these two types of familiarity distinguished? Given that an individual can make a temporally or spatially distinct familiarity judgment (by identifying with a ‘know’ response that a high-frequency word was on a study list), how is that feeling of familiarity placed into the context of time and place? Jacoby and Dallas (1981) propose a process-based familiarity where the fluency of processing the recently-exposed item is what constitutes the basis for a familiarity judgment. Coane and colleagues (Coane et al., 2011) propose a separation of familiarity into baseline levels of pre-existing familiarity for an item and a relative change in familiarity for an item based on recent exposure. They find these two types of familiarity to be behaviorally distinct, representing a fast baseline process and a ‘change detector’ mechanism, which calculates the recent change in relative familiarity. These results indicate that there is a difference in pre-existing familiarity and relative change in familiarity based on recent exposure, but cannot speak to how these two types of familiarity are distinguished. To further this investigation, Bridger and colleagues (Bridger et al., 2014) used ERP data to provide evidence of two topologically distinct familiarity signals that show temporal overlap. They find differences in absolute familiarity in more posteriorly distributed regions while they find a relative familiarity index in more midfrontally distributed regions. These findings support the existence of two cognitively distinct familiarity mechanisms in the brain. The purpose of our research is to determine if recent-single-exposure-based familiarity and pre-existing familiarity recruit similar or different regions and networks of the brain, in order to infer if these two types of familiarity, recently shown to exist, are cognitively distinct.

In the current study we used functional MRI to examine if pre-existing familiarity and recent-single-exposure-based familiarity are neurally distinguishable. This distinction is different than that described by Coane and colleagues, whose study led to familiarity findings based on exposure frequency, and Bridger and colleagues, whose study led to

familiarity findings based on ERP data. The current study builds upon this work, since if pre-existing and recent-single-exposure-based familiarity elicit distinct neural components, then this may provide a mechanism for an individual's awareness of differences, as supported by an ability to distinguish between the two when making a recent-single-exposure-based familiarity judgment on a high frequency item. Under the suggestion that different cognitive processes rely on different brain regions/networks, this 'composition of familiarity' question could be examined using brain imaging. Testing this hypothesis required the examination of how pre-existing familiarity is represented in terms of brain function. Practically, this meant having participants experience well-known items for which they had no additional information other than the sense of familiarity. Brain activity associated with such an experience could then be compared to the brain activity related to recent-single-exposure-based familiarity, where the reported familiarity was only based on recent exposure and had no component of pre-existing familiarity.

To accomplish this goal, we scanned subjects during a task of pre-existing familiarity and a task of recent-single-exposure-based familiarity to compare regions involved in these processes. To do this, we exposed subjects to famous faces and used a modified 'remember-know' paradigm (Tulving, 1989) to isolate familiarity judgments. In a second portion of the experiment, subjects made a traditional remember/know judgment on recently-exposed faces. Traditionally in the remember-know paradigm, a 'remember' judgment is a memory recognition accompanied by some sort of additional information about the encoding event. A 'know' judgment is a memory recognition without conscious recollection of anything specific about its occurrence. In both portions of the study we were only interested in the judgments of familiarity. In order to separate familiarity judgments in each of these memory domains, subjects were given the option of identifying each stimulus as recollected, familiar, or new.

In the recent-single-exposure task, subjects were exposed to new faces before the scan. During scanning, these faces plus novel faces were presented, and the subject made a 'remember,' 'know,' or 'new' judgment on each face. In the pre-existing (multiple-previous-exposure) memory task, during scanning subjects were exposed to faces that they might recognize from everyday life (famous faces), and were asked to make a 'remember,' 'know,' or 'new' judgment on each face. Note that subjects were making both recollection and familiarity judgments in both the recent-single-exposure-based and pre-existing memory tasks. However, the balanced comparison, which is the comparison of interest, is between the pre-existing and recent-single-exposure-based familiarity judgments. The 'recollection' trials were not the focus of this study, given the innate differences in the kinds of additional information retrieved during these two types of recollection. Thus, subjects' judgments of recollection and familiarity were used in this study to isolate familiarity judgments and to assure that differences found between recent-single-exposure-based and pre-existing familiarity would not be attributable to possible differences between these two types of recollection.

This study seeks to compare neural activations associated with recent-single-exposure-based and pre-existing familiarity memory judgments. Given the copious amount of work on recent-single-exposure-based familiarity (referred to in the literature as episodic familiarity),

this phenomenon is relatively well understood (Diana et al., 2007; Montaldi and Mayes, 2010; Vilberg and Rugg, 2007; Yonelinas, 2002). However, the relationship between this kind of familiarity and familiarity due to multiple exposures to an item throughout life is not well understood. Recent behavioral (Coane et al., 2011) and ERP work (Bridger et al., 2014) has suggested that there is a distinction between these two types of familiarity, but how and why they are distinct and how they are distinguished at the neural level are not yet understood. In this study, we examine the neural activity accompanying these two types of familiarity. If the neural bases of newly-acquired recent-single-exposure-based familiarity and pre-existing familiarity due to multiple previous exposures throughout life differ from one another, this might suggest that these two processes may be inherently different in nature. Specifically, if there is a 'reversed association' where regions are differentially activated by memory conditions and there is a crossover interaction between regions and memory type, it can be assumed that these are two separate memory processes in the brain (Henson, 2006). This difference would obviate the need for an additional cognitive mechanism to distinguish an increment of recent-single-exposure-based familiarity from pre-existing familiarity. Based on previous work related to familiarity, this experiment tests the hypotheses: There are two different familiarity processes in the brain, as evidenced by the separation of the regions and networks of activity responsible for two distinct types of familiarity judgments. If this hypothesis is not supported by our data and the two types of familiarity do not differ in their brain activation, this might suggest that there is a change detector mechanism in the brain, allowing for a difference related to the incremental increase in pre-existing familiarity based on an additional exposure.

2. Results

2.1 Experiment 1 - Behavioral validation of multiple-previous-exposures-based familiarity judgments

In order to determine the ability of subjects to recognize a pre-experimentally familiar famous face, a behavioral experiment was conducted where subjects verbally responded to a face with a remember/know judgment (remember, know, or new) and what additional information they recalled about each face (Table 1). For instance, a typical 'R' response would be something like "I know who that person is, his name is Bill Clinton." A typical 'K' response would be something like "I've seen that person before, but I don't know anything about her." Subjects were asked to verbally report the first piece of additional information that came to mind. Testing revealed sufficient R and K responses (49 ± 3% and 14 ± 2% of 377 items, respectively) to allow confidence in moving this task from a behavioral experiment to functional MRI. Of the 2,588 responses where subjects also had additional information about the person, nearly all (2,587) reported additional semantic information. This behavioral test served to validate that subjects could experience multiple-previous-exposures (MPE)-based familiarity and identify a famous face as previously seen with no recollection of any additional information about that person.

2.2 Experiment 2

2.2.1 MRI analysis of recent-single-exposure-based and multiple-previous-exposures-based familiarity and recollection: Behavioral Results—Prior to

scanning, subjects studied non-famous faces presented with a name and made a yes/no judgment about if the name "matched" the face (Figure 1, left). The percentage of later recent-single-exposure (RSE)_R, RSE_K, and RSE_N responses was not different based on if the subject had initially identified the faces as matching or not matching the presented name (all $t < .1$, all $p > 0.90$).

For each face presented during scanning, subjects were asked to respond by making an R, K, or N judgment. An average of nine trials in the RSE runs and nine trials in the MPE runs did not receive a response, and were excluded from further analysis. Percentage of responses and reaction time were similar for R, K, and N judgments in the RSE and MPE memory conditions. During the RSE memory retrieval runs, 23 ± 4% of all responses were RSE_R, 36 ± 3% were RSE_K, and 38 ± 3% were RSE_N. During the MPE memory retrieval runs, 33 ± 4% of all responses were MPE_R, 30 ± 4% were MPE_K, and 34 ± 3% were MPE_N. For a detailed separation of these responses into R and K hits, misses, correct rejections, and false alarms, please see Table 2. In both the RSE and the MPE tasks, participants were able to distinguish between old and new items in their K responses, as evident by the corrected familiarity estimate (d') (Yonelinas, Kroll, Dobbins, Lazzara, & Knight, 1998), which significantly differed from zero in both tasks (RSE: $d' = 0.38$, $p < 0.001$; MPE: $d' = 0.58$, $p < 0.001$). These d' values differed from each other ($t_{(12)} = 0.033$), driven by participants making fewer false alarm K judgments on MPE trials than RSE trials. In a two-factor repeated measures ANOVA, there was no main effect of memory type (RSE/MPE) or response type (R/K/N). In a two-factor repeated measures ANOVA for response time, there was a main effect of both memory type ($F_{(1,12)} = 7.895$, $p < .05$) and response type ($F_{(1,12)} = 19.389$, $p < .001$). Post hoc pairwise comparisons (corrected for multiple comparisons) revealed that during RSE memory retrieval, RSE_R trials and RSE_N trials were faster than RSE_K trials ($p = .009, .044$ respectively). During MPE memory trials, MPE_R trials were faster than MPE_K trials ($p < .001$).

2.2.2 Recent-single-exposure- and multiple-previous-exposures-based familiarity in cortex: Imaging Results—RSE_K and RSE_N trials were examined within RSE runs and MPE_K and MPE_N trials were examined within MPE runs. Differences in activation in each memory condition (deltas) were then compared across the RSE and MPE memory conditions in order to examine how familiarity is supported in whole-brain cortical structures and in MTL sub-structures. 'Miss' trials were not included in further analysis; while RSE stimuli that had been studied could receive an incorrect RSE_N response (miss), a parallel condition does not exist in the MPE task. If a stimulus was given an MPE_N response, there is no way to confirm that this face had or had not been previously experienced, and thus all N responses are classified as correct rejections. (Note that it is likely not possible for subjects to distinguish between a truly novel face and a previously un-encountered famous face. A face given a novel judgment cannot carry any information that would help experimenters to classify the response as a correct rejection or a miss.) In both the RSE and MPE tasks, N correct rejection responses (RSE_N and MPE_N) are used for comparison with familiar hits.

An initial investigation into regions of differential activation between RSE and MPE familiarity (defined as RSE_K versus RSE_N and MPE_K versus MPE_N judgments)

revealed distinct regions of involvement (Figure 2 A,B; Table 3). RSE_K responses, when compared with RSE_N responses, were associated with activation in left dorsolateral prefrontal cortex (dlPFC), left middle frontal cortex, and left parietal cortex (Figure 2A). MPE_K responses, when compared with MPE_N responses, had regions of activation in left occipital lobe, right middle frontal gyrus, and midline cingulate gyrus (Figure 2B).

2.2.3 Recent-single-exposure- and multiple-previous-exposures-based familiarity in MTL sub-regions—Since MTL structures have been implicated in previous studies of episodic memory (for review, see Montaldi and Mayes, 2010), we limited the focus of the next analysis to an anatomically-defined MTL. Focusing only on the MTL, we collapse across familiarity judgments (K) to explore regions involved in familiarity and the inter-regional correlation, or putative network connectivity with other brain structures (see below). Once regions active during K judgments had been identified, beta values were extracted to determine the individual involvement of RSE and MPE judgments. There were two regions in the MTL where activity related to K judgments was different from activity related to N judgments ($p < .05$, corrected for multiple comparisons): right perirhinal cortex and right parahippocampal cortex (Figure 3; Table 3B, top). There were no regions more active for N judgments than K judgments. Further examination (extraction of voxel-wise beta values averaged across the cluster) showed that in the perirhinal cortex, this difference was driven by the RSE_K - RSE_N delta (RSE_K - RSE_N > MPE_K - MPE_N: two-tailed $t_{(12)} = 2.21$, $p < .05$; RSE_K - RSE_N > 0: two-tailed $t_{(12)} = 1.94$, $p < .05$). While the difference between RSE_K and RSE_N judgments was greater than zero in the perirhinal cortex, the difference between MPE_K and MPE_N judgments drove the parahippocampal cortex result (Figure 3; MPE_K - MPE_N > RSE_K -RSE_N: two-tailed $t_{(12)} = 2.206$, $p < .05$; MPE_K - MPE_N > 0: two-tailed $t_{(12)} = 2.446$, $p < .05$). Additionally, the perirhinal and parahippocampal cortices showed an interaction with RSE/MPE memory type ($F_{(1,12)} = 6.78$; $p < .05$). These results showed a ‘reversed association’ necessary to constitute a qualitative difference in RSE_K - RSE_N and MPE_K - MPE_N in these MTL subregions (Henson, 2006); each region was differentially activated by memory condition and there was a crossover interaction between region and RSE/MPE memory.

2.2.4 Recent-single-exposure- and multiple-previous-exposures-based familiarity: whole-brain networks—Given the differences in whole-brain and MTL activation maps for RSE-based and MPE-based familiarity, we were interested in examining cortical regions that correlate with activity in the perirhinal and parahippocampal cortex clusters revealed in the K-N contrast. Cortical regions correlated with perirhinal cortex differed for RSE_K - RSE_N (Figure 4A, green) and MPE_K - MPE_N judgments (Figure 4A, purple) (see Table 4 for a list of functionally-correlated regions). This difference was also seen in the functional correlation with parahipppocampal cortex, where cortical correlations for RSE_K - RSE_N judgments (Figure 4B, green) differed from correlated regions during MPE_K - MPE_N judgments (Figure 4B, purple). Regions in left dlPFC and bilateral superior parietal cortex were functionally correlated with both the perirhinal cortex and parahippocampal cortex during judgments of RSE_K (Figure 4, green). Bilateral inferior medial frontal cortex was functionally correlated with both the perirhinal cortex and parahippocampal cortex during judgments of MPE_K (Figure 4, purple).

2.2.5 Recent-single-exposure and multiple-previous-exposures: Recollection

—In order to determine if differences found between RSE-based and MPE-based familiarity were specific to familiarity and not representative of general RSE and MPE memory retrieval, the same analyses were performed on recollection trials in cortex and medial temporal lobe (Figure 5; Table 5). In contrast to the examination of RSE_K and MPE_K, this analysis showed a high degree of overlap between cortical activity related to RSE_R and MPE_R, compared to RSE_K and MPE_K (Figure 5A,B).

To ensure that RSE recollection showed a similar pattern to previous works relating to episodic memory, we also examined MTL activations related to recollection judgments. Within the anatomically defined medial temporal lobe, recollection judgments showed an area of significant activation in the right PHC where R > K regardless of the memory task (Table 5B). There was increased activation in this cluster for RSE_R relative to RSE_K (Figure 5E, green; two-tailed $t_{(12)} = 9.26$, $p < .001$). Similarly, MPE_R judgments also resulted in increased activation relative to MPE_K judgments (Figure 5E, purple; two-tailed $t_{(12)} = 9.12$, $p < .001$). Unlike for familiarity judgments, there were no differences in the deltas for RSE_R - RSE_K and MPE_R - MPE_K in the MTL (two-tailed $t_{(12)} = 1.59$, $p = .14$). As a second check the same analysis was used to examine regions active across RSE and MPE memory (R-N). Four MTL subregions of activity were found (Table 5B) including two hippocampal clusters, but the R-N delta was not different between RSE and MPE memory judgments (RSE_R - RSE_N vs. MPE_R - MPE_N) in any of the regions (two-tailed $t_{(12)} = 1.82, 1.73, 1.60, 1.43$, all $p > .1$, not displayed).

3. Discussion

Given that familiarity-related activity differs for RSE and MPE memory conditions in non-MTL cortical structures, MTL sub-structures, and MTL functional-correlation with other cortical regions, we suggest that recent-single-exposure-based and pre-existing familiarity may be treated as two separate entities in the brain. We find that regions of non-MTL cortex as well as perirhinal and parahippocampal cortex show differing activity related to RSE-based and MPE-based familiarity; it is only in the presence of retrieval of additional information that activations associated with RSE and MPE memory overlap. To the extent that a brain dissociation is indicative of a cognitive dissociation, the accumulation of evidence we obtained lends support to the notion that recent-single-exposure-based familiarity may be different in nature than pre-existing familiarity.

3.1 Models of MTL Contributions to Recollection and Familiarity

The existing models of MTL contributions to recollection/familiarity have focused on episodic memory, partially due to experimental paradigm constraints. Recent work has shown that semantic memory can be separated into recollection and familiarity as well (Waidergoren et al., 2012). The current study uses a novel approach to show a neural difference between recent-single-exposure-based and multiple-previous-exposure-based familiarity, and can be used to expand previous work. There are many models of how recollection and familiarity-based memories are supported in the brain, and the current study adds important information to the conversation about these models. The binding of item and

context (BIC) model implicates hippocampus for recollection but not familiarity (Diana et al., 2007). In this model, the perirhinal cortex supports item familiarity and the parahippocampal cortex supports context recollection. The convergence, recollection, and familiarity theory differs slightly from the BIC model; perirhinal cortex supports item familiarity and parahippocampal cortex supports context familiarity but neither supports recollection (Montaldi & Mayes, 2010). A third model separates the function of these regions based on memory-strength (Squire, Wixted, & Clark, 2007). Our study fits the predictions of the BIC model where posterior parahippocampal cortex was active for recent-single-exposure-based recollection but not familiarity while perirhinal cortex was active for recent-single-exposure-based familiarity but not recollection.

Previous studies of patients with MTL damage are consistent with the idea that familiarity is supported by the parahippocampal regions (Brown & Aggleton, 2001; Eichenbaum, 2006), although a distinction between the functions of perirhinal and parahippocampal cortices has not been found (Eichenbaum, Yonelinas, & Ranganath, 2007). In a study of patients with hippocampal and parahippocampal lesions, Yonelinas et al. (2002) find that patients with damage to either the anterior or posterior medial temporal lobe substructures show impairments in familiarity, suggesting that both of these regions (perirhinal and parahippocampal cortices) are critical for familiarity. In a recent study, it was shown that a patient with damage localized to the left perirhinal cortex exhibited deficits in familiarity judgments, in memory conditions similar to both RSE and MPE memory (Bowles et al., 2016). This study is in agreement with our finding that the perirhinal cortex supports familiarity in the RSE condition, even though they additionally find that it also supports familiarity in the MPE condition, while we find that MPE familiarity is supported in the parahippocampal cortex. Our findings of perirhinal involvement in recent-single-exposure-based familiarity and parahippocampal involvement in pre-existing familiarity fit with the view derived from studies of patients with MTL damage. Additionally, previous work in rats has identified unique populations of neurons in perirhinal cortex that respond separately to familiarity and recency (Zhu et al., 1995). In the current study, increased activity is observed in this region for recent-single-exposure-based familiarity, which has both a familiar and a recent component.

To extend the prediction of the BIC model, we showed that multiple-previous-exposure-based recollection also shows parahippocampal activation when compared to familiarity. We were surprised, however, to find increased activation in parahippocampus, but not perirhinal cortex, for pre-existing familiarity. The literature suggests that perirhinal cortex encodes items in a manner that supports familiarity (Aggleton & Brown, 1999; Diana et al., 2007; Norman & O'Reilly, 2003; Yonelinas, Otten, Shaw, & Rugg, 2005); even though this work has been specific to episodic familiarity, we had not ruled out the idea that pre-existing familiarity might rely on similar structures. Given that our own result is consistent with the literature showing that this region supports RSE familiarity (akin to episodic familiarity), we expected to also see activity in the perirhinal cortex related to MPE familiarity. We acknowledge that traditionally, familiarity effects in the perirhinal cortex are due to increased activity for novelty compared to familiarity. In this study, we see an increase in activity for familiarity compared to novelty. Recently, there has been work suggesting that prior occurrence of faces elicits patterns of perirhinal cortex activity consisting of voxels

with both decreases and increases in signal, and that this activity organization can be shaped by the stimulus category to which the stimuli belong (Martin et al., 2016). As this study was also done using faces, this study provides some evidence that increased perirhinal activity could be due to familiarity or novelty, depending on the circumstances. While it has been known that the parahippocampal cortex subserves episodic memory (Brewer, Zhao, Desmond, Glover, & Gabrieli, 1998; Davachi, Mitchell, & Wagner, 2003; Gabrieli, Brewer, Desmond, & Glover, 1997; Ranganath et al., 2004; Schacter & Wagner, 1999; Squire, Stark, & Clark, 2004; Wagner, 1998) and semantic memory for context (Bar and Aminoff, 2003; Bar et al., 2008), this study extends these findings to show that parahippocampal cortex is also involved in judgments of pre-existing familiarity. Given these findings, it is possible that the parahippocampus is active not only when context is successfully retrieved (as in our RSE_R and MPE_R conditions), but also when there is some sense that context is present (MPE_K). In order for a subject to make a judgment that a face has pre-existing familiarity, there must be some pre-established contextual trace informing this decision. This idea links to previous work on available versus accessible memory traces, where some memories may be stored in the brain, but inaccessible in an ever-growing network of memories and associations (Tulving and Pearlstone, 1966). While the retrieval of context results in parahippocampal activity, it is possible that context retrieval is not necessary for eliciting parahippocampal activity. Rather, when there is inherent knowledge that sought-for information exists in the brain and motivation to search for this additional information, parahippocampus is active whether the search itself is successful or unsuccessful.

3.2 MTL functional correlations for recent-single-exposure-based- and multiple-previous-exposures-based familiarity

As observed in Figure 5, the patterns of functional correlations for RSE_K and MPE_K are similar for both MTL-subregion seeds. The activation resulting from the contrast of MPE_K - MPE_N was not significantly different from zero in the perirhinal cortex, nor for RSE_K - RSE_N in the parahippocampal cortex (Figure 4A); however, the delta for RSE_K-related activity differed from the delta for MPE_K-related activity in both regions. Therefore, to compare networks that modulate with familiarity-sensitive MTL regions, perirhinal and parahippocampal regions were used as seed regions for the functional connectivity analysis. In their review of the functional differentiation of recollection/familiarity in the MTL, Montaldi & Mayes (2010) suggest that functional-correlations with MTL subregions should be examined to determine whether a specific structure's correlations change as a function of the type of memory. Correlations with perirhinal cortex and parahippocampal cortex seeds show that recent-single-exposure-based and pre-existing familiarity differ in their patterns of correlation from two different MTL substructures (even at $p = .1$ there is no overlap in correlated regions).

During MPE_K judgments, activity in perirhinal and parahippocampal cortex is functionally correlated with ventromedial prefrontal cortex (vmPFC), which has been known to support semantic aspects of a memory (Ishai et al., 2002; Leveroni et al., 2000); its coupling with MTL structures has been associated with the emergence of conceptual knowledge and schema built up around a given item (Frankland and Bontempi, 2006; Kumaran et al., 2009; Takashima et al., 2006; Takehara-Nishiuchi and McNaughton, 2008; van Kesteren et al.,

2010). The schema literature does not yet address which aspects of memory retrieval are reliant on a well-developed schema and vmPFC-MTL correlations. Our results show that a judgment of pre-existing familiarity is sufficient to activate vmPFC, even if an attempt to access additional information in the schema is unsuccessful. Additionally, during judgments of multiple-previous-exposure-based familiarity there were correlations between MTL subregions and the fusiform cortex, occipital regions, inferior parietal lobule, and lateral prefrontal cortex. Each of these regions is known to be involved during visual object priming, with activity modulated with repeated processing of objects (Buckner et al., 1998; Henson et al., 2000; Wagner et al., 2008; Wiggs and Martin, 1998). The fusiform and occipital cortices are involved in semantic processing (Buckner et al., 1998; Henson et al., 2000; Martin and Chao, 2001; Thompson-Schill et al., 1999) while prefrontal cortex is thought to play a role in the controlled retrieval of semantic information (Dapretto and Bookheimer, 1999; Fiez, 1997; Martin and Chao, 2001; Poldrack et al., 1999; Wagner et al., 2000). The known roles of these regions in relation to semantic memory can help us to understand their functional connectivity to MTL substructures during MPE familiarity.

Recent-single-exposure-based familiarity judgments led to correlations with dlPFC and superior parietal cortex (regions traditionally implicated in episodic memory retrieval). Activity in dlPFC, superior parietal cortex, and parahippocampal gyrus is sometimes related to the extra information held in mind during the retrieval of an item (Cabeza and Nyberg, 2000; Daselaar et al., 2008; Rypma and D'Esposito, 1999), however, there are extensive other processes attributed to these regions. Both the activation and correlated activity observed in the dlPFC during recent-single-exposure-based and pre-existing familiarity judgments, each compared to judgments of novelty, could be attributed to failed search for additional details necessary to make a recollection judgment. Additional analysis of the cognitive components at play during this retrieval could help explain the recruitment of these regions during judgments of familiarity. Importantly, pre-existing and recent-single-exposure-based familiarity have different and non-overlapping regions of functional-correlation with perirhinal and parahippocampal cortices, suggesting that these two memory processes recruit different networks.

3.3 Conclusions

Studies of memory have long taken into account varying levels of pre-existing familiarity for items used in an episodic test. In fact, differences in pre-experiment exposure to high- and low-frequency words helps to explain how these words are episodically remembered or forgotten (Reder et al., 2000). As described above, a recent study examining the contribution of familiarity to recognition of high- and low-frequency words separated familiarity into a baseline level of pre-experimental familiarity for an item and a relative change in familiarity based on new episodic exposure (Coane et al., 2011). Using manipulations in the time subjects have to respond in an item recognition test, they found that these two types of familiarity are behaviorally distinct, representing both a fast baseline familiarity process and a fast computation of a relative change in familiarity (change detector mechanism). Using a different paradigm of famous and studied non-famous faces, our results also suggest two different familiarity processes, although we suggest an alternative to the change detector hypothesis. Our results indicate the existence of regional segregation of pre-existing

familiarity signals from recent-single-exposure-based familiarity signals in the brain. At the phenomenological level these two types of familiarity may seem similar since each includes memory for an item without diagnostic information about that item. However, our data suggest that the similarity ends here; recent-single-exposure-based and pre-existing familiarity are supported by two separate sets of regions and networks in the brain, and may be two separate cognitive constructs. This idea can be put in parallel with the similarity of the subjective experience accompanying these two types of familiarity. While some work has suggested that individuals are able to subjectively distinguish between episodic and semantic familiarity (Williams et al., 2013) and our behavioral study indicates the same, a more in depth examination of the interaction between this subjective feeling and the difference in nature between the neural patterns of MPE and RSE based familiarity is warranted.

We note that the data presented here are also consistent with an interpretation of separate cognitive processes associated with the two familiarity conditions (rather than necessarily reflecting two cognitive constructs). The nature of the different cognitive processes associated with recent exposure is an open question that could be related to several different factors. The activations associated with recent-single-exposure-based familiarity may reflect the "relative familiarity" component (Coane et al., 2011); it may reflect the operation of the calculator which computes the difference in "relative familiarity;" it may be related to the computation associated with processing fluency experienced for recently-processed items (Jacoby & Dallas, 1981); it may be related to the known source of the felt recent-single-exposure-based familiarity (as opposed to the unknown source of the pre-existing familiarity); or it could reflect the different search routes taken by the subject when trying to identify or uncover further information about the familiar stimulus. We do not wish to speculate which of these options is more viable based on the pattern of brain activations observed for each type of familiarity (as this would involve committing a reverse inference error). More research aimed specifically at testing each one of these hypotheses is required.

In order to answer the question of if pre-existing familiarity is supported by the same or different neural bases as those supporting recent-single-exposure familiarity, this study was designed with famous faces experienced throughout life contrasted with novel faces learned just before the scan. Inherent in this design is the potential confound of the difference in age of the two kinds of memory. While RSE targets and foils are both recent (targets having been exposed for the first time just before the experiment and foils being exposed for the first time during the experiment), MPE targets are older memories while MPE foils are new. The result of this is a match in age between RSE targets and foils but a mismatch for MPE targets and foils. The influence, however, of age of memory on identified brain activity would be expected to be present in both recollection and familiarity judgments. The comparison of RSE and MPE recollection yielded no differences in MTL activity and minimal differences in cortical activity, in contradistinction to the results identified by the comparison of RSE and MPE familiarity. Thus it is unlikely that the age of the memory was a primary feature driving the differences observed between RSE and MPE familiarity. Possibly related to the age difference inherent in RSE and MPE memories, an analysis of reaction time showed a main effect of memory type. This overall reaction time difference between the RSE and MPE conditions may represent a possible confound of task difficulty when comparing between conditions. However, this is unlikely because contrasts were first

run within a condition, and only then were differences compared between conditions. Additionally, and more importantly, the differences seem to stem from the two bins of no interest in this study, the R and FA bins. For the conditions of interest, reaction time is highly similar, and therefore we believe that it is unlikely that reaction time differences confound these results. It is possible, however, that this difference in reaction time for R responses, as well as the differences in d-prime between the MPE and the RSE conditions, could reflect a difference in difficulty between RSE and MPE, which could have led to the adoption of different retrieval strategies for the two conditions. While being a possible alternative interpretation of our finding, we think the differences between RSE and MPE reported here are not likely to reflect different retrieval strategies, primarily because the retrieval states of interest here were the K responses, which did not differ in RT between the two conditions and are relatively strategy-free (compared to R responses, (Yonelinas, 2002).

It is possible, however, that this difference in reaction time for R responses could reflect a difference in difficulty, which could have led to the adoption of different retrieval strategies for the two conditions.

Our finding raises further questions regarding the eventual integration or transformation of recent-single-exposure-based familiarity into pre-existing familiarity. How different processes influence this change, the contribution of recent-single-exposure-based familiarity to the building blocks of pre-existing familiarity, or the timecourse of the incorporation of recent-single-exposure-based familiarity into pre-existing familiarity all represent fundamental questions that warrant further study.

4. Experimental Procedure

We first behaviorally verified that people can recognize a famous face without retrieving any additional diagnostic information about it (pre-existing familiarity). We then moved the study to the MRI scanner to examine how recent-single-exposure-based and pre-existing familiarity are supported in the brain. Note that in this study, the type of familiarity is defined by the experimental condition.

4.1 Experiment 1 – Behavioral validation of pre-existing familiarity

4.1.1 Participants—Fourteen healthy subjects were recruited from the Hebrew University of Jerusalem community (mean age = 24.0 ± 1.70 years, 6 male). Subjects received either course credit or 10 shekels (equivalent of $3) per 20 minutes of participation and gave informed consent. Each subject was tested in front of a computer screen, and participated in 3 runs of a pre-existing memory retrieval experiment.

4.1.2 Stimuli—During the course of the experiment participants saw 377 famous faces and 100 novel faces collected from various Internet sources. All faces were displayed in color, and placed on a grey background with just the face, neck, and hair visible. Novel faces were chosen to look as if the person could be famous (using face images that were attractive and similar in other qualities to those of the famous faces), since their purpose was to catch false alarms.

4.1.3 Experimental Procedure—During each trial a face appeared on the screen, and subjects were asked to say out loud whether the face was recognized, and if so, what they knew about that person (their name, occupation, etc.). An experimenter recorded both their response and any additional information about each face presented.

4.2 Experiment 2 – Functional MRI exploration of recent-single-exposure and pre-existing recollection and familiarity

4.2.1 Participants—Seventeen healthy right-handed subjects were recruited from the University of California, San Diego (UCSD) community and surrounding area (mean age = 25.1 ± 3.01 years, 8 male). Subjects received $40 for their participation and gave informed consent approved by the Institutional Review Board of UCSD. Four subjects were removed due to excessive motion (>3 mm following motion correction).

4.2.2 Stimuli—Stimuli were 654 color images of faces, of which 252 were famous faces and 402 were non-famous faces. Stimuli included those used in Study 1, plus additional stimuli collected and prepared in the same way.

4.2.3 Experimental Procedure—Prior to scanning, subjects visually studied 252 non-famous faces, each randomly paired with a gender-matched name. They were given 3 seconds to look at the face and make a subjective judgment about if the name presented "matched" the face (yes/no) (Figure 1, left). Subjects were instructed that they would later be tested on the faces. During scanning, runs were divided into a recent single exposure (RSE) condition (Figure 1, middle) and a multiple previous exposures (MPE) condition (Figure 1, right). In RSE runs, subjects saw all 252 studied faces and 102 novel faces and were asked to judge each with a 'remember,' 'know,' or 'new' response. Subjects were instructed to respond 'remember' (R) if they saw the image during the study task and could recall specific diagnostic information about its presentation (the name presented with the face or anything they had thought about during its initial presentation), 'know' (K) if the image was familiar but they did not recall specific information about seeing it before, or 'new' (N) if they thought the image was not presented during the study session (instructions were similar to those used in Yonelinas, 2001). In MPE runs, subjects saw 252 famous faces and 48 novel non-famous faces and made a judgment about each. (Note that in the MPE task we cannot know the exact number of novel faces for each subject since this is idiosyncratic for each participant. While we expect that subjects will not know some of the stimuli that we designate as famous, there is no *a priori* way of knowing how many famous faces will be given a 'new' judgment. The addition of non-famous faces to the MPE scans ensures an adequate number of 'new' responses for subsequent analysis. In fact, looking at subjects' responses, they judged ~34% of faces (102/300) in the MPE scans as new, making the total amount of "novel" faces not different than the amount of new faces presented in the RSE condition.) Subjects were instructed to respond 'remember' (R) if they recognized the face and had additional diagnostic information about the person (their name, occupation, etc.), 'know' (K) if the face was familiar but they did not have diagnostic information about the person, or 'new' (N) if they thought they had never seen the face before. For all runs, subjects responded by pressing one of three buttons on an MRI-compatible button box held in their right hand. Each image was presented for 3 seconds. Trials were jittered with 0.5-6

seconds of fixation-cross baseline with an interval of 0.5 seconds to optimize the study design (Dale, 1999). Each subject underwent a single session of three 470-second event-related runs (RSE) and three 400-second event-related runs (MPE). Based on previous experience in the laboratory, RSE and MPE memory trials were presented in separate runs to alleviate the cognitive juggling that accompanies interleaving these types of trials. The selection of studied and foil stimuli for the RSE runs was random and runs were interleaved and counterbalanced across subjects. Following the scan session, subjects completed an episodic memory task on the 300 faces seen during the MPE memory retrieval scans as well as an additional 120 novel faces. Instructions were identical to those given during the RSE memory retrieval scans.

4.2.4 fMRI Parameters—Imaging data were acquired using a 3T GE scanner at the Keck Center for Functional MRI at the University of California, San Diego. Functional images were acquired using a gradient echo echo-planar, T2*-weighted pulse sequence (repetition time = 2.5 s, one shot per repetition, echo time = 30, flip angle = 90°, bandwidth = 31.25 MHz). Forty slices covering the brain were acquired perpendicular to the long axis of the hippocampus with 3.4 × 3.4 × 4 mm voxels, allowing greater summation of activity along the hippocampal axial plane (Brewer & Moghekar, 2002). A T1-weighted high resolution (1 × 1 × 1 mm), three-dimensional fast spoiled gradient-recalled anatomical dataset was collected.

4.2.5 Data Analysis—Data from each run were field-map corrected to account for in homogeneities in the magnetic field (Smith et al., 2004). Using AFNI (Cox, 1996), slices were reconstructed to a 3-dimensional volume, temporally aligned, and co-registered. A threshold mask of the functional data was applied to remove voxels outside the brain and functional runs were smoothed with a 4mm FWHM Gaussian blur. Runs were corrected for motion and then RSE and MPE runs were each concatenated. For both RSE and MPE memory conditions, a general linear model was constructed using multiple regression analysis and included six motion regressors as well as regressors for RSE_R/MPE_R (remember) and RSE_K/MPE_K (know) hit and miss responses and RSE_N/MPE_N (new) correct rejections and false alarms.

Standard anatomical landmarks (ac-pc) were defined manually, and the anatomical and functional scans were transformed into Talairach space (Talairach & Tournoux, 1988) for whole-brain normalization. Given the *a priori* interest in memory-related medial temporal lobe (MTL) structures, the region of interest large deformation diffeomorphic metric mapping alignment technique (ROI-LDDMM) was then used to improve MTL alignment (Miller et al., 2005). Previously defined landmarks were used to manually draw hippocampus, perirhinal, entorhinal (Insausti et al., 1998), and parahippocampal cortices (Stark and Okado, 2003). These anatomical regions were aligned with a modified model of a previously created template segmentation (Kirwan, Jones, Miller, & Stark, 2007) using ROI-LDDMM. Functional datasets underwent the same transformation to ensure alignment with each subject's anatomical scan.

After individual deconvolution analysis, single-subject parameter estimates were entered into group level analyses. Voxel-wise *t*-tests (two-tailed) were performed to compare average

area under the curve between conditions of interest. Voxel-wise ANOVAs were also performed to look for interactions among clusters of interest. Clusters were defined as including at least 20 voxels with a voxel-center connectivity of 4mm, giving a whole brain/whole region significance of $p < .05$ and a voxel-wise significance of $p < .001$ when corrected for multiple comparisons (using alpha probability simulations calculated with the AFNI plugin, AlphaSim). Clusters were extracted at $p < .05$ (two-tailed, corrected for multiple comparisons) and were displayed as a statistical map overlaid onto an average structural image of all participants. Beta values were extracted for each subject in each cluster of interest and then averaged. Brain activity specific to recollection was explored in RSE_R - RSE_K and MPE_R - MPE_K analyses and brain activity specific to familiarity was explored in RSE_K - RSE_N and MPE_K - MPE_N analyses. In the recollection analysis, a negative t-value indicates more activity in that region for K relative to R and in the familiarity analysis, a negative t-value indicates more activity in that region for N than for K. Throughout the analyses of this study, RSE and MPE memory conditions were only directly examined by comparing the deltas between two retrieval responses (e.g. R vs. K or K vs. N) from each memory condition. By examining activations related to RSE familiarity (compared to novelty) and comparing this delta to its MPE counterpart, these two memory processes could be examined together. While there is a potential for different effects of novelty between the RSE and MPE memory conditions, there was no statistical difference from baseline for RSE or MPE correct rejections in either MTL cluster used in subsequent analyses (all $p > .2$). This is consistent with previous work finding that the novelty of faces typically modulates activity in the fusiform gyrus (Wright et al., 2008), and not in the medial temporal lobe regions examined in this study.

In the anatomically-constrained MTL analysis, R or K trials were collapsed across RSE and MPE conditions to reveal regions where there was a difference in activity between R and K or K and N, regardless of memory condition. In this way, differences found between RSE and MPE conditions could not be attributed to the cluster coming from an analysis of one condition and not the other. Clusters in the MTL were extracted using the same GLM analysis described above for the whole brain, but this analysis was anatomically constrained to the MTL. Once significant clusters were identified, the average beta value across the whole cluster was extracted for each subject, then entered into a second level analysis (two-tailed t-test). All analyses were performed in both directions (ie. K-N and N-K). For all analyses, RSE_N and MPE_N (and collapsed N) bins were the correct rejection (CR) of a novel face. While the analysis of interest for this study is the K vs. N contrast, as a control, whole-brain cortical activations and MTL activations were explored in the RSE_R vs. RSE_K and MPE_R vs. MPE_K contrasts to ensure recollection-related activity consistent with previous findings.

A functional-correlation analysis was used to determine regions with correlated activity to an MTL seed region (perirhinal and parahippocampal clusters taken from the K-N analysis) during different memory conditions. Using AFNI (Cox, 1996), the timecourse of the seed region of interest was extracted and contrast regressors for K and N conditions were obtained to construct the interaction regressor (Heekeren et al., 2004). K trials were examined in comparison to N trials because of the *a priori* interest in studying differences in recent-single-exposure- and multiple-previous-exposures-based familiarity. Correlation

coefficients were converted to Z-scores, analyzed with a t-test, and clustered at a whole-brain threshold of $p < .05$ (corrected for multiple comparisons). Cluster maps were displayed using SUMA (Saad et al., 2004) on the white matter surface of the Talairach and Tournoux N27 average brain from Freesurfer (http://surfer.nmr.mgh.harvard.edu).

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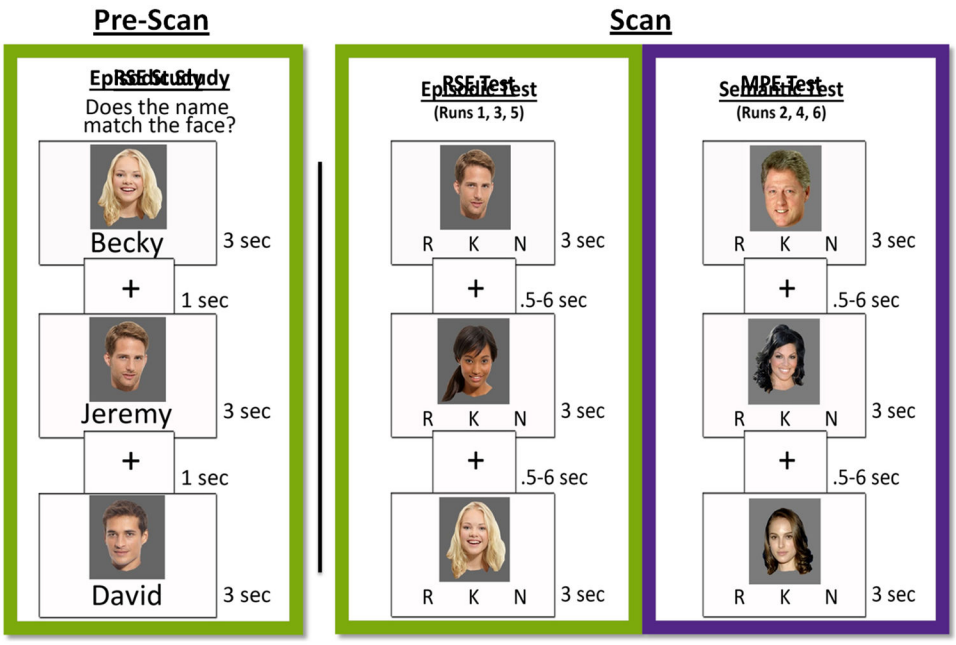

Figure 1. Task Design

Before the scan, subjects studied non-famous faces presented concurrently with a name (Study phase). They were asked to decide if the name "matched" the face by using a yes/no response. During scanning, subjects performed a recent-single-exposure (RSE) retrieval task and a multiple-previous-exposure (MPE) retrieval task. During the RSE task, subjects saw faces that had been studied during the pre-scan session and were asked to identify each with a Remember (R), Know (K), or New (N) response (based on if they remembered seeing the face during study). During the MPE task, subjects saw famous faces or foils and were asked to identify each with an R, K, or N response (based on if they had seen that person before and had any additional information about the person).

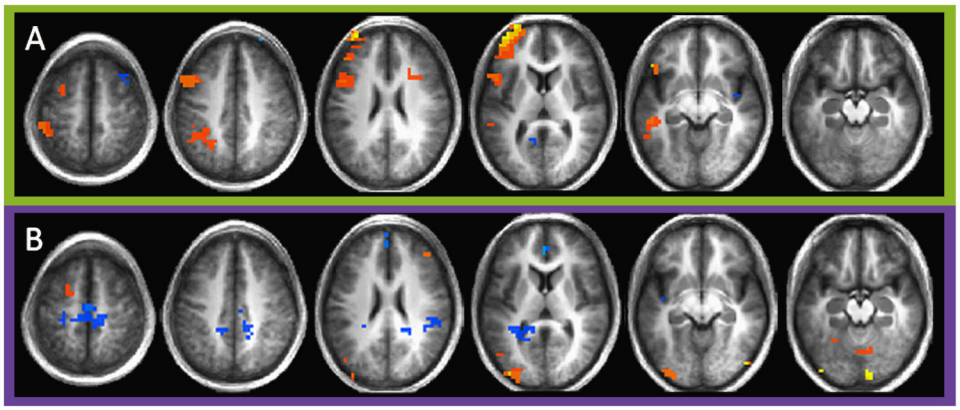

Figure 2. Regions of activation for recent-single-exposure-based- and multiple-exposures-based-familiarity

Clusters represent regions where A) RSE_K responses are significantly different from RSE_N responses and B) MPE_K responses are significantly different from MPE_N responses. Warm colors represent regions where RSE_K/MPE_K > RSE_N/MPE_N and cool colors represent regions where RSE_N/MPE_N > RSE_K/MPE_K. Clusters are significant at $p < .05$, corrected for multiple comparisons and are displayed on an average anatomical scan of all subjects.

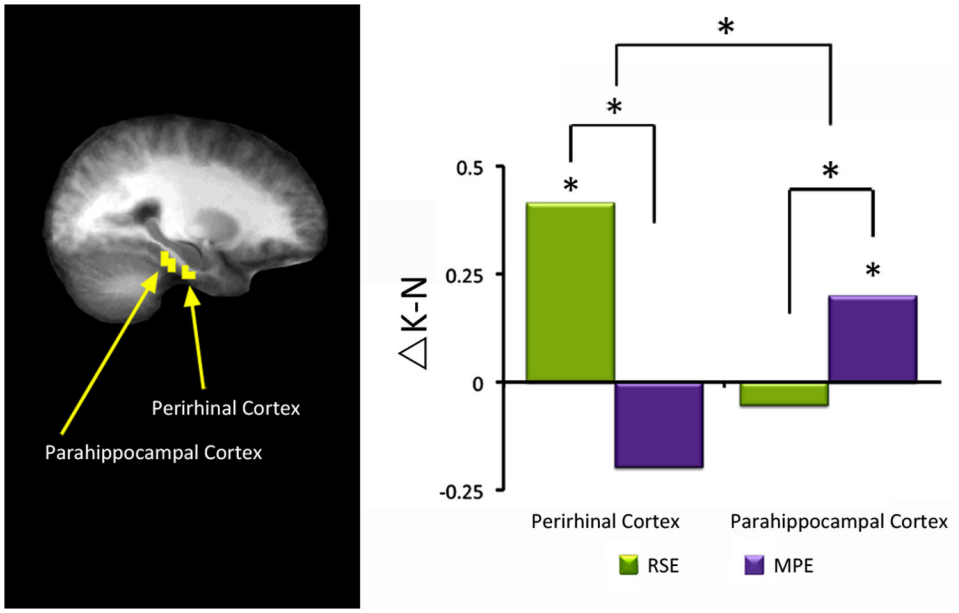

Figure 3. Recent-single-exposure-based and multiple-previous-exposures-based familiarity in the MTL

Right perirhinal cortex showed a greater difference between RSE_K and RSE_N than MPE_K and MPE_N. Right parahippocampal cortex showed a greater difference between MPE_K and MPE_N than RSE_K and RSE_N. An interaction exists between these two regions and RSE/MPE retrieval conditions. Clusters represent regions where K > N at $p < .05$, corrected for multiple comparisons and are displayed on an average anatomical scan of all subjects. Bar graphs represent the difference in beta values for judgments of familiarity and novelty. * $p < .05$.

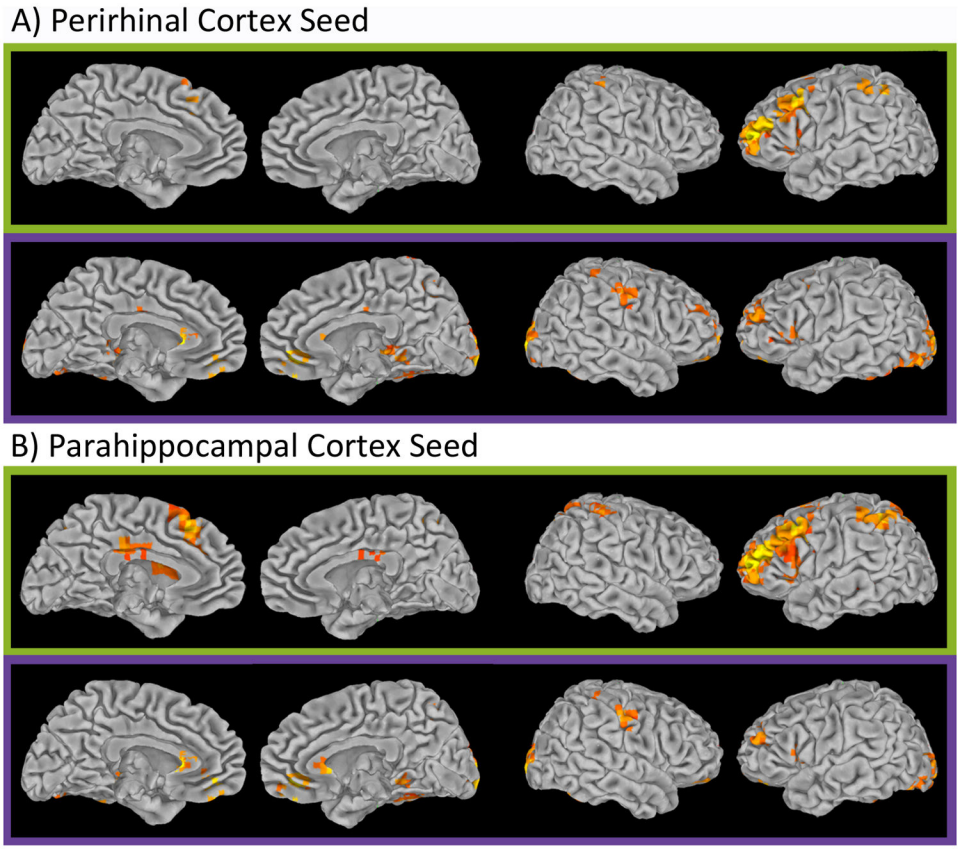

Figure 4. Whole-brain functional-correlations with RSE_K and MPE_K judgments

Displayed are regions correlated with A) perirhinal cortex and B) parahippocampal cortex during RSE_K judgments (green) and MPE_K judgments (purple). Functional-correlations are with the right perirhinal and parahippocampal clusters displayed in Figure 3.

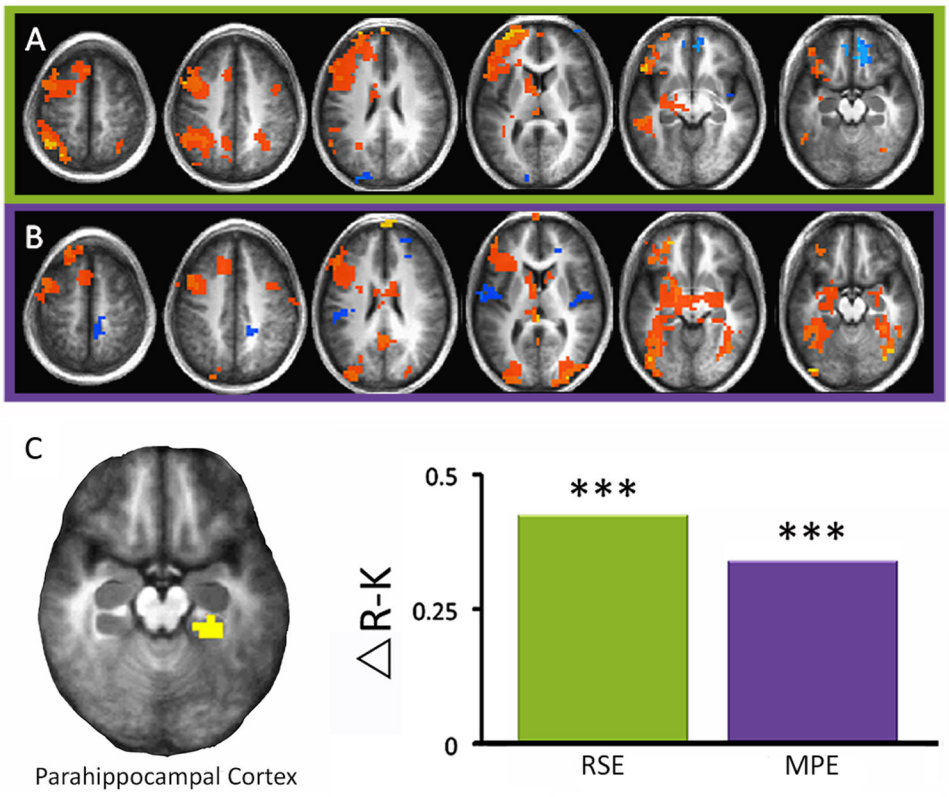

Figure 5. Regions of activation for recent-single-exposure-based- and multiple-previous-exposures-based recollection

Clusters represent regions where A) RSE_R responses are significantly different from RSE_K responses and B) MPE_R responses are significantly different from MPE_K responses. Warm colors represent regions where RSE_R/MPE_R > RSE_K/MPE_K and cool colors represent regions where RSEK/MPE_K > RSE_R/MPE_R. Clusters are significant at $p < .05$, corrected for multiple comparisons and are displayed on an average anatomical scan of all subjects. C) Right posterior parahippocampus showed a difference in activation between recollection and familiarity collapsed across RSE and MPE retrieval conditions. Cluster represents a region where R > K at $p < .001$, corrected for multiple comparisons and is displayed on an average anatomical scan of all subjects. Bar graphs represent the difference in beta values for judgments of recollection and familiarity. Each bar is different from zero, but the two bars are not different from each other. Beta values were extracted from the voxels in this cluster and averaged across subjects for RSE (green) and MPE (purple) memory retrieval conditions.

Table 1

Behavioral responses to famous faces and foils from Study 1

	Famous			Foil	
	R	***K***	***N***	***CR* (*N*)**	***FA***
Mean ± SEM	49 ± 3%	14 ± 2%	36 ± 3%	92 ± 2%	10 ± 1%
Total Count	2588	739	1898	1284	108

Percent and raw count of responses that received an R (Remember), K (Know), or N (New) response to famous faces. Also included are responses to non-famous foils that received a correct rejection (CR) or false alarm (FA).

Table 2

Behavioral responses to studied/famous faces and foils from Study 2

		R	***K***	***Miss* (*N*)**	***CR* (*N*)**	***FA***
RSE (354 trials)	Mean	59 ± 9	91 ± 8	97 ± 8	60 ± 4	R: 9 ± 2 K: 30 ± 3
	RT	1417 ± 54	1647 ± 39	1530 ± 68	1517 ± 57	1509 ± 77
MPE (300 trials)	Mean	83 ± 9	77 ± 10	--	117 ± 6	R: 2 ± 1 K: 12 ± 2
	RT	1318 ± 61	1625 ± 41	--	1534 ± 68	1639 ± 72

Mean number of R (Remember) and K (Know) hit trials (± SEM) for studied (RSE) or famous (MPE) faces. Mean number of N (New) miss trials (± SEM) to studied RSE faces. Also included are foil unstudied or non-famous faces that were either a false alarm (FA) or a correct rejection (CR). Reaction time (RT) for each response type is in milliseconds ± SEM (standard error of the mean).

Table 3

Regions more active during familiarity than during novelty judgments

	Volume	*x*	*y*	*z*	*t*
A) Whole Brain RPE_K-RPE_N					
L. DLPFC (BA 9)	11712	-49	16	25	2.89
L. Mid Frontal (BA 10)	10880	-36	53	13	3.35
L. Sup Frontal (BA 6)	5440	-27	4	66	3.02
L. Inf Parietal (BA 40)	5312	-42	-43	47	2.59
L. Mid Temporal (BA 22)	2304	-53	-35	-1	2.65
R. Cerebellum	1344	20	-30	-35	2.98
R. Insula (BA 13)	1280	42	-4	2	-2.48
L. Post Cingulate (BA 29)	896	-11	-52	11	-2.47
R. Mid Frontal (BA 6)	832	35	17	55	-2.61
R. DLPFC (BA 9)	768	24	57	36	-2.90
MPE_K-MPE_N					
R. Paracentral Lobule (BA 31)	10176	2	-28	47	-2.48
L. Mid Occipital (BA 19)	6144	-37	-87	7	3.00
L. Caudate	2304	-24	-44	13	-2.38
L. Declive	2176	-39	-57	-19	2.72
R. Inf Parietal Lobule (BA 40)	1920	44	-34	27	-2.36
L. Ant Cingulate (BA 32)	1856	-2	43	11	-3.07
L. Pyramis	1664	-9	-82	-28	3.06
R. Mid Frontal (BA 46)	1024	44	42	27	2.64
L. Cingulate (BA 24)	1024	0	3	29	2.48
R. Mid Occipital (BA 19)	960	47	-74	3	2.95
L. Med Frontal (BA 6)	896	-12	5	62	2.43
R. Declive	832	7	-66	-15	2.52
L. Insula (BA 13)	832	-43	-8	2	-2.43
L. Precentral (BA 4)	832	-27	-26	53	-2.27
L. Declive	768	-9	-71	-22	2.59
R. Lingual (BA 18)	768	7	-91	-13	3.20

	Volume	*x*	*y*	*z*	*t*
B) Medial Temporal Lobe K-N					
R. Parahippocampus (BA 35)	576	25	-27	-17	-2.61
R. Perirhinal Cortex (BA 28)	320	22	-14	-24	3.09

A) Whole-brain regions showing a difference in activation between RSE_K/MPE_K judgments and RSE_N/MPE_N judgments (negative number in the *t* column indicates increased activity for N judgments relative to K judgments). B) Medial temporal lobe regions showing a difference in activation between K and N judgments, collapsed across RSE and MPE memory conditions (negative number in the *t* column indicates increased activity for N relative to K). BA = Brodmann Area, volume is in ml, *xyz* coordinates represent the center of mass of the cluster in Talairach space.

Table 4

Regions of correlated activity with perirhinal and parahippocampal seed regions during RSE_K and MPE_K

	Volume	*x*	*y*	*z*	*T*
RSE_K – PRC seed					
L. Mid Frontal (BA 10)	11840	-37	49	14	2.89
L. DLPFC (BA 9)	10688	-46	17	31	2.88
L. Inf Parietal Lobule (BA 40)	5504	-45	-44	47	2.87
L. Sup Frontal (BA 6)	4224	-17	17	54	2.86
R. Inf Parietal Lobule (BA 40)	2112	39	-33	49	2.85
MPE_K – PRC seed					
L. Fusiform (BA 19)	26496	-32	-79	-13	2.85
R. Cerebellum	18432	29	-65	-29	2.85
L. DLPFC (BA 9)	8640	-34	53	26	2.85
R. Mid Occipital (BA 18)	8576	21	-95	5	2.86
R. Ant Cingulate (BA 32)	6208	16	42	-7	2.86
L. Precentral (BA 44)	4288	-44	19	7	2.84
L. Ant Cingulate (BA 32)	3520	-14	45	-8	2.85
L. Caudate	2688	-13	26	13	2.86
R. Inf Parietal Lobule (BA 40)	2368	45	-41	54	2.84
R. Parahippocampus (BA 27)	2304	12	-33	-1	2.83
L. Mid Frontal (BA 6)	1984	-32	2	48	2.83
R. Precentral (BA 4)	1856	58	-14	37	2.83
L. Cerebellum	1664	-16	-51	-26	2.84
R. DLPFC (BA 9)	1536	26	63	26	2.85
L. Thalamus	1472	-10	-29	-1	2.83
R. Precuneus (BA 7)	1280	12	-62	47	2.83
R. Mid Frontal (BA 10)	1216	35	38	25	2.83
R. Sup Frontal (BA 6)	1024	19	17	65	2.85
R. Mid Frontal (BA 10)	960	33	58	8	2.84
L. Cingulate (BA 23)	896	-10	-12	32	2.83
RSE_K – PHC seed					

	Volume	*x*	*y*	*z*	*T*
L. DLPFC (BA 9)	50368	-35	30	28	2.9
L. Inf Parietal Lobule (BA 40)	14400	-38	-51	48	2.88
R. Inf Parietal Lobule (BA 40)	5184	38	-34	49	2.87
L. Caudate	2432	-12	7	12	2.85
R. Sup Parietal Lobule (BA 7)	2240	19	-61	55	2.86
L. Cingulate Gyrus (BA 23)	2176	-4	-22	29	2.85
L. Mid Temporal Gyrus	1856	-52	-38	-5	2.84
MPE_K – PHC seed					
R. Cerebellum	12352	29	-64	-28	2.85
L. Inf Occipital (BA 18)	10304	-29	-86	-9	2.84
R. Cuneus (BA 17)	7040	21	-95	5	2.86
R. Ant Cingulate (BA 32)	5440	16	42	-7	2.86
L. Sup Frontal (BA 10)	5056	-34	53	27	2.85
L. Ant Cingulate (BA 24)	3008	-10	26	9	2.86
L. Mid Frontal (BA 10)	2752	-11	43	-11	2.85
L. Cerebellum	2304	-46	-52	-31	2.84
R. Precentral (BA 4)	1664	58	-14	37	2.84
L. Cerebellum	1344	-16	-51	-26	2.84
R. Inf Parietal Lobule (BA 40)	1344	46	-39	55	2.84
L. Inf Frontal (BA 44)	1280	-45	17	12	2.83
R. Precuneus (BA 7)	1088	12	-63	46	2.83
R. Cerebellus	1024	52	-54	-25	2.84
L. Sup Frontal (BA 10)	960	-23	47	0	2.84
R. Culmen	832	13	-41	-6	2.84
L. Thalamus	768	-11	-26	-2	2.83

BA = Brodmann Area, volume is in ml, *xyz* coordinates represent the center of mass of the cluster in Talairach space.

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Table 5

Regions active during judgments of recollection

	Volume	*x*	*y*	*z*	*T*
A) Whole Brain RSE_R-RSE_K					
L. DLPFC (BA 9)	15360	-8	56	23	3.4
L. Mid Frontal (BA 6)	7296	-37	8	44	2.74
L. Sup Parietal Lobule (BA 7)	6912	-34	-62	47	3.19
R. Cerebellum	6208	31	-68	-24	3.39
L. Precuneus (BA 7)	3840	-8	-57	39	2.55
L. Inf Frontal (BA 46)	1536	-46	27	13	2.57
R. Med Frontal (BA 10)	1280	10	48	-7	-3.71
L. Lentiform	1152	-27	-5	-5	2.42
R. Cerebellum	1024	8	-48	-33	2.47
R. Inf Occipital (BA 18)	896	24	-89	-9	3.39
R. Mid Frontal (BA 10)	896	35	64	6	-3.51
R. Inf Parietal Lobule (BA 7)	896	33	-59	45	2.50
MPE_R-MPE_K					
L. Post Cingulate (BA 29)	21248	-15	-43	15	3.03
L. Sup Frontal (BA 8)	12608	-17	40	49	3.27
L. Precuneus (BA 19)	8000	-36	-72	40	2.80
L. Med Frontal (BA 10)	4160	-3	57	10	3.15
L. Inf Frontal (BA 13)	2304	-39	26	5	2.70
L. Cuneus (BA 17)	1920	-9	-83	6	2.62
R. Post Cingulate (BA 30)	1408	19	-49	10	2.39
L. Inf Parietal Lobule (BA 40)	1408	-52	-45	55	2.78
L. Inf Frontal (BA 9)	1344	-46	8	31	2.48
R. Lentiform Nucleus	1280	22	-13	-3	2.47
R. Mid Frontal (BA 10)	1216	30	38	21	-2.55
L. Lentiform Nucleus	1152	-24	4	-5	2.76
R. Cuneus (BA 19)	1088	22	-85	38	2.81
R. Precuneus (BA 7)	1024	10	-60	51	-2.55

	Volume	*x*	*y*	*z*	*T*
L. Inf Temporal (BA 20)	896	-40	-7	-40	2.68
L. Insula (BA 40)	832	-51	-21	17	-2.45
L. Precentral (BA 4)	832	-51	-7	50	2.60
L. Mid Occipital (BA 19)	768	-31	-92	20	2.72
B) Medial Temporal Lobe R-K					
R. Parahippocampus (BA 35)	256	23	-23	-19	3.16
R-N					
R. Perirhinal Cortex (BA 28)	448	22	-15	-22	2.96
L. Perirhinal Cortex (BA 36)	320	-26	-2	-33	-2.76
L. Hippocampus	320	-25	-19	-8	-2.38
L. Hippocampus	320	-28	-34	-2	-2.31

A) Whole-brain regions showing a difference in activation between RSE_R/MPE_R judgments and RSE_K/MPE_K judgments (negative number in the *t* column indicates increased activity for K judgments relative to R judgments). B) Medial temporal lobe regions showing a difference in activation between R judgments and K and N judgments, respectively (negative number in the *t* column indicates increased activity for K/N relative to R). BA = Brodmann Area, volume is in ml, *xyz* coordinates represent the center of mass of the cluster in Talairach space.