Ventromedial prefrontal cortex recruitment during memory recall varies non-linearly as a function of remoteness

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Short title: vmPFC and remote memory

Competing interests: The authors declare that no competing interests exist.

Abstract

Systems-level consolidation refers to the time-dependent reorganisation of memory traces in the neocortex, a process in which the ventromedial prefrontal cortex (vmPFC) has been implicated. Capturing the precise temporal evolution of this crucial process in humans has long proved elusive. Here, we used multivariate methods and a longitudinal functional MRI design to detect, with high granularity, the extent to which autobiographical memories of different ages were represented in vmPFC and how this changed over time. We observed an unexpected biphasic involvement of vmPFC during retrieval, rising and falling around an initial peak of 8-12 months, before re-engaging for older two and five year old memories. This pattern was replicated in two independent sets of memories. Moreover, it was further replicated in a follow-up study eight months later with the same participants and memories, where the individual memory representations had undergone their hypothesised strengthening or weakening over time. We conclude that the temporal engagement of vmPFC in memory retrieval seems to be non-linear, revealing a complex relationship between systems-level consolidation and prefrontal cortex recruitment that is unaccounted for by current theories.

Introduction

We possess a remarkable ability to retrieve, with ease, one single experience from a lifetime of memories. How these individual autobiographical memories are represented in the brain over time is a central question of memory neuroscience which remains unanswered.

Consolidation takes place on two levels which differ on both a spatial and temporal scale. On a cellular level, the stabilisation of new memory traces through modification of synaptic connectivity takes only a few hours (1), and is heavily dependent upon the hippocampus (2-5). On a much longer timescale, the neocortex integrates new memories, a form of consolidation termed “systems-level” (6). The precise timeframe of this process is unknown. A related long-standing debate which has contributed to this uncertainty is whether or not the hippocampus ever relinquishes its role in autobiographical memory retrieval. One theory asserts that the hippocampus is not involved in the retrieval of memories after they have become fully consolidated to the neocortex (7). Alternate views maintain that vivid, detailed autobiographical memories retain a permanent reliance on the hippocampus for their expression (8-12).

An undisputed feature of systems-level consolidation, however, is the strengthening of neural representations in the neocortex over time. Clarity on the time course of systems-level consolidation is therefore more likely to be achieved through scrutiny of its neocortical targets. While theoretical accounts often fail to specify these cortical locations, animal experiments have consistently implicated the medial prefrontal cortex. While this region has been associated with the formation (13, 14) and recall of recently acquired memories (15-17), in rodents it appears to be disproportionately involved in the retrieval of memories learned weeks previously (18-26). The dependency on this region, which emerges over time, is facilitated by post-learning activation (27) and structural changes (28-30).

The evolutionary expansion of prefrontal cortex in humans makes it challenging to make direct anatomical comparisons with rodents, but the ventromedial prefrontal cortex (vmPFC) has been proposed as a homologous site of long-term memory consolidation (31). It may appear

surprising that an association between impaired autobiographical memory retrieval and vmPFC lesions has only recently started to be more precisely characterised (32). However, there are a number of confounding factors in this field (33) - non-selectivity of vmPFC lesions, methodological differences in memory elicitation, and the tendency of patients with vmPFC damage to recollect events which have never occurred, a phenomenon known as confabulation (34).

Numerous functional MRI (fMRI) studies of vmPFC activity during autobiographical memory recall have been conducted, but with inconclusive results. Delay-dependent increases in retrieval-related activity have been observed in some studies (35, 36) but not others (37-39). Autobiographical memory in particular induces robust vmPFC engagement (40) but it is unclear whether this activity increases (41), decreases (42), or remains constant in accordance with memory remoteness (43-52).

A powerful method of fMRI analysis which can help to bridge the empirical gap between the human and animal literatures is multi-voxel pattern analysis (MVPA), due to its increased sensitivity to specific neural representations (53). Using this approach, Bonnici et al. (54) demonstrated that remote 10 year old autobiographical memories were more detectable in the vmPFC than recent two week old autobiographical memories, consistent with its proposed role as a long-term consolidation site. This difference was not apparent in other cortical areas, nor did it emerge from a standard univariate analysis. A follow up study two years later with the same participants and memories, demonstrated that the original two week old memories were now as detectable in the vmPFC as the remote memories (55). This suggested the recent memories had been fully consolidated in the vmPFC after just two years, and perhaps even sooner.

The identification of this two year time window represented an opportunity to resolve the time course of systems-level consolidation with high precision. To do so, we sampled memories from four month intervals spanning a two year period, and compared their neural representations using fMRI. Differences in the strength of memory representations across time periods were interpreted as delay-dependent engagement of the vmPFC. To verify observed time-sensitive differences, we

99 followed the neural evolution of individual memories in a follow up study with the same participants
100 and memories eight months later. The selection of numerous time-points characterised the
101 consolidation process with unprecedented temporal resolution, while the longitudinal design was
102 not only an opportunity to replicate these findings, but to observe systems-level consolidation in
103 action.

104 Systems-level consolidation is generally assumed to be an incremental process, therefore,
105 we considered a gradual linear trajectory of vmPFC recruitment as the most likely outcome. The
106 alternative hypothesis was a rapid strengthening of vmPFC neural representations in the first few
107 months after an event. The results conformed to neither scenario, and revealed an unexpected
108 temporal relationship - a transient recruitment of the vmPFC beginning in the months following the
109 initial experience, followed by an enduring signature of more remote memories. The second,
110 longitudinal, experiment confirmed this finding. This is the first demonstration, to our knowledge, of
111 such a temporal dissociation in vmPFC-mediated memory retrieval.

112

113 Results

114 Experiment 1

115 One week prior to the fMRI scan, with the assistance of personal photographs, participants (n=30)
116 verbally recalled and rated the characteristics of autobiographical memories from eight time
117 periods: memories that were 0.5 months old (0.5M, i.e., two week old memories), 4M, 8M, 12M,
118 16M, 20M, 24M and also 60M old – these latter memories serving as a definitive benchmark for
119 remote (5 year old) memories (see Materials and methods, Fig 1A). Two memories from each time
120 period which were sufficiently vivid, detailed, specific and unique in time and place were chosen for
121 subsequent recall in the scanner. This meant that there were two full sets of memories. Participants
122 created a short phrase pertaining to each autobiographical memory, which was paired with the
123 photograph to facilitate recall during the subsequent fMRI scan.

124

Comparable subjective recall phenomenology across memories

While all memories satisfied the criteria of being vivid and detailed, and the ratings were high (Fig 1; see means and SDs in Table S1A), subjective vividness nevertheless varied as a function of memory age ($F_{(7,203)}$ = 3.45, p = 0.002), with the most recent, 0.5M old, memories rated higher than 12M (t_{29} = 4.08, p = 0.009), 20M (t_{29} = 3.88, p = 0.016), 24M (t_{29} = 4.18, p = 0.007) and 60M old memories (t_{29} = 3.45, p = 0.049, Fig 1B). Subjective ratings of detail also differed across time-points ($F_{(7,203)}$ = 5.74, p < 0.001), once again the most recent 0.5M old memories were rated higher than 4M (t_{29} = 4.45, p = 0.003), 8M (t_{29} = 3.97, p = 0.012), 12M (t_{29} = 5.00, p < 0.001), 16M (t_{29} = 4.96, p < 0.001), 20M (t_{29} = 5.37, p < 0.001), 24M (t_{29} = 4.51, p = 0.003) and 60M old memories (t_{29} = 3.98, p = 0.012, Fig 1C). The expenditure of effort during recall also varied according to remoteness of memories ($F_{(7,203)}$ = 5.79, p < 0.001), with 0.5M old memories being easier to recollect than 12M (t_{29} = -5.29, p < 0.001), 16M (t_{29} = -3.90, p = 0.015), 20M (t_{29} = -3.67, p = 0.027) and 60M old memories (t_{29} = -4.55, p = 0.003, Fig 1D). No significant difference was observed across time periods from 4M to 60M on any of these characteristics (all p > 0.05), nor did memories differ in their personal significance ($F_{(7,203)}$ = 1.66, p = 0.120, Fig 1E) or emotional valence ($F_{(7,203)}$ = 1.51, p = 0.166, Fig 1F) as a function of age.

In addition to these main ratings of interest, no difference was reported in the extent to which memories were recalled as active or static ($F_{(7,203)}$ = 1.36, p = 0.224), or from a first or third person perspective ($F_{(3.69,107.02)}$ = 1.09, p = 0.365) across time periods. The reported frequency at which memories were recalled since the original event (rated on a five point scale from “never” to “very frequently”), differed as a function of time ($F_{(5.11,148.04)}$ = 4.36, p < 0.001), with the most recent 0.5M old memories thought about more frequently than 12M (t_{29} = 4.37 p = 0.004), 16M (t_{29} = 3.47, p = 0.046) and 24M (t_{29} = 3.71, p = 0.024) old memories.

Overall, therefore, memories were generally well matched on subjective phenomenological ratings, satisfied the criteria of high quality of memory recall, with only small differences observed for the most recent 0.5M old memories compared to the other autobiographical memories, as might be expected.

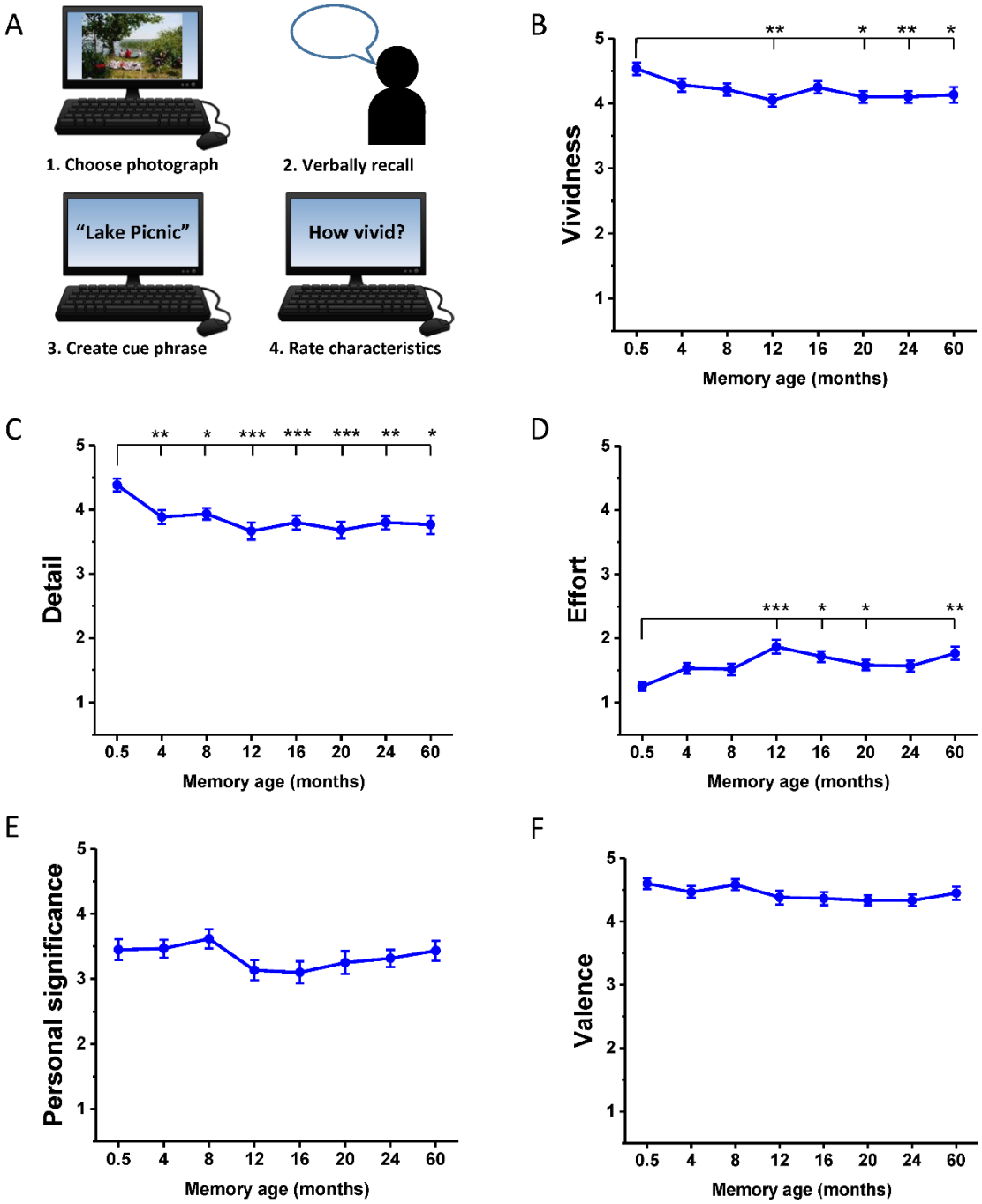


Fig 1. Memory harvesting and subjective ratings. (A) Schematic of the interview where the autobiographical memories were harvested. Participants recalled a memory which was cued by a personal photograph, chose a phrase to help remind them of this memory during the subsequent scanner task, and rated its characteristics. (B-F) Subjective ratings (means +/- 1SEM; see also Table S1A) of memory characteristics at each time period for Experiment 1, averaged across the two sets of memories. Ratings were on a scale of 1 to 5, where 1 was low and 5 was high. For emotional valence: 1-2 = negative, 3 = neutral, 4-5 = positive. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Consistent level of details recalled across memories

To complement the subjective ratings of memory characteristics with a more objective assessment of their content, transcripts of participants' memory interviews were scored using the Autobiographical Interview protocol [(56); Materials and methods]. In total for this first experiment, 10,187 details were scored. The mean (SD) number of internal details (bound to the specific 'episodic' spatiotemporal context of the event) and external details (arising from a general 'semantic' knowledge or references to unrelated events) are shown in Table S1B (see also Fig 2). They were then compared across time periods. In contrast to the subjective ratings of memory detail, there was no difference in the number of details recalled across memories from different time periods ($F_{(4.54,131.66)} = 1.92$, $p = 0.101$). As expected, the number of internal and external details differed ($F_{(1,29)} = 206.03$, $p < 0.001$), with more internal details recalled for every time period (all $p < 0.001$). No interaction between time period and type of detail was observed ($F_{(7,203)} = 1.87$, $p = 0.077$). While a more targeted contrast of the most recent (0.5M) and most remote (60M) memories did reveal that 0.5M events contained more internal details ($t(29) = 3.40$, $p = 0.002$), this is consistent with participants' subjective ratings, and implies that any observed strengthening of neural representations over time could not be attributable to greater detail at remote time-points. The number of external details recalled was remarkably consistent across all time periods, emphasising the episodic nature of recalled events irrespective of remoteness. Inter-rater reliabilities for the scoring (see Materials and methods) were high for both internal (ICC = 0.94) and external (ICC = 0.81) details.

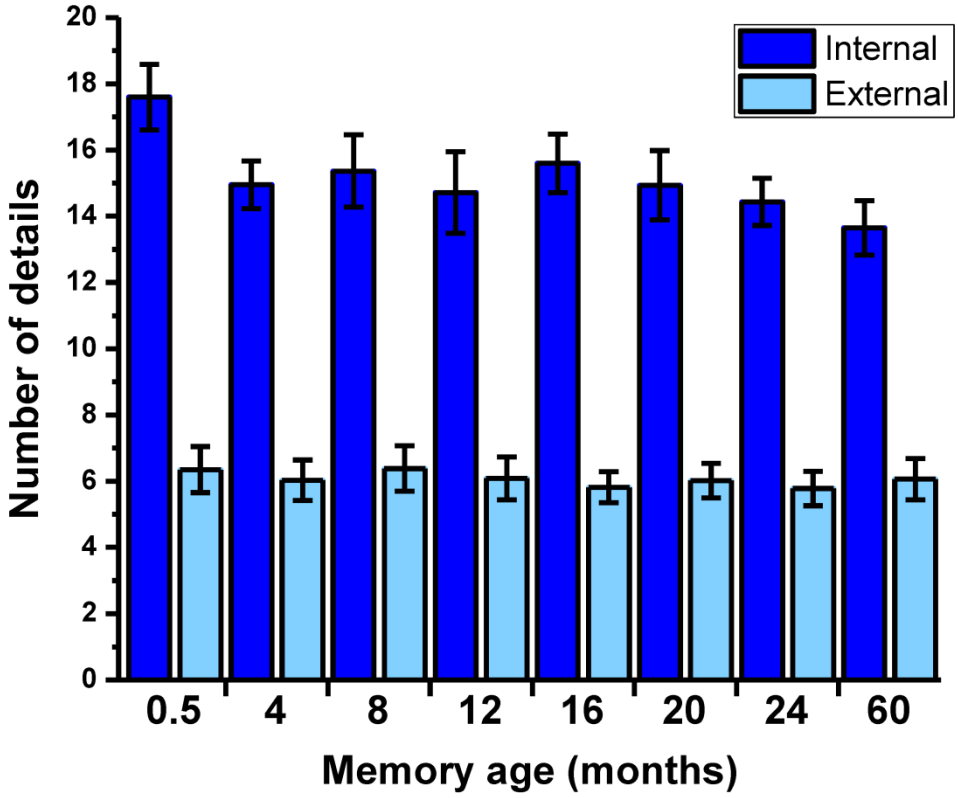


Fig 2. Objective scores for memory details. The mean +/- 1SEM (see also Table S1B) number of internal and external details at each time period, averaged across the two sets of autobiographical memories.

vmPFC engagement during recall is temporally biphasic

vmPFC was delineated as the ventral medial surface of the frontal lobe and the medial portion of the orbital frontal cortex (57). This comprises areas implicated in memory consolidation (31, 54, 55), namely Brodmann Areas 14, 25, ventral parts of 24 and 32, the caudal part of 10 and the medial part of BA 11 (Fig 3A, and Materials and methods).

On each trial, the photograph and associated pre-selected cue phrase relating to each event were displayed on a screen for 3 seconds. Following removal of this cue, participants then closed their eyes and recalled the memory. After 12 seconds, the black screen flashed white twice, to cue the participant to open their eyes. The participant was then asked to rate how vivid the memory recall had been using a five-key button box, on a scale of 1-5, where 1 was not vivid at all, and 5 was highly vivid (Fig 3B).

We used Representational Similarity Analysis (RSA) to quantify the extent to which the strength of memory representations in the vmPFC differed as a function of memory age. This was achieved by contrasting the similarity of neural patterns when recalling the same memory with their similarity to other memories to yield a "neural representation" score for each memory (see Materials and methods, Fig 3C). As there were two memories recalled per time period, the neural representation scores were averaged to produce one value for that time period.

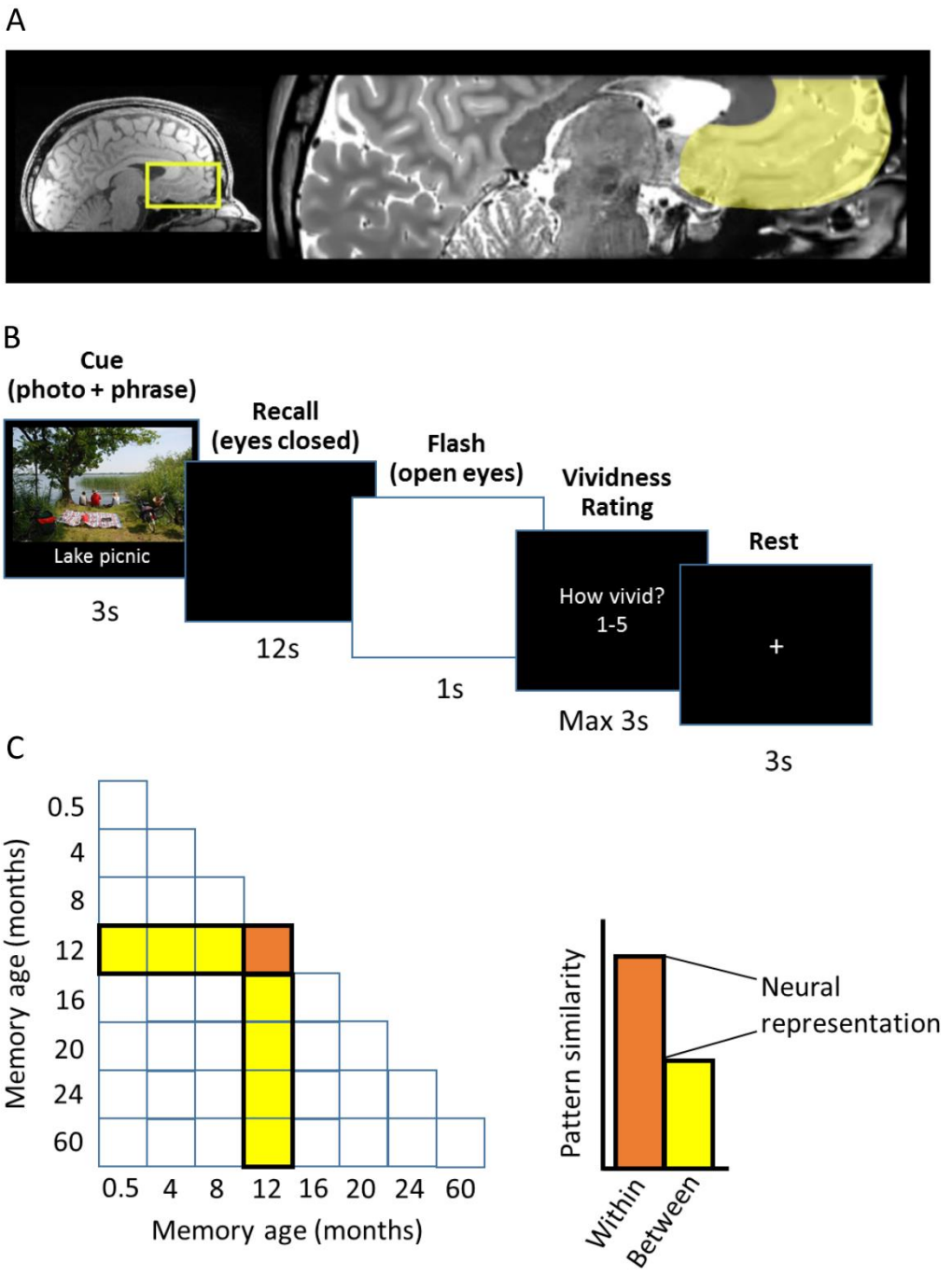


Fig 3. Experimental details. (A) The vmPFC is highlighted on an example participant's structural MRI scan. (B) The timeline of an example trial from the scanning task. (C) Graphical illustration of the neural representation score calculation using RSA. The neural pattern similarity across trials recalling the same memory (orange) minus the mean pattern similarity between that memory and other memories (yellow) generates a "neural representation" score. A score significantly higher than zero indicates a neural pattern distinct to that memory is present in the vmPFC.

We anticipated an increase in the strength of memory representations at some point between 0.5M and 24M, in line with the results of Bonnici and Maguire (55). This is what we observed, where the most recent 0.5M memories were undetectable (t_{29} = 0.72, p = 0.477) in vmPFC, in contrast to the distinct neural signatures observed for 4M (t_{29} = 2.85, p = 0.008), 8M (t_{29} = 3.09, p = 0.004) and 12M (t_{29} = 3.66, p < 0.001) old memories (Fig 4A). These changes in the strength of memory representations were significant across time periods ($F_{(7,203)}$ = 2.22, p = 0.034), with an observed increase in vmPFC recruitment from 0.5M to 8M (t_{29} = 2.07, p = 0.048) and 12M (t_{29} = -2.20, p = 0.036).

However, what was observed for the following two time periods was unexpected – an apparent disengagement of the vmPFC over the next eight months as we observed weak detectability of memory representations in vmPFC for 16M (t_{29} = 1.85, p = 0.074) and 20M (t_{29} = 1.03, p = 0.310) old memories. Neither 16M (t_{29} = -1.06, p = 0.298) nor 20M memories (t_{29} = -0.40, p = 0.691) were more strongly represented than the recent 0.5M old memories. In contrast, the more remote 24M (t_{29} = 4.34, p < 0.001) and 60M (t_{29} = 3.55, p = 0.001) memories were detectable in the vmPFC, and significantly more so than the most recent memories (24M vs 0.5M, t_{29} = -2.93, p = 0.007; 60M vs 0.5M, t_{29} = -2.54, p = 0.017) as well as the more temporally proximal 20M old memories (24M vs 20M, t_{29} = -2.50, p = 0.018; 60M vs 20M, t_{29} = -2.32, p = 0.028).

The experimental design afforded us the opportunity to verify this biphasic pattern. As we sampled two memories per time-point, this time-dependent pattern should be evident in both sets of memories. As shown in Fig 4B, the two sets of memories followed a similar time-course of changes in representation within vmPFC. This is a compelling replication, given that the two memories from each time-period were unrelated in content as a prerequisite for selection, recalled in separate sessions in the scanner and analysed independently from each other.

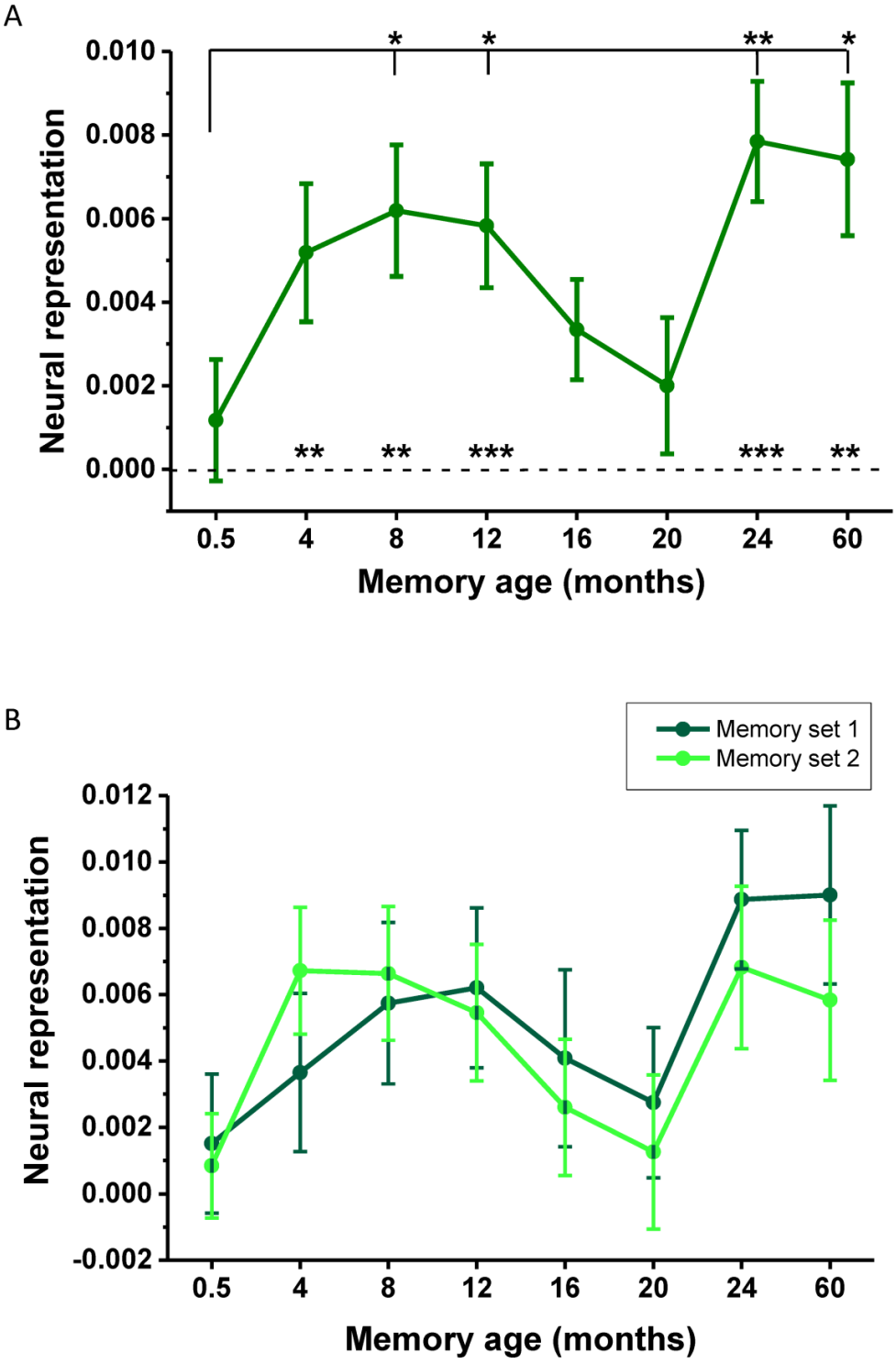


Fig 4. fMRI results of Experiment 1. (A) Mean +/- 1SEM neural representation scores at each time-point averaged across the two sets of memories. Asterisks above the dotted line indicate detectability of memories in vmPFC at each time-point. Asterisks above the solid line indicate significant increases in memory representations compared to the most recent (0.5M old) memories. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. See Fig S1 for the underlying representational similarity matrix and Fig S2 for a boxplot distribution of these data. (B) Neural representation scores at each time-point plotted separately for the two sets of autobiographical memories.

The availability of two memories at each time-point also permitted the use of an alternative approach to calculating neural representation scores. Instead of using the similarity to memories from other time-points as a baseline, we could also assess if memories were similar to their temporally matched counterpart in the other set. As can be seen in Fig S3, the biphasic pattern is preserved even when just using one identically aged memory as a baseline. In other words, the distinguishable patterns are specific to each individual memory rather than attributable to general retrieval processes associated with any memory of the same age.

The observed temporal relationship is unique to vmPFC

Our main focus was the vmPFC, given previous work highlighting specifically this region's role in representing autobiographical memories over time (54, 55). We also scanned within a partial volume (to attain high spatial resolution with a reasonable TR), so were constrained in what other brain areas were available for testing (see Materials and methods). Nevertheless, we examined the same brain areas as Bonnici et al. (54), Bonnici and Maguire (55), and in no case did we observe a significant change in memory detectability across time periods - entorhinal/perirhinal cortex ($F_{(7,203)}$ = 1.55, p = 0.154), hippocampus ($F_{(7,203)}$ = 0.98, p = 0.445), posterior parahippocampal cortex ($F_{(7,203)}$ = 1.41 p = 0.202), retrosplenial cortex ($F_{(7,203)}$ = 0.74, p = 0.641), temporal pole ($F_{(7,203)}$ = 1.78, p = 0.093) or lateral temporal cortex ($F_{(4.86,141.03)}$ = 0.68, p = 0.636). Of note, memories which were undetectable in the vmPFC were still represented in other regions at these time points (Table S2).

Following scanning, participants completed three additional ratings. They were asked to indicate the extent to which the memories were changed by the 6 repetitions during scanning on a scale ranging from 1 (not at all) to 5 (completely). They reported that the memories were not changed very much by repetition (mean: 2.61, SD: 0.74). They were also asked how often during scanning they thought about the memory interview one week previous on a scale of 1 (not at all) to 5 (completely), with participants indicating they rarely thought about the interview (mean: 2.29, SD: 1.01). Finally, participants were asked the extent to which the recall of memories from each time

period unfolded in a consistent manner over the course of the session. A difference was observed ($F_{(7,203)}$ = 2.78, p = 0.009), with the most recent 0.5M old memories being rated as more consistently recalled than the most remote 60M memories (t_{29} = 3.97, p = 0.012).

In addition to the ROI-based approach, a searchlight analysis was also conducted in MNI group normalised space to localise areas within the vmPFC where memories displayed high detectability across participants (see Materials and methods). We discovered a significant bilateral cluster of 652 voxels (Fig S4A), and subsequently used RSA to quantify the strength of neural representations at each time-point within this area (Fig S4B). The results were highly similar to the whole-ROI analysis in native space, suggesting the main result may be driven by more spatially confined activity within the vmPFC. However a searchlight approach is sub-optimal to answer the current research question, as it requires an *a priori* model RSM against which to compare the neural patterns at each searchlight sphere, whereas the ROI approach makes no such assumptions.

We also conducted a standard mass-univariate analysis on the whole volume with memory remoteness as a parametric regressor, and this did not reveal any significant results, consistent with the findings of Bonnici et al. (54). In a similar parametric analysis, we did not find evidence of the modulation of univariate activity by in-scanner vividness ratings as might be suggested by the findings of Sheldon and Levine (59), however, all memories chosen for the current study were highly vivid in nature.

Rationale and predictions for Experiment 2

The biphasic pattern we observed in the fMRI data did not manifest itself in the subjective or objective behavioural data. In fact, the only difference in those data was higher ratings for the most recent 0.5M old memories. However, these were paradoxically the most weakly represented memories in the vmPFC, meaning the neural patterns were not driven by memory quality. The objective scoring of the memories confirmed comparable levels of detail provided for all memories, without any significant drop in episodic detail or increase in the amount of semantic information

provided as a function of time. Therefore, the amount or nature of the memory details were not contributing factors.

Nevertheless, to verify that the results genuinely represented the neural correlates of memory purely as a function of age, one would need to study the effects of the passage of time on the individual neural representations. Therefore we invited the participants to revisit eight months later to recall the same memories again both overtly and during scanning; 16 of the participants agreed to return. In order to generate specific predictions for the neural representations during Experiment 2, we took the actual data for the 16 subjects from Experiment 1 who returned eight months later (Fig 5 green line, where the biphasic pattern is still clearly evident), and shifted it forwards by two time-points to simulate the expected pattern eight months later (Fig 5 dark grey line). Note that for the 28M and 32M time periods in Experiment 2 we assumed they would have the same level of detectability as 24M old memories given the absence of data relating to these time periods from Experiment 1. We further assumed the neural representations between 60M and 68M would be unchanged.

A significant difference between original and predicted neural representation scores from any time period would generate a hypothesised change. Accordingly, 0.5M old memories were hypothesised to be more detectable eight months later (t_{15} = -2.85, p = 0.012), while the original 4M (t_{15} = -0.40, p = 0.695) and 8M (t_{15} = 0.80, p = 0.436) old memories should remain unchanged. Twelve month old memories from Experiment 1 should decrease in detectability (t_{15} = 2.61, p = 0.020), whereas 16M old memories should not differ significantly in their representations at 24M (t_{15} = -1.53, p = 0.146). Original 20M old memories should be better represented at 28M (t_{15} = -4.15, p < 0.001). Finally, the original 24 and 60 month memories were not assumed to change over time in the strength of neural representations. Overall, therefore, while an increase in detectability in vmPFC of the 0.5M memories eight months later is an obvious prediction, the unexpected predictions generated by the Experiment 1 data were a decrease in detectability of the previously well-

represented 12M old memories and an increase in the detectability of the previously undetectable 20M old memories, with no concomitant changes in the behavioural data.

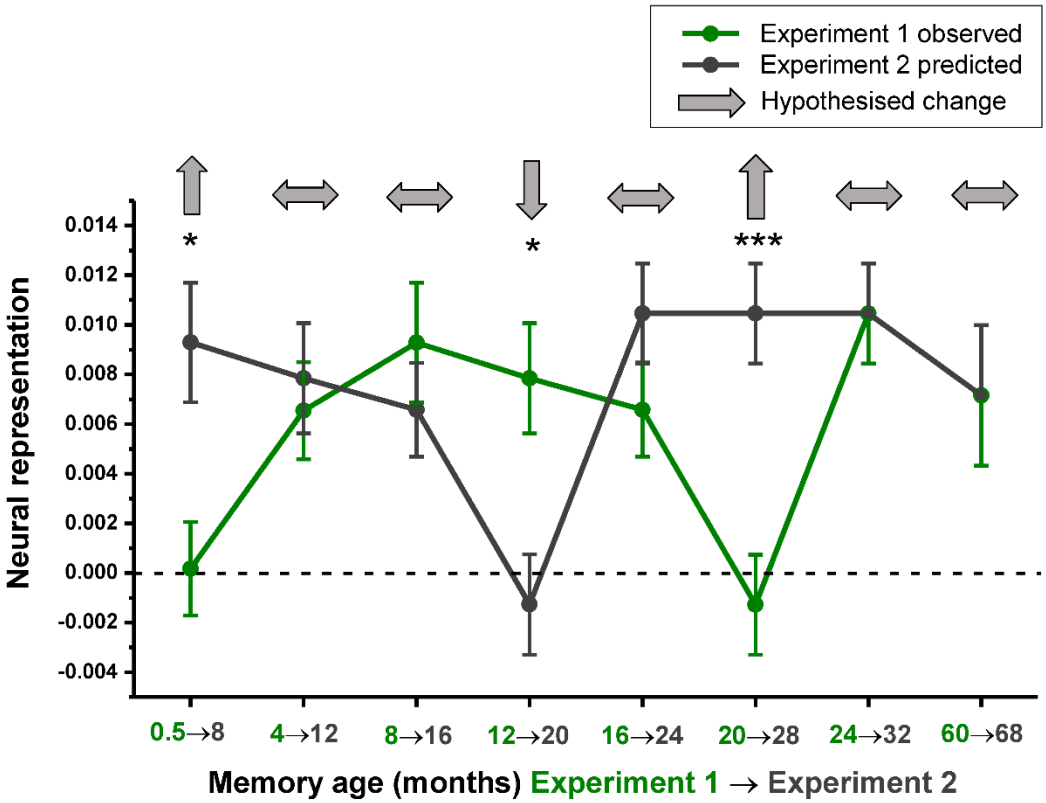


Fig 5. Predicted fMRI changes eight months later in Experiment 2. Predicted mean +/- 1SEM changes in the neural representations of individual autobiographical memories after eight months (dark grey line), based on shifting the original observed data forward by two time-points for the 16 participants from Experiment 1 (green line) who returned for Experiment 2. Light grey arrows indicate the hypotheses. * $p < 0.05$, ** $p < 0.01$.

Experiment 2 (eight months later)

One week prior to the fMRI scan, with the assistance of the personal photographs and previously chosen phrases which were used as cues in Experiment 1, the participants verbally recalled and rated the characteristics of their autobiographical memories just as they had done eight months previously (see Materials and methods and Fig 6A).

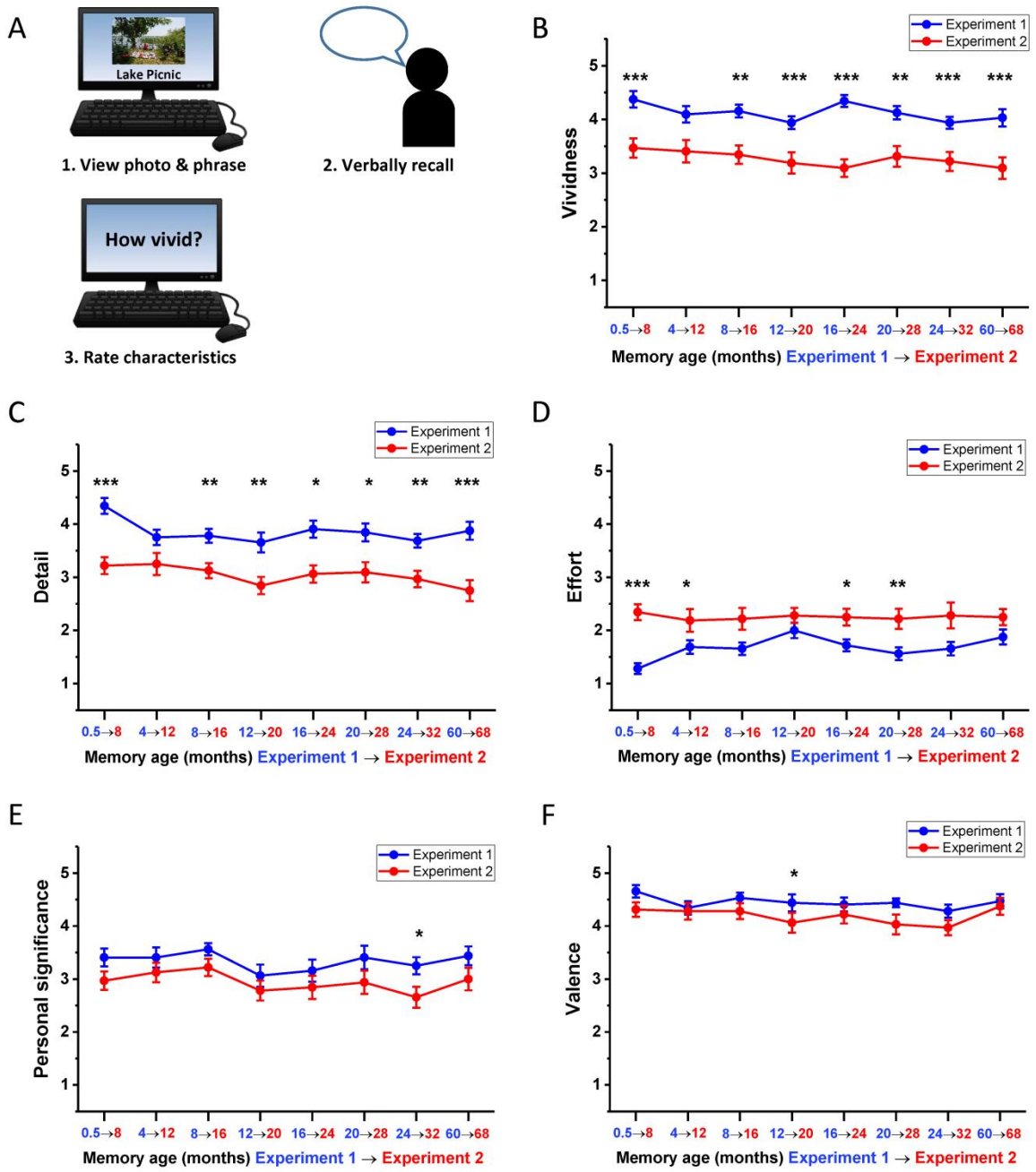
Subjective ratings of phenomenology remain equivalent across memories

Means and SDs are provided in Table S3A. Autobiographical memories recalled during Experiment 2 did not differ across time periods on vividness ($F_{(7,105)}$ = 0.83, p = 0.564), detail ($F_{(7,105)}$ = 1.30, p = 0.257), effort ($F_{(7,105)}$ = 0.11, p = 0.998), personal significance ($F_{(7,105)}$ = 1.49, p = 0.180), valence ($F_{(7,105)}$ = 1.06, p = 0.397), viewpoint ($F_{(3.42,51.22)}$ = 1.24, p = 0.31) or motion ($F_{(3.95,59.32)}$ = 1.43, p = 0.237). When asked how frequently they had thought about the autobiographical memories in the eight months between experiments (rated on a five point scale from "never" to "very frequently"), participants reported some change across time periods ($F_{(7,105)}$ = 3.04, p = 0.006). However, the only significant difference between time periods was a lower recall frequency for now 32M old memories compared to the now 12M (t_{15} = 3.87, p = 0.042). Given the range of responses to this question across conditions (1.50-2.03), clearly participants had not given the memories much thought in the intervening eight months. Therefore, all memories recalled in Experiment 2 were extremely well matched in terms of their phenomenology, which reflects the consistency observed in ratings from eight months onwards in Experiment 1.

There were, however, differences in the absolute values of subjective ratings between the two experiments. There was a decrease in the reported vividness of all memories from Experiment 1 to Experiment 2 ($F_{(1,15)}$ = 88.45, p < 0.001), from 0.5M to when they were 8M old (t_{15} = 6.21, p < 0.001), 8M to 16M (t_{15} = 4.21, p = 0.006), 12M to 20M (t_{15} = 5.48, p < 0.001), 16M to 24M (t_{15} = 7.07, p < 0.001), 20M to 28M (t_{15} = 4.10, p = 0.008), 24M to 32M (t_{15} = 5.97, p < 0.001) and 60M to 68M (t_{15} = 5.33, p < 0.001; Fig 6B). A comparable change was observed in the subjective impression of memory detail recalled following the eight month interlude ($F_{(1,15)}$ = 126.81, p < 0.001), with a drop from 0.5M to 8M (t_{15} = 6.26, p < 0.001), 8M to 16M (t_{15} = 4.03, p = 0.009), 12M to 20M (t_{15} = 4.78, p = 0.002), 16M to 24M (t_{15} = 3.72, p = 0.016), 20M to 28M (t_{15} = 3.67, p = 0.018), 24M to 32M (t_{15} = 4.55, p < 0.003) and 60M to 68M (t_{15} = 9.67, p < 0.001; Fig 6C). Recalling memories eight months later was also perceived as more effortful ($F_{(1,15)}$ = 43.32, p < 0.001), from 0.5M to 8M (t_{15} = -7.81, p < 0.001), 4M to 12M (t_{15} = -3.30, p = 0.039), 16M to 24M (t_{15} = -1.95, p = 0.021), and 20M to 28M (t_{15} =

-4.03, p = 0.009; Fig 6D). The elapsed time between experiments also led to a reduction in the reported personal significance of memories ($F_{(1,15)}$ = 11.82, p = 0.004), from 24M to 32M (t_{15} = 3.58, p = 0.022; Fig 6E). Ratings of emotional valence also changed over the eight month period ($F_{(1,15)}$ = 9.78, p = 0.007), with a reported attenuation of the positivity of memories from 12M to 20M (t_{15} = 3.87, p = 0.012; Fig 6F). In addition to these main ratings, no difference was reported in the extent to which memories were recalled from a first or third person perspective ($F_{(1,15)}$ = 0.513, p = 0.485) over the eight month period. The extent to which memories were recalled as active or static was altered by the passage of time between experiments ($F_{(1,15)}$ = 11.01, p = 0.005), with the original 0.5M old memories becoming more static when 8M old (t_{15} = -3.42, p = 0.031).

Despite the observed changes in some subjective ratings from Experiment 1 to Experiment 2, they were unidirectional across all time periods. As such, if the pattern of hypothesised emergence and disappearance of neural representations in vmPFC were to be supported in Experiment 2, then it could not be accounted for by changes in subjective ratings. Additionally, although the changes in subjective ratings across time tend to suggest a comparable degradation in memory quality across all time periods, this may be misleading. The ratings overall were still high, and these absolute changes in values could be influenced by participants' expectations of their ability to recall memories after an extended period of time with high fidelity, because the objective scoring of memory detail revealed no such pattern, as we report in the next section.



396

397 **Fig 6. Memory recall and subjective ratings.** (A) Schematic of the interview where participants
398 recalled an autobiographical memory using their previously chosen photograph and cue phrase and
399 rated its characteristics. (B-F) Subjective ratings (means +/- 1SEM; see also Tables S1A, S3A) of
400 memory characteristics at each time period for Experiment 1 (blue line, n=16 participants) and how
401 the ratings of the same memories differed eight months later during Experiment 2 (red line, the
402 same n=16 participants) averaged across the two sets of memories in both cases. Ratings were on a
403 scale of 1 to 5, where 1 was low and 5 was high. For emotional valence: 1-2 = negative, 3 = neutral,
404 4-5 = positive. Asterisks indicate significant differences in memory ratings between Experiments 1
405 and 2; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.
406

407

A similar level of detail was recalled across experiments

As with Experiment 1, transcripts of participants' memory interviews during Experiment 2 were scored using the Autobiographical Interview protocol [(56); see Materials and methods)]. A total of 6,444 details were scored (see Table S3B for means, SD). There was a difference in the number of details recalled across different time periods in Experiment 2 ($F_{(7,105)} = 2.49$, $p = 0.021$). However, this difference was only observed for external details ($F_{(7,105)} = 3.25$, $p = 0.004$), with more provided for 28M memories than 12M memories ($t_{15} = -4.68$, $p = 0.008$). As with Experiment 1, the number of internal and external details differed ($F_{(1,15)} = 72.57$, $p < 0.001$), with more internal details recalled for every time period (all $p < 0.01$). No interaction between time period and type of detail was observed ($F_{(7,105)} = 0.87$, $p = 0.530$).

When the objective scores for both experiments were compared, no significant difference was observed in the overall number of details provided eight months later ($F_{(1,15)} = 1.93$, $p = 0.185$; Fig 7). Furthermore, there was no significant interaction between experiment and time period ($F_{(1,15)} = 1.97$, $p = 0.066$), indicating that the amount of details provided for memories from any particular time period in Experiment 1 were not affected by the passage of time. Finally, no interaction was observed between experiment and type of detail provided ($F_{(1,15)} = 2.27$, $p = 0.153$), showing that the ratio of internal to external details was preserved across experiments.

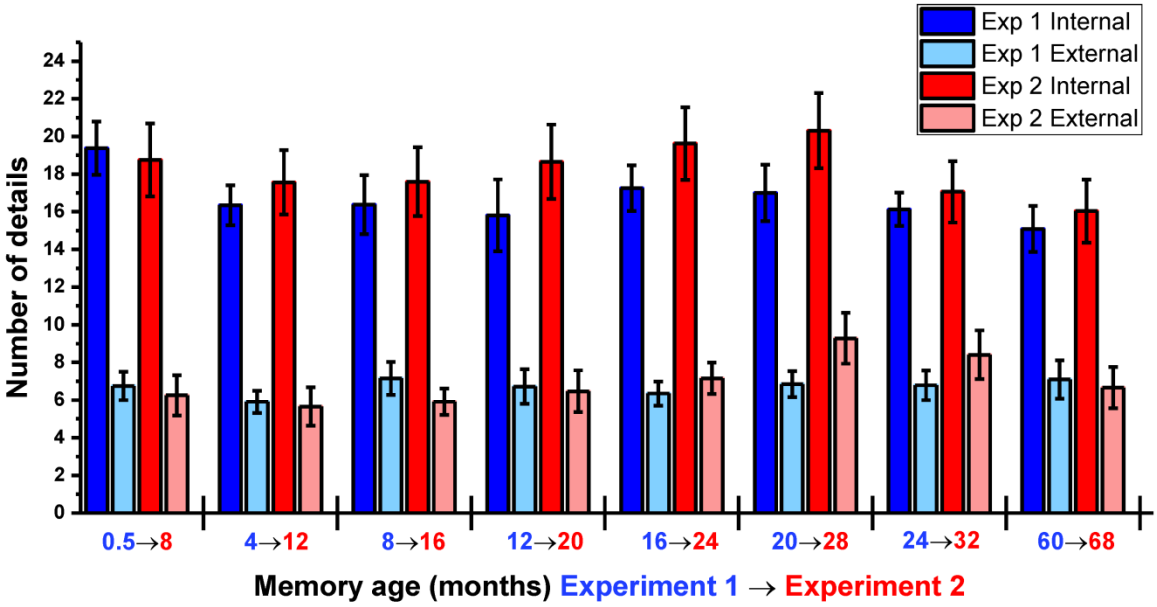


Fig 7. **Objective scores for memory details over time.** The mean +/- 1SEM (see also Tables S1B, S3B) number of internal and external details at each time period for Experiment 1 (blue bars, n=16 participants) and Experiment 2 (red bars, the same n=16 participants), averaged across the two sets of autobiographical memories.

vmPFC memory representations undergo the predicted time-dependent changes

Participants were scanned in an identical fashion as Experiment 1 (see Materials and methods and Fig 3B), and neural representation scores for memories from each time point were again calculated.

When comparing the neural representation scores of memories from the eight original time periods in Experiment 1 with those of the same memories eight months later during Experiment 2, a main effect for experiment ($F_{(1,15)}$ = 2.35, p = 0.146), or time period ($F_{(7,105)}$ = 1.18, p = 0.323), was not observed, however, an interaction between experiment and time period emerged ($F_{(7,105)}$ = 3.46, p = 0.002). Closer examination via our planned comparisons (see Fig 5 for a reminder of our predictions) revealed that seven out of the eight predictions made on the basis of the Experiment 1 findings were supported (Fig 8A). The original 0.5M old memories had increased in their representational strength in vmPFC eight months later (t_{15} = -1.84, p = 0.043), while the neural representation scores of the 4M and 8M old memories were essentially unchanged at 12M (t_{15} = 0.43, p = 0.677) and 16M (t_{15} = 1.22, p = 0.242) respectively. As expected, the original 12M old memories from Experiment 1 were eight

months later more poorly represented in vmPFC when 20M months old (t_{15} = 1.85, p = 0.042). The original 16M old memories were unchanged in their representational strength at 24M (t_{15} = 1.38, p = 0.187), while 20M old memories were significantly more detectable in vmPFC at 28M (t_{15} = -2.69, p = 0.008). The most remote 60M memories did not differ in their neural representation scores eight months later (t_{15} = 0.86, p = 0.402). In fact the only finding which was inconsistent with the predictions generated by Experiment 1 was a decrease in the representation of 24M old memories when they were 32M of age (t_{15} = -2.69, p = 0.009). However, this prediction was based on the assumption that memories do not undergo further dynamic shifts in neural representation between two and five years, which may not be the case, and we did not have 32M data from Experiment 1 to corroborate this finding.

For completeness, Fig 8B plots the neural representation scores for the two sets of memories in Experiment 2. As previously observed in Experiment 1, the two sets of memories displayed a similar time-course in terms of their neural representations, despite being recalled in separate scanning sessions, in a randomised order and analysed separately. As with Experiment 1, when examining other brain areas within the partial volume in Experiment 2, in no case did we find a significant difference in memory detectability across time periods.

Following scanning in Experiment 2, participants completed three additional ratings. They were asked to indicate the extent to which the memories were changed by the 6 repetitions during scanning on a scale ranging from 1 (not at all) to 5 (completely). As in Experiment 1, they reported that the memories were not changed very much by repetition (mean: 2.56, SD: 0.81). They were also asked how often they thought of the experience of recalling the memories in Experiment 1 while performing the scanning task in Experiment 2 on a scale of 1 (not at all) to 5 (during every memory). Participants indicated they rarely thought about Experiment 1 (mean: 1.75, SD: 0.93). Finally, the consistency of recall across time periods during the scanning session did not differ in Experiment 2 ($F_{(7,105)}$ = 0.59, p = 0.761) or between the two experiments ($F_{(1,15)}$ = 0.12, p = 0.733; see also Tables S1A and S3A).

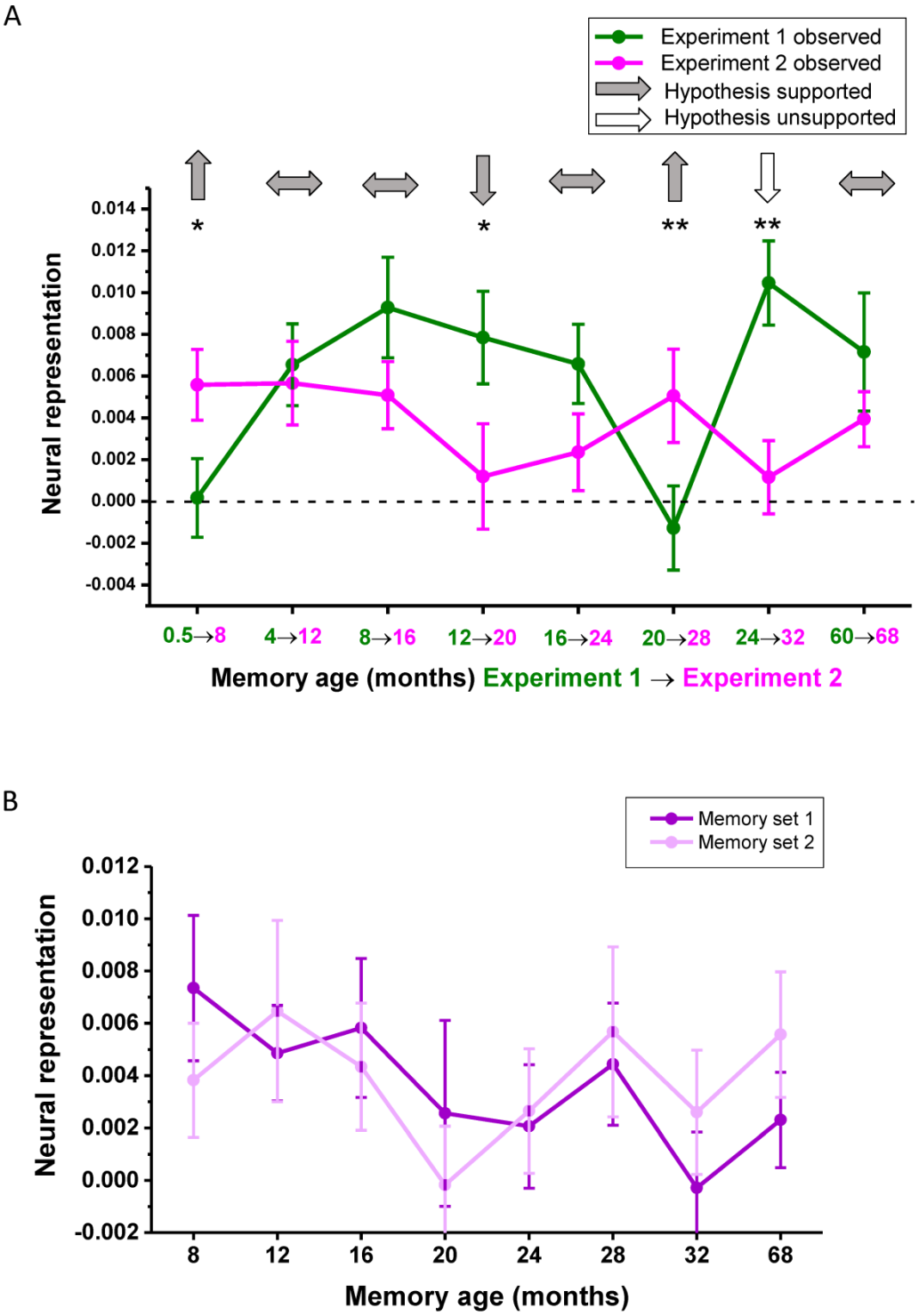


Fig 8. fMRI results of Experiment 2. (A) Mean +/- 1SEM neural representation scores at each time-point averaged across the two sets of memories for Experiment 2 (pink line, n=16 participants) compared to the same memories from eight months previously (green line, the same n=16 participants). Light grey and white arrows indicate supported and unsupported hypotheses respectively; * $p < 0.05$, ** $p < 0.01$. (B) Neural representation scores at each time-point for Experiment 2, plotted separately for the two sets of autobiographical memories.

Discussion

This study exploited the sensitivity of RSA to detect not only the extent to which memories of different ages were represented in the vmPFC, but how these representations changed over time. During Experiment 1, we observed detectability in vmPFC for memories at 4M to 12M of age, which was also evident at 24M and 60M. As expected, recent 0.5M old memories were poorly represented in vmPFC in comparison. Curiously, however, the same lack of detectability in vmPFC was observed for memories that were 16M to 20M old. This pattern persisted across separate sets of memories and was replicated in a follow-up study eight months later with the same participants and memories. Behavioural data failed to account for these time-dependent representational changes in either experiment, and other regions failed to show a significant change in memory representations over time. These findings are difficult to accommodate within existing theoretical frameworks of long-term memory consolidation (9, 12, 60-62), as neocortical recruitment is generally assumed to involve an ascending linear trajectory. Consolidation has been characterised as fluid and continuous (63), but the biphasic vmPFC engagement observed here suggests additional complexity in its temporal recruitment.

Processing of consolidated memories in the vmPFC

The observed weak representation of recent memories is consistent with the time-dependent nature of systems-level consolidation. Likewise, the progressive increase in vmPFC memory detectability from 4 to 12 months is indicative of memories being consolidated with the passage of time. However the subsequent weakening of memory representations from 12 to 20 months, and a re-engagement for more remote memories, suggests the vmPFC performs separate operations on consolidated representations, one medium and one longer-term.

The initial period of detectability (4-12M) represents a congested memory space (64) compared to remote life periods. Therefore interference from related memories may be an issue. The vmPFC is involved in the inhibition of irrelevant memories (65, 66), which may be the medium-

term cognitive process underlying the first phase of recruitment. Remote memories (>24M) are potentially less affected by interference, but may require more cognitive flexibility to retrieve due to sharing fewer features with the current spatiotemporal context. Such facilitation by the vmPFC may arise from the deployment of schema by this region (67) which refers to the abstraction of elements common to multiple experiences. Such schema could be used to rapidly and preconsciously confine memory search to a subset of temporally distant representations. This would likely become a necessary long-term strategy for all remote memories. Memories of an interim age may simply not rely as much on the vmPFC for successful retrieval due to minimal interference from related memories which have decayed, and sufficient temporal proximity to render schema-mediated retrieval unnecessary.

It is worth nothing, however, that the observed neural patterns are unlikely to reflect time-sensitive general processes which are independent of memory content. If that were the case, the two sets of memories would be indistinguishable from each other at every time period. However, neural patterns for individual memories were as distinct from their temporally matched counterparts as memories of different ages. The neural activation is therefore memory-specific, suggestive of a locally-stored representation at the very least, and more likely an additional associated executive process. The strengthening of neural connections over time may therefore be linear, but the extent to which the vmPFC utilises these representations during retrieval is not, and remains highly sensitive to memory age. Fully appreciating the role of the vmPFC in memory retrieval may involve a combination of both storage and processing in this region, and how they interact (68).

Using an autobiographical memory paradigm to study consolidation is preferable to laboratory-based episodic memory tests by virtue of its ecological validity, availability of temporally distant stimuli, clinical significance and context-dependent equivalence to animal tasks. However, studying autobiographical memory carries with it potential confounds which can affect interpretation of results. Below we consider why these factors cannot account for our observations.

Consistency of recall and forgetting

Older memories may yield a higher RSA score if they are more consistently recalled. Here, however, participants actually rated 0.5M memories as more consistently recalled than 60 month old memories. Older memories were not impoverished in detail when compared to the detail available for recent memories. Moreover, an inspection of interview transcripts across experiments revealed participants rarely offered new details for previous memories when retested, countering the suggestion that increased detectability of old memories may arise from the insertion of new episodic or semantic details (69). The consistency in recalled detail across experiments could be attributable to participants recalling in Experiment 2 what they had said during Experiment 1. However whether or not participants remembered by proxy is irrelevant, as they still recalled the specific details of the original event, removing forgetting as a potential explanation of changes in neural patterns over time.

The influence of repetition

Retrieving a memory initiates reconsolidation, a transient state where memories are vulnerable to interference (70, 71). Therefore, repeated retrieval may cause this process to have an influence on neural representations. However, all memories were recalled one week before the fMRI scan, so if such an effect was present it would be matched across time-points. Retrieval at this stage may also accelerate consolidation (72), yet if this was a major influence, we would likely have found 0.5M memories to be more detectable than they were. Further repetition of memories within the scanner in Experiment 1 took place over a timescale that could not affect consolidation processes or interpretation of the initial neural data. Nevertheless, this could arguably affect vmPFC engagement over a longer period of time (73) and thus perturb the natural course of consolidation, influencing the results of Experiment 2. However, given that seven out of the eight specifically hypothesised temporally sensitive changes in neural representations were supported, an altered or accelerated

559 consolidation time-course appears highly unlikely. Again, recall recency was matched in Experiment
560 2 by the memory interview, and recall frequency between experiments was low.
561 Taking a more general and parsimonious perspective, the ratings demonstrate that,
562 naturally, all memories are recalled on an occasional basis (Table S1), therefore it seems highly
563 unlikely that a mere six repetitions within a scanning session would significantly alter the time
564 course of systems-level consolidation. It should also be noted that successful detection of neural
565 patterns relied on the specific content of each memory, rather than being due to generic time-
566 related retrieval processes (Fig S3). One alternative to the current two-experiment longitudinal
567 design to limit repetition across experiments would be to have a different group of participants with
568 different memories for the second experiment. However the strength of the current approach was
569 the ability to track the transformation in neural patterns of the same memories over time.
570
571 **The effect of selection**
572 An alternative interpretation of the time-sensitive vmPFC engagement is a systematic bias in the
573 content of selected memories. For example, annual events coinciding across all participants, such as
574 a seasonal holiday. However, recruitment took place over a period of five months in an evenly
575 spaced manner, ensuring that such events did fall into the same temporal windows across
576 participants. The occurrence of personal events such as birthdays was also random across
577 participants. The use of personal photographs as memory cues also limited the reliance on time of
578 year as a method for strategically retrieving memories. Furthermore, the nature of memory
579 sampling was that unique, rather than generic, events were eligible, reducing the likelihood of
580 events which were repeated annually being included. Memory detectability was high at 12 month
581 intervals such as one, two and five years in this study, suggesting perhaps it is easier to recall events
582 which have taken place at a similar time of year to the present. However this should have been
583 reflected in behavioural ratings, and equivalently strong neural representations for recent
584 memories, but neither was observed. Most importantly, if content rather than time-related

585 consolidation was the main influence on memory detectability, then we would not have observed
586 any change in neural representation scores from Experiment 1 to Experiment 2, rather than the
587 hypothesised shifts which emerged.

588 A related concern is that memories across time differ in nature because they differ in
589 availability. Successful memory search is biased towards recency, meaning there are more events to
590 choose from in the last few weeks, than remote time periods. Here, this confound is circumvented
591 by design, given that search was equivalently constrained and facilitated at each time-point by the
592 frequency at which participants took photographs, which was not assumed to change in a major way
593 over time. These enduring "snap-shots" of memory, located within tight temporal windows (see
594 Materials and methods) meant that memory selection was not confounded by retrieval difficulty or
595 availability. It could also be argued that selection of time-points for this study should have been
596 biased towards recency given that most forgetting occurs in the weeks and months after learning.
597 However, it is important to dissociate systems-level consolidation from forgetting, as they are
598 separate processes which are assumed to follow different time-courses. Memory forgetting follows
599 an exponential decay (74), whereas systems-level consolidation has generally been assumed, until
600 now, to be gradual and linear (75). Our study was concerned only with vivid, unique memories which
601 were likely to persist through the systems-level consolidation process.

602

603 **Value**

604 Given that the medial prefrontal cortex is often associated with value and emotional processing (76),
605 could these factors have influenced the current findings? Humans display a bias towards
606 consolidating positive memories (77), and remembered information is more likely to be valued than
607 that which is forgotten (78). Activity in vmPFC during autobiographical memory recall has been
608 found to be modulated by both the personal significance and emotional content of memories (79).
609 However, in the current two experiments, memories were matched across time periods on these
610 variables, and the selection of memories through photographs taken on a day-to day basis also

611 mitigated against this effect. In the eight months between experiments, memories either remained
612 unchanged or decreased slightly in their subjective ratings of significance and positivity, suggesting
613 that these factors are an unlikely driving force behind the observed remote memory representations
614 in vmPFC. For example, if recent memories in Experiment 1 were not well-represented in vmPFC
615 because they were relatively insignificant, there is no reason to expect them to be more so eight
616 months later, yet their neural representation strengthened over time nonetheless.
617
618 **Relation to previous findings**
619 A methodological discrepancy between this experiment and that conducted by Bonnici et al. (54), is
620 the additional use of a photograph to assist in cueing memories. One possible interpretation of the
621 neural representation scores is they represent a role for the vmPFC in the maintenance of visual
622 working memory following cue offset. However, the prefrontal cortex is unlikely to contribute to
623 maintenance of visual information (80). Furthermore, were this to be the driving effect behind
624 neural representations here, the effect would be equivalent across time-periods, yet it is not.
625 There is, however, an obvious inconsistency between the findings of the current study and
626 that of Bonnici, et al. (54). Unlike that study, we did not detect representations of 0.5M old
627 memories in vmPFC. It could be that the support vector machine classification-based MVPA used by
628 Bonnici et al. (54) is more sensitive to detection of memory representations than RSA, however, the
629 current study was not optimised for such an analysis because it necessitated an increased ratio of
630 conditions to trials. Nonetheless, the increase in memory representation scores from recent to
631 remote memories was replicated and additionally refined in the current study with superior
632 temporal precision. One observation which was consistent with the Bonnici findings was the
633 detection of remote memories in the hippocampus, which also supports theories positing a
634 perpetual role for this region in the vivid retrieval of autobiographical memories (10, 12). However,
635 the weak detectability observed at more recent time points may reflect a limitation of the RSA

636 approach employed here to detect sparsely encoded hippocampal patterns, which may be overcome
637 by a more targeted subfield analysis (81).

638 In the light of our hypotheses, Experiment 2 generated one anomalous finding. Twenty-four
639 month old memories from Experiment 1 were no longer well represented eight months later. Why
640 memories around 32M of age are not as reliant on vmPFC is unclear, but unlike other time-periods,
641 we cannot verify this finding in the current experiment, as we did not sample 32M memories during
642 Experiment 1.

643

644 **Summary**

645 The current results revealed a two-stage process of autobiographical memory retrieval in the vmPFC
646 over the course of systems-level consolidation, which was remarkably preserved across completely
647 different sets of memories in one experiment, and closely replicated in a subsequent longitudinal
648 experiment with the same participants and memories. These findings support the notion that the
649 vmPFC becomes increasingly important over time for the retrieval of remote memories. Two
650 particularly novel findings emerged. First, this process occurs relatively quickly, by four months
651 following an experience. Second, vmPFC involvement after this time fluctuates in a highly consistent
652 manner, depending on the precise age of the memory in question. Further work is clearly needed to
653 explore the implications of these novel results. Overall, we conclude that our vmPFC findings may
654 be explained by a dynamic interaction between the changing strength of a memory trace, the
655 availability of temporally adjacent memories, and the concomitant differential strategies and
656 schemas that are deployed to support the successful recollection of past experiences.

657

658

Materials and methods

Ethics statement

This study was approved by the local research ethics committee (University College London Research Ethics Committee, approval reference 6743/002). All investigations were conducted according to the principles expressed in the Declaration of Helsinki. Written informed consent was obtained for each participant.

Experiment 1

Participants

Thirty healthy, right handed participants (23 female) took part (mean age 25.3, SD 3.5, range 21-32). All had normal or corrected-to-normal vision.

Memory interview and selection of autobiographical memories

Participants were instructed to select at least three photographs from each of eight time-points in their past (0.5M, 4M, 8M, 12M, 16M, 20M, 24M and 60M relative to the time of taking part in the experiment) which reminded them of vivid, unique and specific autobiographical events. The sampling was retrospective, in that the photographs were chosen from the participants' pre-existing photograph collections and not prospectively taken with the study in mind. Highly personal, emotionally negative or repetitive events were deemed unsuitable. An additional requirement was that memories from the same time period should be dissimilar in content. For the four most recent time periods (0.5M-12M), the memories should have taken place within a temporal window two weeks either side of the specified date yielding a potential window of one month, for the next three time points (16M-24M), three weeks either side to allow a window of six weeks, and one month either side for the most remote time point (60M), giving a two month window. This graded approach was adopted to balance temporal precision with the availability of suitable memories at more remote time-points.

685 Participants were asked to describe in as much detail as possible the specific
686 autobiographical memory elicited by a photograph. General probes were given by the interviewer
687 where appropriate (e.g., "what else can you remember about this event?"). Participants were also
688 asked to identify the most memorable part of the event which took place within a narrow temporal
689 window and unfolded in an event-like way. They then created a short phrase pertaining to this
690 episode, which was paired with the photograph to facilitate recall during the subsequent fMRI scan
691 (Fig 1A). Participants were asked to rate each memory on a number of characteristics (see main text,
692 Figs 1 and 6, Tables S1 and S3), and two memories from each time period which satisfied the criteria
693 of high vividness and detail, and ease of recall were selected for recollection during the fMRI scan.
694
695 ***Behavioural analyses***
696 The interview was recorded and transcribed to facilitate an objective analysis of the details, and the
697 widely-used Autobiographical Interview method was employed for scoring (56). Details provided for
698 each memory were scored as either "internal" (specific events, temporal references, places,
699 perceptual observations and thoughts or emotions) or "external" (unrelated events, semantic
700 knowledge, repetition of details or other more general statements). To assess inter-rater reliability, a
701 subset of sixteen memories (n=2 per time period) were randomly selected across 16 different
702 subjects and scored by another experimenter blind to the aims and conditions of the study. Intra-
703 class coefficient estimates were calculated using SPSS statistical package version 22 (SPSS Inc,
704 Chicago, IL) based on a single measures, absolute-agreement, 2-way random-effects model.
705 As two memories per time period were selected for later recall in the scanner, behavioural
706 ratings were averaged to produce one score per time period. Differences in subjective memory
707 ratings across time periods were analysed using a one-way repeated measures ANOVA with
708 Bonferroni-corrected paired t-tests. Differences in objective memory scores of internal and external
709 details across time periods were analysed using a two-way repeated measures ANOVA with
710 Bonferroni-corrected paired t-tests. A threshold of $p < 0.05$ was used throughout both experiments.

711 All ANOVAs were subjected to Greenhouse-Geisser adjustment to the degrees of freedom if
712 Mauchly's sphericity test identified that sphericity had been violated.
713
714 ***Task during fMRI scanning***
715 Participants returned approximately one week later (mean 6.9 days, SD 1) to recall the memories
716 while undergoing an fMRI scan. Prior to the scan, participants were trained to recall each of the 16
717 memories within a 12 second recall period [as in Bonnici et al. (54), Bonnici and Maguire (55)], when
718 cued by the photograph alongside its associated cue phrase. There were two training trials per
719 memory, and participants were asked to vividly and consistently recall a particular period of the
720 original event which unfolded across a temporal window matching the recall period.
721 During scanning, participants recalled each memory six times (6 trials x 16 memories = 96
722 trials). The two memories from each time period were never recalled together in the same session,
723 nor was any one memory repeated within each session, resulting in 12 separate short sessions with
724 eight trials in each, an approach recommended for optimal detection of condition-related activity
725 patterns using MVPA (82). Trials were presented in a random order within each session. On each
726 trial, the photograph and associated pre-selected cue phrase relating to each event were displayed
727 on screen for three seconds. Following removal of this cue, participants then closed their eyes and
728 recalled the memory. After 12 seconds, the black screen flashed white twice, to cue the participant
729 to open their eyes. The participant was then asked to rate how vivid the memory recall had been
730 using a five-key button box, on a scale of 1-5, where 1 was not vivid at all, and 5 was highly vivid.
731 When the least vivid trials were excluded, the mean number of trials (/6) selected for analysis from
732 each time-point were as follows: 0.5M: 5.65 (SD 0.57), 4M: 5.50 (SD 0.56), 8M: 5.43 (SD 0.55), 12M:
733 5.50 (SD 0.63), 16M: 5.50 (SD 0.59), 20M: 5.43 (SD 0.65), 24M: 5.42 (SD 0.56), 60M: 5.23 (SD 0.69).
734
735
736

737 ***MRI data acquisition***

738 Structural and functional data were acquired using a 3T MRI system (Magnetom TIM Trio, Siemens
739 Healthcare, Erlangen, Germany). Both types of scan were performed within a partial volume which
740 incorporated the entire extent of the ventromedial prefrontal cortex (Fig 3A).

741 Structural images were collected using a single-slab 3D T2-weighted turbo spin echo
742 sequence with variable flip angles (SPACE) (83) in combination with parallel imaging, to
743 simultaneously achieve a high image resolution of ~500 µm, high sampling efficiency and short scan
744 time while maintaining a sufficient signal-to-noise ratio (SNR). After excitation of a single axial slab
745 the image was read out with the following parameters: resolution = 0.52 x 0.52 x 0.5 mm, matrix =
746 384 x 328, partitions = 104, partition thickness = 0.5 mm, partition oversampling = 15.4%, field of
747 view = 200 x 171 mm 2, TE = 353 ms, TR = 3200 ms, GRAPPA x 2 in phase-encoding (PE) direction,
748 bandwidth = 434 Hz/pixel, echo spacing = 4.98 ms, turbo factor in PE direction = 177, echo train
749 duration = 881, averages = 1.9. For reduction of signal bias due to, for example, spatial variation in
750 coil sensitivity profiles, the images were normalized using a prescan, and a weak intensity filter was
751 applied as implemented by the scanner's manufacturer. To improve the SNR of the anatomical
752 image, three scans were acquired for each participant, coregistered and averaged. Additionally, a
753 whole brain 3D FLASH structural scan was acquired with a resolution of 1 x 1 x 1 mm.

754 Functional data were acquired using a 3D echo planar imaging (EPI) sequence which has
755 been demonstrated to yield improved BOLD sensitivity compared to 2D EPI acquisitions (84). Image
756 resolution was 1.5mm^3 and the field-of-view was 192mm in-plane. Forty slices were acquired with
757 20% oversampling to avoid wrap-around artefacts due to imperfect slab excitation profile. The echo
758 time (TE) was 37.30 ms and the volume repetition time (TR) was 3.65s. Parallel imaging with GRAPPA
759 image reconstruction (85) acceleration factor 2 along the phase-encoding direction was used to
760 minimize image distortions and yield optimal BOLD sensitivity. The dummy volumes necessary to
761 reach steady state and the GRAPPA reconstruction kernel were acquired prior to the acquisition of
762 the image data as described in Lutti et al. (84). Correction of the distortions in the EPI images was

763 implemented using B0-field maps obtained from double-echo FLASH acquisitions (matrix size 64x64;
764 64 slices; spatial resolution 3mm^3; short TE=10 ms; long TE=12.46 ms; TR=1020 ms) and processed
765 using the FieldMap toolbox available in SPM (86).
766
767 ***MRI data preprocessing***
768 fMRI data were analysed using SPM12 (www.fil.ion.ucl.ac.uk/spm). All images were first bias
769 corrected to compensate for image inhomogeneity associated with the 32 channel head coil (87).
770 Fieldmaps collected during the scan were used to generate voxel displacement maps. EPIs for each
771 of the twelve sessions were then realigned to the first image and unwarped using the voxel
772 displacement maps calculated above. The three high-resolution structural images were averaged to
773 reduce noise, and co-registered to the whole brain structural scan. EPIs were also co-registered to
774 the whole brain structural scan. Manual segmentation of the vmPFC was performed using ITK-SNAP
775 on the group averaged structural scan normalised to MNI space. The normalised group mask was
776 warped back into each participant's native space using the inverse deformation field generated by
777 individual participant structural scan segmentations. The overlapping voxels between this
778 participant-specific vmPFC mask and the grey matter mask generated by the structural scan
779 segmentation were used to create a native-space grey matter vmPFC mask for each individual
780 participant.
781
782 ***Representational Similarity Analysis***
783 Functional data were analysed at the single subject level without warping or smoothing. Each recall
784 trial was modelled as a separate GLM, which comprised the 12 second period from the offset of the
785 memory cue to just before the white flash which indicated to the participant they should open their
786 eyes. Motion parameters were included as regressors of no interest. RSA (88), was performed using
787 the RSA toolbox (http://www.mrc-cbu.cam.ac.uk/methods-and-resources/toolboxes/) and custom
788 MATLAB (version R2014a) scripts. In order to account for the varying levels of noise across voxels

789 which can affect the results of multivariate fMRI analyses, multivariate noise normalisation (89) was
790 performed on the estimated pattern of neural activity separately for each trial. This approach
791 normalises the estimated beta weight of each voxel using the residuals of the first-level GLM and the
792 covariance structure of this noise. This results in the down-weighting of noisier voxels and a more
793 accurate estimate of the task-related activity of each voxel.

794 The average number of voxels analysed in the vmPFC across the two sets of memories was
795 5252 (SD 1227). Whole ROI-based analysis was preferred to a searchlight approach which would
796 involve comparing neural with model similarity matrices (90), as we did not have strong *a priori*
797 hypothesis about changes in neural representations over time against which to test the neural data,
798 nor did we want to make assumptions regarding the spatial distribution of informative voxels in the
799 vmPFC.

800 As participants recalled two memories per time-point, the dataset was first split into two
801 sets of eight time points, which were analysed separately using RSA. To characterise the strength of
802 memory representations in the vmPFC, the similarity of neural patterns across recall trials of the
803 same memory was first calculated using the Pearson product-moment correlation coefficient,
804 resulting in a "within-memory" similarity score. Then the neural patterns of each memory were
805 correlated with those of all other memories, yielding a "between-memory" similarity score. Both
806 within- and between-memory correlations were performed on trials from separate runs. For each
807 memory, the between-memory score was then subtracted from the within-memory score to provide
808 a neural representation score (Fig 3C). This score was then averaged across the two memories at
809 each time-point. Results for the left and the right hemispheres were highly similar, and therefore the
810 data we report here are from the vmPFC bilaterally. A distinctive neural pattern associated with the
811 recall of memories at each time period would yield a score significantly higher than zero, which was
812 assessed using a one-sample t-test. Strengthening or weakening of memory representations as a
813 function of remoteness would result in a significant difference in memory representation scores
814 across time periods, and this was assessed using a one-way repeated measures ANOVA with post-

hoc two-tailed paired t-tests. Error bars on graphs displaying neural representation scores were normalised to reflect within- rather than between-subject variability in absolute values, using the method recommended by Cousineau (91) for within-subjects designs. The range of values that we observed are entirely consistent with those in other studies employing a similar RSA approach in a variety of learning, memory and navigation tasks in a wide range of brain regions (92-101).

Searchlight analysis

An RSA searchlight analysis was conducted in normalised space, on multivariate noise-normalised data within the ROI. This approach selected every voxel within the ROI, and using a volumetric approach which is constrained by the shape of the ROI, expanded the area around that voxel until an area of 160 voxels was reached. Within each of these spheres, memories were correlated with themselves, and other memories, analogous to the standard ROI approach. Then the resulting neural RSM was correlated using Spearman's rank correlation coefficient with a model RSM which consisted of ones along the diagonal and zeros on the off-diagonal. This model RSM was used to detect if individual memories were detectable across all time-points. For every voxel, the average correlation from every sphere it participated in was calculated, to generate a more representative score of its informational content. Parametric assumptions regarding the spatial distribution of unsmoothed data may not hold. Therefore we used statistical nonparametric mapping (SnPM13) on the resulting searchlight images. We used 10,000 random permutations, a cluster-based significance threshold of t=3, and a family-wise-error corrected threshold of $p<0.05$ within the ROI.

Experiment 2

Participants

Sixteen of the 30 participants who took part in Experiment 1 returned to take part in Experiment 2 (14 female, mean age 24.7, SD 3.1, range 21-33) approximately eight months later (8.4 months, SD 1.2).

841

842 ***Memory interview***

843 Participants were presented with the 16 photographs and cue phrases associated with the
844 autobiographical memories in Experiment 1 and were asked to describe in as much detail as possible
845 the specific event which they had recalled previously. General probes were given by the interviewer
846 where appropriate (e.g. "what else can you remember about this event?"). The interviewer availed
847 of summarised transcripts from Experiment 1 to verify the same memory and details were being
848 recalled. Participants then rated each memory on the same characteristics assessed in Experiment 1.
849 The memory interview during Experiment 2 was also recorded and transcribed.

850

851 ***Behavioural analyses***

852 The analysis of subjective and objective ratings for Experiment 2 followed exactly the same
853 procedure as Experiment 1. The extent to which subjective ratings for the same memory had
854 changed between Experiment 1 and Experiment 2 was assessed using a two-way (experiment x time
855 period) repeated measures ANOVA with Bonferroni-corrected paired t-tests. Differences in objective
856 memory ratings across experiments were analysed using a two (experiment) x two (detail) x eight
857 (time period) repeated measures ANOVA with Bonferroni-corrected paired t-tests.

858

859 ***Task during fMRI scanning***

860 Participants returned approximately one week later for the fMRI scan (mean 5.5 days, SD 3.7). Prior
861 to scanning, only one reminder training trial per memory was deemed necessary given the prior
862 experience of performing the task in Experiment 1. The scanning task remained unchanged from
863 Experiment 1, aside from the re-randomisation of trials within each session. When the least vivid
864 trials were excluded, the mean number of trials (/6) selected for analysis from each time period
865 were as follows: 8M: 5.94 (SD 0.25), 12M: 5.97 (SD 0.13), 16M: 5.88 (SD 0.29), 20M: 5.88 (SD 0.29),
866 24M: 5.94 (SD 0.25), 28M: 5.94 (SD 0.17), 32M: 5.84 (SD 0.40), 68M: 5.81 (SD 0.36).

867

868 ***MRI data acquisition***

869 Structural and functional data were acquired using the same scanner and scanning sequences as
870 Experiment 1. However the prior acquisition of the partial volume structural MRI scans negated the
871 need to include these in the protocol of Experiment 2.

872

873 ***MRI data preprocessing***

874 fMRI data were preprocessed using the same pipeline as Experiment 1, with the additional step of
875 co-registering the functional scans of Experiment 2 to the structural scans of Experiment 1, which
876 enabled the use of the vmPFC masks from Experiment 1. First-level GLMs of each recall trial were
877 constructed in an identical manner to Experiment 1.

878

879 ***Representational Similarity Analysis***

880 RSA of the Experiment 2 fMRI data was conducted in an identical manner to Experiment 1. The
881 average number of voxels analysed in the vmPFC across the two sets of memories for all participants
882 was 5228 (SD 1765). To generate predicted changes in representations in the eight months from
883 Experiment 1 to Experiment 2, the scores from Experiment 1 were shifted by two time-points, and a
884 two-tailed paired t-test was performed on each memory's original neural representation score and
885 its expected score eight months later (Fig 5). To ascertain whether the observed neural
886 representation scores had changed between Experiments 1 and 2, a two-way (experiment x time
887 period) repeated measures ANOVA was performed. To investigate if these changes mirrored the
888 predictions generated by the original data, paired t-tests were performed between the actual neural
889 representation scores for each memory from Experiment 1 and Experiment 2, one-tailed if there was
890 a hypothesised increase or decrease.

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Funding

E.A.M. and D.N.B are supported by a Principal Research Fellowship from Wellcome to E.A.M (101759/Z/13/Z). The Wellcome Centre for Human Neuroimaging is supported by a Centre Award from Wellcome (203147/Z/16/Z).

Author Contributions

D.N.B. and E.A.M designed the experiment, with input from M.J.C. D.N.B. conducted the experiment. D.N.B. analysed the data with input from E.A.M. and M.J.C. D.N.B. and E.A.M. wrote the paper, with input from M.J.C.

Acknowledgements

We thank David Bradbury and the Imaging Support team for technical assistance.

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