Dynamics of memory over time: Mechanisms and modulation

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Abstract

Memories evolve over time, with emotional experiences often retained more vividly than mundane ones. This dissertation elucidates the evolution of memory, from repeated encoding and immediate retrieval to the neural reorganization of memory over time, and examines the influence of emotional arousal on this process. In the first study, we focused on the neural underpinnings of the emotional enhancement of immediate memory for recurring events. Analysis of fMRI data revealed that memory for emotional images, compared to neutral ones, is enhanced by stable neocortical encoding patterns across repetitions, which is modulated by amygdala activity at initial exposure. Thus, amygdala activation when first encountering an emotional event may enhance memory for this experience through more precise pattern reinstatement during subsequent encounters. Study 2 investigated the effect of noradrenergic stimulation on time-dependent memory reorganization by pharmacologically elevating post-encoding noradrenergic arousal and conducting fMRI scans at encoding and memory test 1d or 28d later. Noradrenergic stimulation was associated with a time-dependent increase in hippocampal activity and encoding-retrieval pattern similarity, coupled with a decrease in neocortical activity. These results challenge the traditional notion of an invariable memory reorganization from hippocampus to neocortex, suggesting that this process can be altered, and even reversed. Lastly, we investigated the nature of qualitative changes in memory over time by employing a recognition test 1d or 28d after encoding that included lures that were semantically or perceptually related to original images. Contrary to the common view of memories fading over time, our findings show that memories undergo a semantic transformation, a process amplified by stimulus-transient emotional arousal. Multivariate fMRI analyses reveal an increase in semanticized neocortical memory representations over time, and distinct representational changes within the hippocampus, indicating a time-dependent memory transformation that is semantic, but not perceptual, in nature. These findings demonstrate that the fundamental characteristic of memory, its evolution over time, is far more dynamic than traditionally thought and critically influenced by emotional arousal, potentially explaining the enduring vividness of emotional memories.

Contents

1 Introduction **1**

1.1 Memory over time . . . 1

1.1.1 Memory reorganization . . . 2

1.1.2 Memory transformation . . . 4

1.1.3 Scene construction . . . 6

1.2 Memory along the hippocampal long axis . . . 7

1.2.1 Early differentiation accounts . . . 7

1.2.2 Spatial granularity . . . 8

1.2.3 Scene construction . . . 8

1.2.4 Memory transformation . . . 9

1.3 Memory modulation . . . 11

1.3.1 Modulating encoding . . . 11

1.3.2 Modulating consolidation . . . 12

1.4 Research goals . . . 14

2 Experimental studies **16**

2.1 Study 1: Modulating immediate memory . . . 16

2.1.1 Background . . . 16

2.1.2 Methods . . . 16

2.1.3 Results . . . 17

2.1.4 Conclusion . . . 18

2.2 Study 2: Modulating systems consolidation . . . 19

2.2.1 Background . . . 19

2.2.2 Methods . . . 19

2.2.3 Results . . . 20

2.2.4 Conclusion . . . 20

2.3 Study 3: The nature of memory transformation . . . 21

2.3.1 Background . . . 21

2.3.2 Methods . . . 22

2.3.3 Results . . . 23

2.3.4 Conclusion . . . 24

3 General discussion **25**

3.1 Modulating memory over time . . . 26

3.2 Memory transformation along the hippocampal long axis 29
3.3 The state of systems consolidation 32
3.4 Future directions 33
3.5 Conclusion 35

References **37**

A Appendix: Study 1 **59**

B Appendix: Study 2 **91**

C Appendix: Study 3 **110**

List of Figures

1 Two perspectives on memory reorganization over time 3
2 Two perspectives on memory transformation along the hippocampal long axis . . . 9
3 Amygdala activity at first exposure boosts subsequent emotional memory via neocortical encoding pattern stability 18
4 Noradrenergic stimulation increased multivariate memory reinstatement over time . 21
5 Memories are semantically but not perceptually transformed over time 23

List of Abbreviations

aHC	anterior hippocampus
BLA	basolateral amygdala
BOLD	blood oxygen level dependent
ERS	encoding-retrieval similarity
FA	false alarm
IFG	inferior frontal gyrus
mHC	mid hippocampus
mPFC	medial prefrontal cortex
MTL	medial temporal lobe
MTT	Multiple Trace Theory
pHC	posterior hippocampus
PLAC	placebo
PTSD	post-traumatic stress disorder
ROI	region of interest
RSA	representational similarity analysis
SCT	Standard Consolidation Theory
SPL	superior parietal lobule
TTT	Trace Transformation Theory
vmPFC	ventromedial prefrontal cortex
VTA	ventral tegmental area
YOH	yohimbine

1 Introduction

Our memories define who we are and guide our daily actions. However, memories are not instantaneous records of our lives; rather, they undergo changes over time, with some memories seeming to fade more rapidly than others. The memory of significant events, such as the birth of a child or the passing of a loved one, can persist in a uniquely vivid manner, unlike the details of mundane events, such as where we parked our car earlier in the day or the name of an acquaintance we met briefly. This dissertation aims to elucidate the evolution of memory over time, from repeated encoding and immediate memory retrieval to long-term memory reorganization, and to examine the modulation of this process by emotional arousal.

1.1 Memory over time

In a series of experiments with healthy participants, Müller and Pilzecker (1900) observed that new stimuli disrupted associative memories shortly after their encoding. However, after approximately ten minutes, these memories became resistant to interference (Lechner et al., 1999). Müller and Pilzecker (1900) thus introduced the term *consolidation*, derived from the Latin 'consolidare', meaning 'to make firm together' (Dudai, 2004; Dudai et al., 2015), to describe a process by which memories become stabilized and resistant to interference (Lechner et al., 1999). The idea of memory consolidation was soon linked to observations in patients, where memory loss due to brain damage appeared to follow a temporal gradient, with recent memories more affected than remote ones (Burnham, 1903; Korsakoff, 1889; Ribot, 1882).

Although these and subsequent (Hebb, 1949; Russell, 1948) observations provided first insights into the time-dependent formation of memories, it remained unclear which, or if any (see Hebb, 1949; Lashley, 1950), neural regions may be particularly related to memory. This changed with the report of the now famous patient H.M. (Scoville & Milner, 1957), who, after bilateral resection of the medial temporal lobe (MTL), suffered severe and permanent anterograde amnesia for explicit declarative memories, without general intellectual impairment or perceptual disabilities (Scoville & Milner, 1957; Squire & Wixted, 2011). Furthermore, similar to previous clinical observations of temporal gradients in memory loss (Burnham, 1903; Korsakoff, 1889; Ribot, 1882; Russell, 1948), H.M. exhibited retrograde amnesia that appeared to be limited to a short period prior to surgery (Penfield & Milner, 1958; Squire, 2009; Squire & Wixted, 2011). Subsequent observations in patients with more focused lesions revealed that particularly damage to the hippocampus is linked to temporally graded retrograde amnesia (Beatty et al., 1987; Rempel-Clower et al., 1996; Salmon et al., 1988; Squire et al., 1975; see Frankland and Bontempi, 2005).

Notably, the extent of memory loss in these clinical observations exceeded far beyond the time frame reported for memory stabilization in psychological experiments conducted by Müller and Pilzecker (1900), hinting at the involvement of related, yet different processes. Accordingly, the concept of memory consolidation has evolved to encompass at least two processes: (i) a rapid consolidation process involving cellular and synaptic neurochemical events, accomplished within minutes or hours after learning (Dudai, 2004; Kandel, 2001; Kandel et al., 2014), and (ii) *systems consolidation*, which involves the reorganization of memory across large-scale neural networks, including the hippocampus and neocortical structures, in which memories are interleaved into existing knowledge structures (McClelland et al., 1995; McGaugh, 2000; Squire & Alvarez, 1995). While the rapid consolidation on the cellular level has been widely accepted, long-term consolidation mechanisms, particularly the role of the hippocampus in remote memories, and the nature of the information represented in the cortical regions, have remained a matter of debate (Frankland & Bontempi, 2005; Nadel & Moscovitch, 1997; Squire & Alvarez, 1995; Squire & Bayley, 2007; Winocur, Moscovitch, Rosenbaum, & Sekeres, 2010).

1.1.1 Memory reorganization

The crucial role of the hippocampus in encoding and retaining recently acquired declarative memory is now well established (Moscovitch et al., 2016; Nadel, 1991; O'Keefe & Nadel, 1978; Rosenbaum et al., 2001; Winocur & Moscovitch, 2011; Winocur et al., 2001). In this context, hippocampal neurons are understood to function as a pointer or index to distributed neocortical representations of the engram, encapsulating the content, context, and experience of an encoded event (Moscovitch, 1995; Teyler & DiScenna, 1986; Teyler & Rudy, 2007). When a memory is retrieved, it is theorized to interact with this hippocampal index, leading to the reactivation of the engram and the recollection of a detailed memory.

In addition to remembering due to external cues, evidence suggests that the reinstatement of hippocampal and neocortical activity patterns occurs during post-encoding rest and sleep (Hermans et al., 2017; Tambini & Davachi, 2013). In particular, research on hippocampal replay, involving the repeated reactivation of encoding-related hippocampal activity patterns, provides strong evidence for sleep-dependent consolidation (Buzsáki, 1989; Davidson et al., 2009; Girardeau & Zugaro, 2011; Wilson & McNaughton, 1994). These replay events in the hippocampus appear to be synchronized with similar reactivations in neocortical areas (Ji & Wilson, 2007; Peyrache et al., 2009; Wierzynski et al., 2009), and disruption of this process has been associated with impaired memory consolidation (Ego-Stengel & Wilson, 2010).

According to the standard view of systems consolidation (*Standard Consolidation Theory*, SCT), repeated reactivation of the hippocampal-cortical network strengthens cortico-cortical connections to the extent that they can be reactivated without hippocampal input, marking the end of the consolidation process (Frankland & Bontempi, 2005; McClelland et al., 1995; Squire & Alvarez, 1995). At this point, memories are expected to be retrieved directly from the neocortex, independently of the hippocampus (Frankland and Bontempi, 2005; Moscovitch, 1992, 1995; Squire and Alvarez, 1995; see Figure 1a). Thus, SCT defines the hippocampus as a fast learner with a transient role in memory, while long-lasting neocortical memory representations evolve

slowly over time (McClelland et al., 1995). Notably, SCT implies this process for all declarative memories and that all memories are reorganized from the hippocampus to the neocortex in their original form (Nadel & Moscovitch, 1997). In addition to the observations mentioned above in patients with temporally graded retrograde amnesia, human fMRI studies that indicate a decrease in hippocampal activity in memory retrieval over time (Niki & Luo, 2002; Piefke et al., 2003; Takashima et al., 2006; Takashima et al., 2009), have been interpreted to support the view that episodic memories become less dependent on the hippocampus over time.

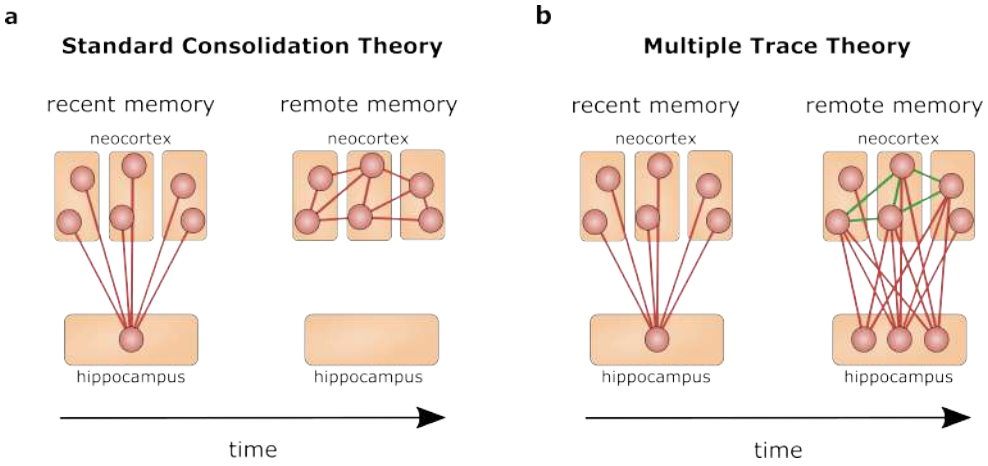

Figure 1. Two perspectives on memory reorganization over time. a The standard view on systems consolidation proposes that a declarative memory (a past event or factual information) is initially encoded in a hippocampal-neocortical trace (left, red lines and spheres) but, over time, becomes stabilized in a pattern of connectivity between neocortical modules. After this consolidation period, the memory can be retrieved, in its original form, by the neocortex. **b** Multiple Trace Theory states that, over time, memories are repeatedly (implicitly or explicitly) reactivated, each time resulting in a new memory trace that is never identical to the previous one. The statistical overlap of repeatedly reactivated memories results in a less specific memory representation, which eventually can be retrieved independently of the hippocampus (green lines). Episodic, detailed memories remain dependent on the hippocampus. Adapted from Barry and Maguire (2019), with permission from Elsevier.

The assumption that all remote memories become independent of the hippocampus was challenged by observations in patients with hippocampal damage who exhibited virtually ungraded loss of autobiographical memories (Damasio et al., 1985; Sanders & Warrington, 1971; Squire & Alvarez, 1995; Tulving et al., 1988; Zola-Morgan et al., 1986). Moreover, preserved remote memories appeared to be less detailed and more semantic in nature (Damasio et al., 1985; Warrington & Duchen, 1992). These findings led to the development of alternative theories of systems consolidation, such as Multiple Trace Theory (MTT; Nadel and Moscovitch, 1997). According to MTT, each time an episodic memory is (implicitly or explicitly) reinstated, it is reencoded by the hippocampus, resulting in multiple memory traces that are similar, but not identical, to the original trace (see Figure 1b). The statistical overlap of these reactivations would result in less specific memory representations, which could eventually be retrieved by neocortical areas independently of the hippocampus. Thus, according to both SCT and MTT, memories are, at least partly, reorganized over time. However, while SCT posits no qualitative differences between hippocampus-dependent and neocortical memory representations, MTT suggests hippocampus-independent memories to represent less specific versions of the original

memory (Nadel & Moscovitch, 1997). Critically, MTT posits that the hippocampus, which functions as an index to the distributed neocortical representation of the encoded event (Teyler & DiScenna, 1986; Teyler & Rudy, 2007), remains necessary for episodic memory over time (Moscovitch & Nadel, 1998; Nadel & Moscovitch, 1997).

The main premise of MTT is corroborated by empirical findings in human patients, where hippocampal damage is observed to affect the recollection of detailed autobiographical memories of any period before damage (Cipolotti et al., 2001; Steinvorth et al., 2005). Similarly, damage to the fornix, the main output tract of the hippocampus, has been associated with complete retrograde amnesia for detailed, episodic memories, while indicating a temporal gradient for semantic memory (Gilboa et al., 2006; Poreh et al., 2006). In rodents, hippocampal lesions result in ungraded retrograde amnesia for contextual fear memories (Kim & Fanselow, 1992; Ocampo et al., 2017), even after allowing for more than 100 days of consolidation prior to hippocampal resection (Broadbent & Clark, 2013). Furthermore, fMRI data in neurologically intact human participants have repeatedly shown comparable activity during the retrieval of recent and remote autobiographical memory events (Svoboda et al., 2006), provided that recollective quality remains comparable (Ryan et al., 2001) or is statistically accounted for (Addis et al., 2004). Thus, a convergence of evidence from human and animal studies challenges the traditional view that remote memories are reorganized to the neocortex in their original form, while indicating an enduring role of the hippocampus in episodic memory retrieval.

1.1.2 Memory transformation

While emphasizing the enduring role of the hippocampus in episodic memory, MTT (Nadel & Moscovitch, 1997) did not account for mechanisms beyond the extraction of statistical regularities in the formation of neocortical, hippocampus-independent memories (Moscovitch & Gilboa, 2021; Nadel & Moscovitch, 1997). Transformation Hypothesis, which later evolved into Trace Transformation Theory (TTT; Robin and Moscovitch, 2017a; Sekeres, Winocur, and Moscovitch, 2018), expands on MTT while highlighting the dynamic nature of memory over time. TTT posits that as memories progress from hippocampal to extra-hippocampal structures, they undergo a transformation process, resulting in less specific, semanticized memories accessible independently of the hippocampus while detailed, episodic memories are expected to remain hippocampus-dependent. Furthermore, TTT suggests the coexistence of episodic and less specific memory forms, with their expression depending on their relative strength and the context at retrieval (Winocur & Moscovitch, 2011; Winocur, Moscovitch, & Bontempi, 2010). Empirical evidence for the transformation of memory over time is derived primarily from animal models. For example, while initially showing context-specific fear responses, rats eventually exhibited conditioned fear responses in both original and similar contexts, suggesting a decrease in context specificity over time (Winocur et al., 2007). Furthermore, the hippocampus has been associated with the expression of context-sensitive fear shortly after conditioning, in contrast to the less specific fear responses at longer time intervals after learning (Sekeres, Winocur, Moscovitch, et al., 2018; Wiltgen et al., 2010; Winocur et al., 2007). This evolution from context-specific to generalized memories has been associated with hippocampally mediated formation of engram cells in the

Box 1: Memory types

In its most recent version, Trace Transformation Theory (Robin & Moscovitch, 2017a; Sekeres, Winocur, & Moscovitch, 2018) differentiates not only between episodic and semantic, but also between schematic and gist-like memories. A fully episodic memory, as characterized by Tulving (1983, 2002), involves reinstating detailed contextual elements of an event, allowing its vivid re-experiencing. For example, the detailed remembering of a museum visit may include the vivid retrieval of the tour guide's explanations, the detailed patterns and colors in a particular painting, and the ambiance of the exhibit halls. On the contrary, the gist of this memory may include the overall experience and key themes of the visit, such as the enjoyment of art and learning, without fine details (Reyna & Brainerd, 1995). This gist, while less detailed, remains tied to a specific event. Schemas represent common elements from multiple similar experiences, such as general expectations of museum visits, including viewing art and learning history. Semantic memory is related to broader, context-independent knowledge, for instance the concept of a museum and its cultural significance (Binder et al., 2009; Tulving, 1972).

medial prefrontal cortex (mPFC; Josselyn and Tonegawa, 2020; Kitamura et al., 2017; Sekeres, Winocur, Moscovitch, et al., 2018). The mPFC has been particularly linked to the formation of long-term memories that may be more schematic in nature (Richards et al., 2014; Sekeres, Winocur, Moscovitch, et al., 2018). Intriguingly, hippocampus-independent, generalized memories have been shown to regain context-specificity and hippocampus-dependency upon reactivation in the original learning environment (Winocur et al., 2009), highlighting the dynamic nature of memory over time, as proposed by TTT (Robin & Moscovitch, 2017a; Sekeres, Winocur, & Moscovitch, 2018; Winocur & Moscovitch, 2011; Winocur, Moscovitch, & Bontempi, 2010; Winocur et al., 2007).

In humans, remote autobiographical memories have been reported to be retrieved less vividly than recent ones, with recollective quality being positively associated with hippocampal activity and inversely associated with activity in the ventromedial prefrontal cortex (vmPFC; Cabeza and St Jacques, 2007; Petrican et al., 2010; Piolino et al., 2009). Although autobiographical memory research offers potential insight into episodic memory throughout the lifespan (Cabeza & St Jacques, 2007), evaluating the precision and quality of these memories is challenging, particularly since subjective vividness may not reliably indicate memory specificity (Cooper and Ritchey, 2022; see also Schacter, 1999). A prospective study indicated sustained hippocampal activity up to three months after encoding to remember encoded film clips, with a significant decrease in hippocampal activity for familiarity-based memory, suggesting that hippocampal involvement in remote memory may depend on retrieval demands (Furman et al., 2012). Furthermore, when differentiating recalled details one week after encoding film clips, participants remembered more central aspects than peripheral details (Sekeres, Winocur, Moscovitch, et al., 2018; Sekeres et al., 2016), indicating that the memory of perceptual details may fade faster compared to the memory of core elements of an event.

While these findings hint at a change in memory quality over time, the nature of this transformation remains unclear. One possible mechanism would be a perceptual transformation, in which a detailed, perceptually rich episodic trace evolves over time into a less specific trace containing knowledge of general perceptual features of the original event (for example, 'I remember the

painting contained a lot of red and brown'). Indeed, the hippocampus has been shown to be critically involved in remembering perceptual details, and this perceptual transformation perspective may be close to the common view that memories fade away and simply lose (perceptual) detail over time (Cooper et al., 2019). Alternatively, with time, memories may not just be a perceptually degraded version of the original trace, but become semantically transformed into representations that carry the semantic gist, with only minimal (detailed or generalized) perceptual information (for example, 'I remember the painting showed an apple on a table'). This semantization of memories over time may provide a better explanation of how episodic experiences are integrated into abstract knowledge structures than a mere decay of (perceptual) features of a memory trace. Dandolo and Schwabe (2018) provided evidence for semantic transformation, showing that after 28d, participants were more likely to confuse learned material with semantically similar but novel items, accompanied by decreased hippocampal activity and increased neocortical contribution during memory tests, compared to tests one day after learning. However, since semantically similar items often share perceptual characteristics to original material, it remains unknown whether this transformation may be purely semantic, perceptual, or a combination of both. Thus, the nature of memory transformation over time has, so far, remained elusive.

1.1.3 Scene construction

While SCT (Frankland & Bontempi, 2005; McClelland et al., 1995; Squire & Alvarez, 1995) and MTT/TTT (Nadel & Moscovitch, 1997; Robin & Moscovitch, 2017a; Sekeres, Winocur, & Moscovitch, 2018; Winocur & Moscovitch, 2011; Winocur, Moscovitch, & Bontempi, 2010; Winocur et al., 2007) propose a time-limited or an enduring role of the hippocampus in memory, respectively, Scene Construction Theory (Barry & Maguire, 2019; Maguire & Mullally, 2013) offers an intriguing alternative account, positing a time-limited role for the hippocampus in memory storage, while also highlighting its enduring role in vivid memory over time. This theory suggests that the hippocampal function of imagining novel events and thinking about the future (Hassabis, Kumaran, Vann, & Maguire, 2007; Kwan et al., 2010) is based on the same process as remembering, namely scene construction (Maguire & Mullally, 2013). This process allows the hippocampus to reinstate past experiences in the absence of the original hippocampal trace. Scene Construction Theory further proposes that changes in memory quality over time are associated with a decay of cortico-cortical connections, rather than decayed hippocampal traces as suggested by TTT (Moscovitch et al., 2016). Due to this decay of cortico-cortical traces, neural reinstatement becomes increasingly divergent from recent to remote memories (Bonnici & Maguire, 2018). While MTT, SCT, and TTT suggest an indexing role for the hippocampus (Moscovitch, 1995; Teyler & DiScenna, 1986; Teyler & Rudy, 2007), Scene Construction Theory introduces a temporal element to this role. It posits that the hippocampal indexing function, which depends on the existence of hippocampal traces, diminishes rapidly. Consequently, in the absence of the hippocampal trace, the role of the hippocampus in remote memory retrieval is posited to be based on its capacity to reconstruct past experiences rather than indexing to existing neocortical representations (Barry & Maguire, 2019).

1.2 Memory along the hippocampal long axis

Although Scoville and Milner (1957) and early studies in rodents (Grant & Jarrard, 1968; Hughes, 1965; Nadel, 1968) suggested a functional differentiation along the longitudinal axis of the hippocampus, subsequent theories on memory over time defined the hippocampus as a functionally homogeneous region (McClelland et al., 1995; Nadel & Moscovitch, 1997; Squire & Alvarez, 1995; Squire & Bayley, 2007; Winocur, Moscovitch, & Bontempi, 2010; Winocur et al., 2007). More recently, tracer studies in animal models have revealed minimal direct connectivity between the ventral and dorsal hippocampus in rodents or the anterior hippocampus (aHC) and posterior hippocampus (pHC) in monkeys (Fanselow & Dong, 2010; Sloviter & Lømo, 2012), further highlighting a functional differentiation along the long axis of the hippocampus.

1.2.1 Early differentiation accounts

Place cells, crucial in the formation of internal maps of the environment (O'Keefe & Nadel, 1978), have been observed mainly in the dorsal hippocampus of rodents (Jung et al., 1994) and the pHC in monkeys (Colombo et al., 1998). These spatial functions are essential to represent episodic memory that requires specific contextual information (Nadel & Hardt, 2011; Tulving, 1972). Similarly, human studies have localized responses to spatial manipulations in the pHC (Hirshhorn et al., 2012; Ryan et al., 2010), and increased pHC volume has been linked to spatial learning in London taxi drivers (Woollett & Maguire, 2011). Therefore, according to a prominent line of research, the posterior two-thirds of the hippocampus are primarily involved in cognitive (spatial) processes (Bannerman et al., 2014; Fanselow & Dong, 2010; Greicius et al., 2003; Moser & Moser, 1998), while the aHC, based on its prominent connectivity with the amygdala, is involved in emotional responses, reward (Bannerman et al., 2014; Fanselow & Dong, 2010; Moser & Moser, 1998), or decision-making (Viard et al., 2011). However, although less numerous, place cells are also present in the ventral hippocampus (Ekstrom et al., 2003). Furthermore, a smaller volume of the aHC has been associated with a reduced performance in spatial tests in taxi drivers, linking the aHC to spatial processes (Woollett & Maguire, 2012).

Meta-analyses show a consistent involvement of the aHC in successful memory encoding (Spaniol et al., 2009). Consequently, another prominent framework expects that the aHC is primarily involved in memory encoding, while linking the pHC to memory retrieval (Langnes et al., 2019, 2020; Lepage et al., 1998; Parsons et al., 2006; Schacter & Wagner, 1999). The hippocampal encoding/retrieval network model (Kim, 2015) suggests that this differentiation is based on differential network properties, with aHC connectivity to the dorsal attention network and pHC connectivity to the default mode network, which may facilitate attention to external and internal stimuli, respectively.

It has been suggested that regions that are sensitive to novelty are also related to successful memory encoding (Kirchhoff et al., 2000). Accordingly, the aHC has been repeatedly linked to stimulus novelty (Cowan, Fain, et al., 2021; Daselaar et al., 2006; Doeller et al., 2008; Kafkas & Montaldi, 2018; Köhler et al., 2002; Poppenk et al., 2010; Strange et al., 1999), while the pHC has been associated with previously encountered stimuli (Daselaar et al., 2006; Poppenk et al.,

2010; Strange et al., 1999). Novelty activates the ventral tegmental area (VTA) and the substantia nigra to elicit dopamine release (Lisman & Grace, 2005). The strong functional and structural connectivity of the aHC with the VTA (Elliott et al., 2023; Haber & Knutson, 2010; Krebs et al., 2011) and a recent framework (Cowan, Fain, et al., 2021) suggest a bidirectional aHC-VTA circuit, where the aHC responds to environmental novelty, activating the VTA to enhance hippocampal plasticity (Huang & Kandel, 1996; Li et al., 2003; Lisman & Grace, 2005; Shohamy & Adcock, 2010).

1.2.2 Spatial granularity

Previous data in rodents have shown that the firing fields of ventral hippocampal place cells are larger compared to those in the dorsal hippocampus (Kjelstrup et al., 2008). This observation has been interpreted as abstract and specific representations in the aHC and pHC, respectively (Collin et al., 2015; Poppenk et al., 2013). Importantly, the ventral hippocampal cell population of rodents can still decode precise locations, despite the fact that individual cells represent larger environmental areas (Keinath et al., 2014).

In humans, a similar global-local gradient in spatial representation and navigation has been observed. An fMRI study in a virtual environment suggested that while pHC activation is related to fine-grained local environmental representations for navigation, activity more anteriorly along the hippocampus was associated with the use of coarse, global environmental representations (Evensmoen et al., 2013). A similar gradient was implicated in an object-room geometry association task, where the most fine-grained positional representations were found in the pHC, with more coarse-grained representations in the aHC (Evensmoen et al., 2015). Additionally, using graph measures of real-world topology in a navigation task associated aHC activity with global metrics, while the pHC was linked to local graph-theoretic centrality metrics (Javadi et al., 2017).

Extending this framework to spatial aspects of autobiographical memories, the pHC has been implicated in the retrieval of spatial relations within personal event memories, while the aHC may be more engaged when retrieving general information about places (Nadel et al., 2013). This gradient may extend to the representation of multi-event narratives, with individual event-pair associations represented in the pHC, intermediate event representations in the mid hippocampus (mHC), and large-scaled narratives in the aHC (Collin et al., 2015).

1.2.3 Scene construction

The aHC has been repeatedly associated with a range of integral functions in scene construction, underscoring its critical role in this cognitive process (Barry & Maguire, 2019; Zeidman & Maguire, 2016). This involvement includes the construction of static atemporal scenes (Hassabis, Kumaran, & Maguire, 2007), the elaboration of imagined events (Addis et al., 2007), and the visualization of scenarios set in both past and future contexts (Addis et al., 2009). Additionally, the aHC is pivotal in the retrieval of autobiographical memories (Addis et al., 2012; McCormick et al., 2015), which is expected to require the reassembly of past experiences into coherent and contextually rich scenes. Evidence of direct overlap in neural activity patterns between the perception and

imagination of scenes within the aHC (Zeidman, Mullally, & Maguire, 2015) points to a role of the aHC in representing perceptual features. Accordingly, the aHC has been particularly associated with the construction of specific, detailed scenarios, as opposed to more generalized ones (Addis et al., 2011). These collective findings highlight the significant role of aHC in constructing and reconstructing vivid and detailed mental scenes, positioning it as a crucial hub for scene construction (Barry & Maguire, 2019; Zeidman & Maguire, 2016). While the aHC is particularly linked to the recent and detailed reconstruction of memories, remote memory reconstruction has been hypothesized to involve additional processing by the pHC (Barry & Maguire, 2019).

1.2.4 Memory transformation

In its most recent version (Robin & Moscovitch, 2017a; Sekeres, Winocur, & Moscovitch, 2018), TTT introduced a differentiation along the longitudinal axis of the hippocampus, suggesting distinct roles for the aHC and pHC in memory transformation over time. According to TTT, detailed memories are represented by the pHC, while gist-like memories are expected to rely on the aHC (see Figure 2a). As time progresses, remembering is expected to rely more on gist-like compared to detailed memory representations, represented by a shift from posterior to anterior involvement in memory over time (Sekeres, Winocur, & Moscovitch, 2018). The authors base this functional differentiation on the connectivity of the aHC to the temporal pole (Kahn et al., 2008) and the vmPFC (Poppenk et al., 2013), which are hypothesized to support semantic and schema memory, respectively (Sekeres, Winocur, & Moscovitch, 2018). Conversely, perceptually rich memory representations are expected to be supported by connectivity of the pHC to the posterior neocortex (Poppenk et al., 2013; Robin & Moscovitch, 2017a; Sekeres, Winocur, & Moscovitch, 2018).

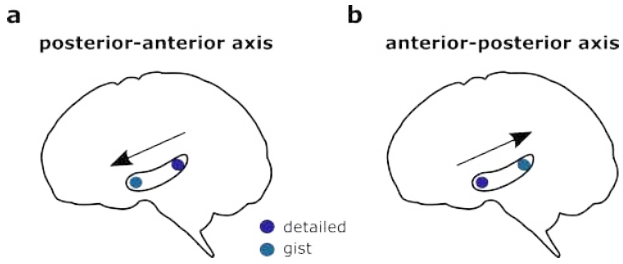

Figure 2. Two perspectives on memory transformation along the hippocampal long axis. a The most recent version of Trace Transformation Theory (Robin & Moscovitch, 2017a; Sekeres, Winocur, & Moscovitch, 2018) proposes that detailed memories are represented by the posterior hippocampus (pHC), while gist-like memories rely on the anterior hippocampus (aHC). As time progresses (visualized by the arrow), remembering is expected to rely less on detailed, but more on gist-like memory representations, represented in a shift from posterior to anterior involvement in memory over time **b** Emerging research (e.g. Dandolo and Schwabe, 2018; Tompary and Davachi, 2017) points to the exact opposite direction, with a time-dependent transformation of memory from the aHC to the pHC representing detailed and gist-like memory, respectively.

FMRI data on time-dependent memory transformation along the anterior-posterior hippocampal axis have been mixed. Some studies align with the predictions of TTT, showing decreased pHC activity in memory retrieval one day after learning (Bosshardt et al., 2005; Ritchey et al., 2015;

Takashima et al., 2009) or when retrieving remote compared to recent autobiographical memories (Gilmore et al., 2021). Other research indicates a reduction in aHC activity from three days to three months after learning, without a corresponding decrease in pHC activity (Harand, Bertran, La Joie, et al., 2012). Furthermore, the magnitude of aHC activity has been positively associated with the recall of recent autobiographical memories compared to remote ones (Gilboa et al., 2004), correct source memory retrieval (Ekstrom et al., 2011; Ezzyat & Davachi, 2014; Langnes et al., 2019), and vivid autobiographical memory retrieval (Svoboda et al., 2006). The later findings point to a role of the aHC in maintaining detailed and context-rich memory representations, even over extended periods.

While univariate fMRI analyses allow investigating differences in blood oxygenation level dependent (BOLD) signal magnitude between different regions and offer valuable insights into *which* regions may be related to memory retrieval over time, multivariate pattern analyses, particularly representational similarity analyses (RSAs), allow inferences on *how* regions of the brain represent information (Dimsdale-Zucker & Ranganath, 2018). Studies applying this methodology showed that the aHC carries contextual information immediately or one day after learning (Hannula et al., 2013; Ritchey et al., 2015), indicating its role in representing contextual details of recent memories. Moreover, the pHC has been shown to represent remote rather than recent events (Bonnici et al., 2012; Bonnici et al., 2013), indicating a shift from memory representation from anterior to posterior hippocampus over time. This anterior-posterior transformation was further supported by findings that object-word associations, after one night of sleep, show more differentiated representations in the aHC and are positively associated with source memory, while the pHC was linked to more generalized memory representations (Cowan, Liu, et al., 2021). Similarly, activation patterns of overlapping memories were more similar in the pHC a week after learning, indicating the emergence of generalized memory representation over time (Tompary & Davachi, 2017). Importantly, Dandolo and Schwabe (2018) showed that aHC involvement during memory testing decreased from 1d to 28d after encoding and was positively associated with memory specificity, while pattern representations in the pHC became more similar to semantically related material over time.

Thus, emerging evidence from multivariate analyses of memory over time suggests that, contrary to the assumption of TTT (Robin & Moscovitch, 2017a; Sekeres, Winocur, & Moscovitch, 2018), memories are transformed from the anterior to the posterior hippocampus, with the aHC representing more specific, recent memories and the pHC representing less specific memory representations at a remote time point (see Figure 2b). These findings align with the consistent association of the aHC with memory encoding (Langnes et al., 2019, 2020; Lepage et al., 1998; Parsons et al., 2006; Schacter & Wagner, 1999), novelty detection (Cowan, Fain, et al., 2021), and scene construction (Zeidman & Maguire, 2016), which may require specific memory representations.

1.3 Memory modulation

The memory of events surrounding emotional experiences, such as the birth of a child or the death of a loved one, can persist in a manner unlike that of more mundane events. Emotional arousal is a powerful modulator of various memory processes, from initial memory encoding and consolidation to retrieval mechanisms (Roozendaal & Hermans, 2017). Although emotional enhancement of memory is essential for survival as it aids in the avoidance of future threats (Hamann, 2001; LeDoux, 2012), the persistent and vivid recollection of aversive experiences can affect our mental well-being and contribute to psychopathology (Brewin et al., 2010; Ehlers & Clark, 2000).

It is well established that emotional events, compared to neutral ones, recruit specific neural mechanisms that enable their preferential storage in memory. A key role in this process is attributed to the noradrenergic arousal-induced activation of the amygdala, which modulates memory plasticity processes in the hippocampus and neocortex (Cahill et al., 1994; Cahill & McGaugh, 1995; Fastenrath et al., 2014; McGaugh, 2000; McIntyre et al., 2012). This arousal-related mechanism specifically promotes the long-term consolidation of emotional memories (Cahill & McGaugh, 1998; McReynolds & McIntyre, 2012). However, enhanced recall of emotional events over neutral ones is also evident immediately after encoding, before a consolidation delay (Kang et al., 2014; Murty et al., 2011; Schümann et al., 2018; Talmi & McGarry, 2012; Talmi et al., 2007). This emotional enhancement of immediate memory has been primarily attributed to the preferential processing of emotionally negative items compared to neutral ones at encoding, which may particularly influence the subsequent free recall of these items (Talmi, 2013).

1.3.1 Modulating encoding

The emotional enhancement of immediate memory has been attributed to the characteristics of emotional information, which may promote preferential processing of and increased attention to emotional items over neutral ones at encoding, thus facilitating their immediate free recall (Talmi, 2013; Talmi & McGarry, 2012; Talmi et al., 2007). Indeed, emotional information has been shown to be rapidly processed (Globisch et al., 1999) and to interfere with the processing of other information (Dolcos et al., 2020; Hartikainen et al., 2000; Tipples & Sharma, 2000; Vuilleumier et al., 2001). This preferential processing of emotional over neutral information has been observed in increased gaze fixation on emotional stimuli compared to neutral stimuli (Bradley et al., 2015) and increased involvement of perceptual, prefrontal, and parietal cortices in emotional memory encoding (Mickley Steinmetz & Kensinger, 2009; Mickley Steinmetz et al., 2010; Murty et al., 2011; Talmi et al., 2007).

The locus coeruleus-noradrenaline system, the primary source of noradrenaline in the brain, has been identified as the primary attractor towards emotional stimuli (Markovic et al., 2014; Mather et al., 2016; Pourtois et al., 2013; Roozendaal & Hermans, 2017; Sara & Bouret, 2012). Increased neural activity in the central noradrenergic system has been linked to activation of a neural network that coordinates various cognitive functions crucial for processing salient stimuli and includes the dorsal anterior cingulate cortex and the amygdala (Hermans et al., 2011; Menon,

2011; Seeley et al., 2007). Accordingly, enhanced attention to emotionally salient material has been associated with the amygdala and its interactions with the central noradrenergic system (Markovic et al., 2014; Mather et al., 2016). Furthermore, amygdala activity has been linked to the the immediate recollection of emotional items (Kensinger et al., 2011). It has been suggested that the amygdala plays a crucial role in allocating processing resources to salient stimuli via frontoparietal attention and cognitive control cortices, as well as sensory pathways (Bowen et al., 2018; Kensinger, 2009; Mather & Sutherland, 2011; Pessoa, 2009; Pessoa & Adolphs, 2010; Pourtois et al., 2013).

The aHC, which is anatomically (Pitkänen et al., 2000) and functionally (Dolcos et al., 2004b; Tillman et al., 2018) connected to the amygdala, has also been repeatedly linked to the successful encoding of emotional memory (Dolcos et al., 2004b; Murty et al., 2011). Findings in patients with medial temporal lobe pathology (Richardson et al., 2004) suggest reciprocal interactions between the aHC and amygdala during the encoding of emotional material. Moreover, both the amygdala (Balderston et al., 2011; Blackford et al., 2010; Ranganath & Rainer, 2003) and the aHC (Cowan, Fain, et al., 2021; Kafkas & Montaldi, 2018; Strange et al., 1999) have been associated with the detection of novel stimuli, which may promote attention to and encoding of novel stimuli (Ranganath & Rainer, 2003).

While these findings implicate the anterior MTL in encoding novel, salient stimuli, emotional events are often encountered repeatedly. Repeated study is well known to strengthen memory (Ebbinghaus, 1885; Hebb, 1961; Shao et al., 2022). An encoding variability account (Bower, 1972; Estes, 1955; Johnston, 1976) postulates that each encounter of an event is encoded differently due to variations in the temporal or spatial encoding context, multiplying access routes to the memory and thus promoting future retrieval (Howard & Kahana, 2002; Johnston, 1976; Raaijmakers & Shiffrin, 1992). An alternative account suggests that each encoding episode reactivates and thus strengthens the memory representation formed during previous encoding (Appleton-Knapp et al., 2005; Thios & D'Agostino, 1976). Studies that contrast these two accounts indicate that successful memory formation occurs when the same neocortical representations are reactivated across subsequent encoding episodes rather than when activation patterns are more variable across repetitions (Feng et al., 2019; Xue et al., 2010; Xue et al., 2013). However, these studies included only neutral events; therefore, it remains unknown whether the evolution of emotional memory across repeated encoding is based on more stable or more variable (re)activation patterns.

1.3.2 Modulating consolidation

Decades of research have shown that emotional arousal or stress after encoding results in stronger and more lasting memories (Christianson & Mjörndal, 1985; McGaugh, 2006, 2000). While human studies have focused predominantly on the effect of emotional arousal on memory encoding, animal studies often employ a post-learning treatment paradigm to demonstrate enhanced consolidation independently of emotional modulation of encoding (McGaugh & Cahill, 1997; McGaugh, 2000; Roozendaal & Hermans, 2017). Specifically, pharmacological studies in animals have employed targeted administration of noradrenaline or noradrenergic agents to relevant brain regions (Roozendaal & Hermans, 2017; Roozendaal & McGaugh, 2011). Administering

noradrenaline or β-adrenoceptor agonists into the basolateral amygdala (BLA) immediately after training results in a dose-dependent improvement in memory consolidation (Barsegyan et al., 2014; Ferry & McGaugh, 1999; Hatfield & McGaugh, 1999; Liang et al., 1990; Roozendaal et al., 2008; Yang & Liang, 2014). On the contrary, infusions of β -adrenoceptor antagonists after training impair memory retention and prevent the enhancement of memory caused by co-administered noradrenaline (Barsegyan et al., 2014; Roozendaal et al., 2008). In addition to β-adrenoceptor influences, α_1-adrenoceptor agonist infusions into the BLA after training also enhance memory consolidation (Ferry et al., 1999b). The memory enhancement induced by α_1-adrenoceptor activation likely involves interaction with β-adrenoceptors, as post-training infusions of a β-adrenoceptor antagonist into the BLA block the memory enhancement caused by activation of α_1-adrenoceptors (Ferry et al., 1999a). While the amygdala is not a storage site itself (Packard et al., 1994; Packard & Teather, 1998), it is expected to modulate memory storage in other brain regions (McGaugh, 2000). Evidence indicates that the BLA, upon emotional arousal or noradrenergic activation, modulates information transfer and neural plasticity mechanisms in different memory circuits to enhance the consolidation of various types of training experiences (Izquierdo et al., 2016; Paz & Pare, 2013; Roozendaal & Hermans, 2017; Roozendaal et al., 2008). Consequently, post-training noradrenergic manipulation of BLA activity can influence neuroplasticity and information storage processes in other brain regions known to be involved in memory processing, including the hippocampus (Lovitz & Thompson, 2015; Roozendaal & Hermans, 2017; Roozendaal & McGaugh, 2011).

Human research has demonstrated that administering the noradrenergic stimulant yohimbine (YOH)–an α_2-adrenoceptor antagonist–before learning can enhance memory (O'Carroll et al., 1999). Conversely, pre-learning administration of the β-adrenoceptor antagonist propranolol, which blocks the effects of endogenous noradrenaline, results in impaired memory for emotionally arousing events (Cahill et al., 1994). FMRI studies (Strange & Dolan, 2004; van Stegeren et al., 2005) indicate that propranolol reduces amygdala activity during the encoding of emotional stimuli, resulting in a reduction in hippocampal activity during retrieval of the same stimuli. While these studies affected noradrenergic arousal during encoding and thus do not allow for a differentiation between effects of noradrenergic arousal on memory encoding or memory consolidation, research employing post-encoding exposure to psychosocial (Abercrombie et al., 2006; Preuß & Wolf, 2009), or physiological (Cahill et al., 2003; Smeets et al., 2008; Zoladz et al., 2015) stressors, indicated that post-encoding emotional arousal also facilitates memory after a consolidation delay.

Thus, it is well established that emotional arousal-related noradrenergic activation increases memory storage processes. However, the long-term effects of noradrenergic activity, particularly whether noradrenergic arousal after encoding may affect time-dependent system consolidation of memories, have been largely unknown. Beyond their increased strength, emotionally enhanced memories are often characterized by increased vividness and the subjective feeling of remembering (Sharot et al., 2004; Talarico & Rubin, 2003), suggesting that emotional arousal may affect the transformation of memories over time (Robin & Moscovitch, 2017a; Sekeres, Winocur, & Moscovitch, 2018; Winocur, Moscovitch, & Bontempi, 2010). A study in rodents (Atucha et al.,

2017) indicated for the first time that noradrenergic arousal may influence the dynamics of time-dependent memory reorganization. The results showed that rats administered noradrenaline into the BLA shortly after training on an inhibitory avoidance task did not show the typical decrease in memory specificity as observed in saline-treated rats. Instead, rats treated with noradrenaline preserved specific memory at the 28d retention test. Moreover, this maintenance of memory specificity in rats treated with noradrenaline was accompanied by a greater dependence on the hippocampus over time, along with altered patterns of DNA methylation and mRNA expression of memory-related genes in both the hippocampus and the neocortex after 28d (Atucha et al., 2017). These findings suggest that noradrenergic stimulation shortly after learning may not only delay but even reverse the process of systems consolidation, challenging the textbook view of a linear progression of time-dependent memory reorganization from the hippocampus to the neocortex. However, whether post-encoding noradrenergic arousal affects the time-dependent reorganization of memories in humans remains unknown.

1.4 Research goals

Memories evolve over time, with some fading rapidly while others appear to persist vividly. Emotional arousal plays a crucial role in this dynamic process, influencing both memory encoding and consolidation. While the persistent and vivid recollection of emotional events may be crucial for survival by helping to avoid future threats, such recollections can also impact our mental well-being and contribute to psychopathology (Brewin et al., 2010).

Emotional events are often encountered repeatedly, and memories are shaped through these recurrent (re)encoding processes (Dudai, 2012; Nadel & Moscovitch, 1997). In *study 1*, we aimed at elucidating the neural mechanisms underlying memory enhancement for repeatedly encountered emotional events. Participants encoded emotionally negative or neutral scene images across three consecutive runs in an MRI scanner, followed by an immediate free recall test. We expected that emotional enhancement of subsequent memory would be characterized by increased activity of the amygdala and aHC during initial encoding (Cowan, Fain, et al., 2021; Dahlgren et al., 2020; Murty et al., 2011; Ranganath & Rainer, 2003), and more consistent pattern representations across encoding runs in visual and frontoparietal cortices associated with attention and cognitive control processes.

While study 1 focused on the effects of emotional arousal at encoding and its impact on immediate memory, *study 2* aimed to modulate the dynamics of system consolidation through noradrenergic stimulation at initial consolidation. This involved a single pharmacological elevation of post-encoding noradrenergic arousal using the α_2-adrenoceptor antagonist YOH, combined with fMRI scanning during image encoding and recognition testing 1d or 28d later. Drawing on previous findings in rodents (Atucha et al., 2017), we hypothesized that noradrenergic arousal would improve delayed memory performance compared to placebo (PLAC) and decelerate or even reverse the course of systems consolidation, indicated by increased hippocampal involvement and decreased neocortical involvement in memory over time.

It has been proposed (Nadel & Moscovitch, 1997; Winocur & Moscovitch, 2011; Winocur, Moscovitch, & Bontempi, 2010) that the time-dependent reorganization of memories from the hippocampus to the neocortex is accompanied by a decrease in memory specificity over time. Recent evidence furthermore suggests a transformation within the hippocampus itself, from specific, detailed memory representations in the aHC to more gist-based representations in the pHC (Cowan, Liu, et al., 2021; Dandolo & Schwabe, 2018; Tompary & Davachi, 2017). However, the nature of these qualitative changes, particularly whether memory transformation over time is semantic or perceptual in nature, remains unknown. In *study 3*, we investigated the nature of memory transformation over time and whether it occurs equally for both emotionally negative and neutral items. Participants encoded scene images in the fMRI and returned for a recognition test 1d or 28d later. Critically, to probe memory specificity, this test included original, novel, and novel images that were either semantically or perceptually related to the original image. We expected a semantic transformation over time, manifesting as increased confusion of original items with items sharing the semantic gist of the original memory. This time-dependent memory semantization was hypothesized to be linked with a reorganization of memories from the hippocampus to the neocortex and within the hippocampus itself, from its anterior to its posterior pole.

2 Experimental studies

2.1 Study 1: Modulating immediate memory

Krenz, V., Alink, A., Roozendaal, B., Sommer, T., & Schwabe, T. (under peer-review). *Memory boost for recurring emotional events is driven by initial amygdala response promoting stable neocortical patterns across repetitions*. – (Appendix A)

2.1.1 Background

Emotionally arousing events are typically vividly remembered (Christianson, 1992; Kensinger & Ford, 2020; McGaugh, 2006), which is generally highly adaptive but may contribute to mental disorders such as PTSD. Previous research on emotional memory has focused primarily on events that were experienced once (Dahlgren et al., 2020; Dolcos et al., 2004b; Kensinger, 2009; Murty et al., 2011), leaving the mechanisms underlying the memory of repeatedly encountered emotional events largely unexplored. In this study, our objective was to elucidate the brain mechanisms associated with memory for recurring emotional events. Specifically, we sought to determine whether memory enhancement for recurring emotional events is linked to more variable neural representations, as predicted by the an encoding variability account (Bower, 1972; Estes, 1955; Johnston, 1976), or to more stable representations across repetitions, as suggested by a memory reinstatement account (Thios & D'Agostino, 1976). Furthermore, we investigated whether transient anterior MTL activity may modulate sustained activation patterns over repetitions associated with emotional enhancement of subsequent memory.

2.1.2 Methods

One hundred and three right-handed young adults (51 males and 52 females) were repeatedly presented with 30 emotionally negative and 30 neutral scene images during three consecutive encoding runs in an MRI scanner. Memory for these images was tested in a free recall test, immediately after encoding. We applied single-trial region of interest (ROI) based analyzes to investigate dynamic changes in univariate activity over runs associated with emotional enhancement of subsequent memory. Furthermore, a multivariate encoding pattern similarity analysis (Feng et al., 2019; Xue et al., 2010; Xue et al., 2013) probed the stability (vs. variability) of activation patterns across repetitions. We expected an emotional enhancement of immediate free recall, associated with enhanced anterior MTL (amygdala and aHC) activity at initial exposure, i.e. in the first encoding run, and more consistent pattern representations across encoding runs specifically in visual cortices and frontoparietal cortices associated with attentional and cognitive control processes. Using moderated mediation analyzes, we further examined the link between

transient anterior MTL involvement and stable neocortical encoding patterns during successful encoding of recurring emotional events.

2.1.3 Results

Analyzing univariate activity related to successful encoding revealed that emotional memory encoding was associated with elevated amygdala and aHC activity at initial event exposure, consistent with previous findings associating the anterior MTL with detecting novel, salient stimuli (Cowan, Fain, et al., 2021; Ranganath & Rainer, 2003) and emotional memory (Dahlgren et al., 2020; Murty et al., 2011). Notably, our findings demonstrate a dynamic involvement of the anterior MTL in successful emotional memory encoding, with a decrease in activation over repeated exposures. This trajectory of decreased anterior MTL (amygdala and aHC) activity across repetitions was mirrored by anterior temporal cortices and the right inferior frontal gyrus (IFG), which have both been linked to attention allocation based on stimulus salience (Corbetta & Shulman, 2002), emotional memory enhancement (Dolcos et al., 2004a; Ritchey et al., 2011; Weintraub-Brevda & Chua, 2018), novelty detection (Ranganath & Rainer, 2003), and semantic memory (Binder & Desai, 2011; Patterson et al., 2007; Ralph et al., 2017). In sharp contrast to the trajectory in anterior temporofrontal regions, successful encoding of neutral images was associated with an increase in activation over repetitions in posterior temporal and parietal regions, including the angular gyrus, previously associated with semantic memory processes (Binder & Desai, 2011; Liebenthal et al., 2014; Patterson et al., 2007; Ralph et al., 2017).

Furthermore, the results of our multivariate pattern analyzes revealed that successful encoding of emotional images was associated with stable activation patterns over encoding repetitions in frontoparietal cognitive and attention control regions such as the orbitofrontal cortex, anterior cingulate cortex, as well as the superior parietal lobule (SPL). Importantly, a multilevel moderated mediation analysis revealed that emotional memory, mediated by SPL encoding pattern stability (path $a_1 \times b$ indirect effect; see Figure 3, left panel), was enhanced by the extent of amygdala activation at initial exposure (index of moderated mediation; see Figure 3, right panel).

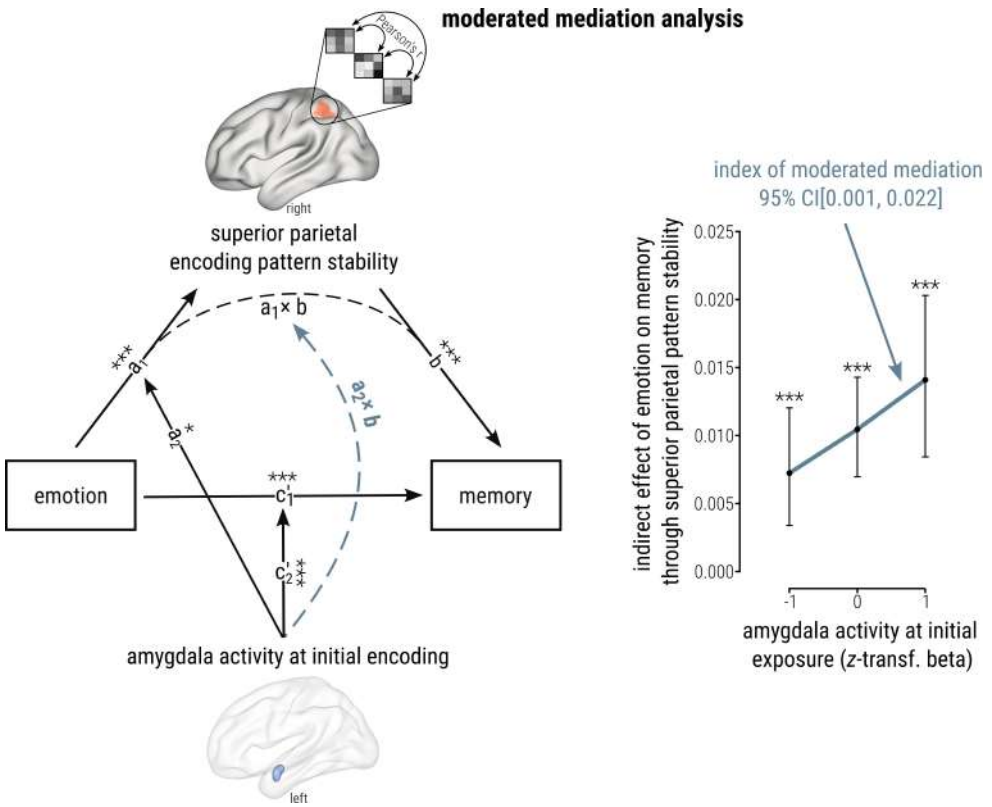

Figure 3. Amygdala activity at first exposure boosts subsequent emotional memory via neocortical encoding pattern stability. *Left:* Multilevel moderated mediation analyzes revealed a significant mediation of emotional memory enhancement through superior parietal encoding pattern stability (indirect effect; $a_1 \times b$). *Right:* The indirect effect of emotion on subsequent memory through stable neocortical encoding patterns was significantly enhanced by amygdala activity during initial stimulus exposure, as indicated by the index of moderated mediation ($a_2 \times b$). These findings underscore the pivotal role of rapid amygdala engagement in emotional memory encoding and its interaction with the superior parietal lobule in enhancing memory for recurring emotional events. Inference statistical testing of the index of moderated mediation is based on bias-corrected, bootstrapped confidence interval (as recommended by Hayes, 2015). Points represent conditional indirect effects at low (-1SD), mean, and high ($+1$SD) levels of the moderator $\pm$ SE. Regression line illustrates the index of moderated mediation as the linear change in the indirect effect as a function of the moderator. All $n = 103$. Depicted p-values are two-tailed and FDR-corrected for multiple comparisons, accounting for the number of regions of interest in this analysis (p_{corr}). ***$p < 0.001$; *$p < 0.050$.

2.1.4 Conclusion

These findings reveal a dynamic interplay between transient amygdala activation and persistent neocortical activation patterns in the successful encoding of recurring emotional events. Moreover, our data indicate distinct trajectories of neocortical activity over encoding repetitions of emotional and neutral events, with a decrease in the involvement of anterior temporofrontal regions for emotionally salient stimuli and a progressive increase in posterior temporal and parietal activation for neutral events.

2.2 Study 2: Modulating systems consolidation

Krenz, V., Sommer, T., Alink, A., Roozendaal, B., & Schwabe, L. (2021). Noradrenergic arousal after encoding reverses the course of systems consolidation in humans. *Nature Communications*, 12(1), 6054. https://doi.org/10.1038/s41467-021-26250-7 – (Appendix B)

2.2.1 Background

The time-dependent redistribution of memory from the hippocampus to neocortical areas has been a focus of memory research for decades (Frankland & Bontempi, 2005; McClelland et al., 1995; Scoville & Milner, 1957; Squire & Alvarez, 1995; Winocur & Moscovitch, 2011). Recent evidence suggests that systems consolidation may be more dynamic than originally assumed (Brodt et al., 2018; Brodt et al., 2016). However, whether systems consolidation can be experimentally manipulated and shaped by conditions such as emotional arousal remained unclear. Based on initial findings in rodents (Atucha et al., 2017), we investigated whether noradrenergic stimulation shortly after encoding may influence and even reverse the course of systems consolidation in humans.

2.2.2 Methods

One hundred and four right-handed young adults encoded 30 emotionally negative and 30 emotionally neutral scene images over three consecutive encoding runs in an MRI scanner. Right before scanning, participants received orally PLAC or YOH, an α_2-adrenoceptor antagonist that leads to increased noradrenergic stimulation. PLAC and YOH pills were indistinguishable, allowing for a randomized and double-blinded pharmacological manipulation. The timing and dosage of YOH administration were chosen according to previous studies (Kluen et al., 2017; Schwabe et al., 2012) and based on the known pharmacodynamics of YOH showing that significant drug action can be expected about 60 minutes after drug intake. Systolic and diastolic blood measurements throughout experimental Day 1 confirmed that YOH was not effective during encoding, but elevated noradrenergic arousal 85 minutes after drug intake until the end of experimental Day 1. Critically, to probe time-dependent systems consolidation, recognition memory performance was tested 1d or 28d after encoding, again in an MRI scanner, allowing the assessment of changes in neural representations from encoding to test using univariate as well as multivariate fMRI analyzes. Thus, the final study consisted of a 2 (drug) $\times$ 2 (delay) between-subjects design with 26 participants (12 females, 12 males) per group.

We predicted that YOH administration would enhance memory performance, as measured by sensitivity index d', after 28d and decelerate or even reverse the course of systems consolidation, as reflected by an increased hippocampal but reduced neocortical involvement over time. Moreover, leveraging a searchlight-based multivariate pattern analysis for the assessment of encoding-retrieval similarity (ERS), an indicator of episodic memory reinstatement (Ritchey et al., 2013; Staresina et al., 2012; Tompary & Davachi, 2017; Tompary et al., 2016; Wing et al., 2015; Xiao et al., 2017), we hypothesized that hippocampal representational patterns of memories at

the remote test should become even more similar to the pattern at encoding if noradrenergic stimulation was elevated after encoding.

2.2.3 Results

As expected, memory performance decreased from 1d to 28d after memory encoding. This time-dependent decrease in memory performance was significantly lower for negative compared to neutral images. Most importantly, noradrenergic stimulation shortly after encoding decreased the time-dependent decline in behavioral memory performance, regardless of the emotionality of the encoded stimuli.

On the neural level, hippocampal activity decreased from 1d to 28d after encoding in the PLAC group, representing a neural reorganization of memory over time (Frankland & Bontempi, 2005; McClelland et al., 1995; Squire, 1992; Squire & Alvarez, 1995). Similarly, hippocampal ERS decreased significantly over time in the PLAC group (see Figure 4), suggesting that activity patterns at memory test became more distinct from the encoding-related patterns as time after encoding proceeded. This decrease in hippocampal involvement in memory was paralleled by a time-dependent increase in prefrontal (left IFG) and posterior parietal (precuneus and angular gyrus) cortices previously implicated in remote, schematic memory Binder and Desai, 2011; Brodt et al., 2018; Brodt et al., 2016; Sommer, 2016; Takashima et al., 2009; van der Linden et al., 2017. Notably, the increase in prefrontal activity at recognition testing was directly associated with the decrease in memory performance over time.

Critically, noradrenergic stimulation after encoding markedly altered all of these time-dependent neural changes. For hippocampal activity, there was not only no decrease but even an increase from 1d to 28d after encoding. Similarly, hippocampal activity patterns during recognition testing resembled the encoding-related patterns even more at the 28d versus 1d delayed test in the YOH group (see Figure 4). Conversely, prefrontal and posterior parietal activity even decreased over time in the YOH group. Moreover, psychophysiological interaction analysis indicated that while the connectivity between the left IFG and hippocampus increased in the PLAC group from 1d to 28d, there was even a decrease in IFG-hippocampus connectivity at 28d compared to memory testing after 1d in the YOH group. As an increase in hippocampal-IFG connectivity has been linked with the generation of semantic associations (Addis & McAndrews, 2006), this finding further indicates that noradrenergic activation after encoding may reverse systems consolidation dynamics.

2.2.4 Conclusion

We show that pharmacologically enhanced noradrenergic activity shortly after encoding reduces the time-dependent decline of memory performance and, more importantly, increases hippocampal but decreases neocortical involvement in memory from 1d to 28d after encoding. Thus, our results mirror previous findings in rodents (Atucha et al., 2017) and provide the first evidence in humans that noradrenergic stimulation at initial consolidation may have long-lasting effects on memory by altering the process of time-dependent neural reorganization of memory. These findings critically

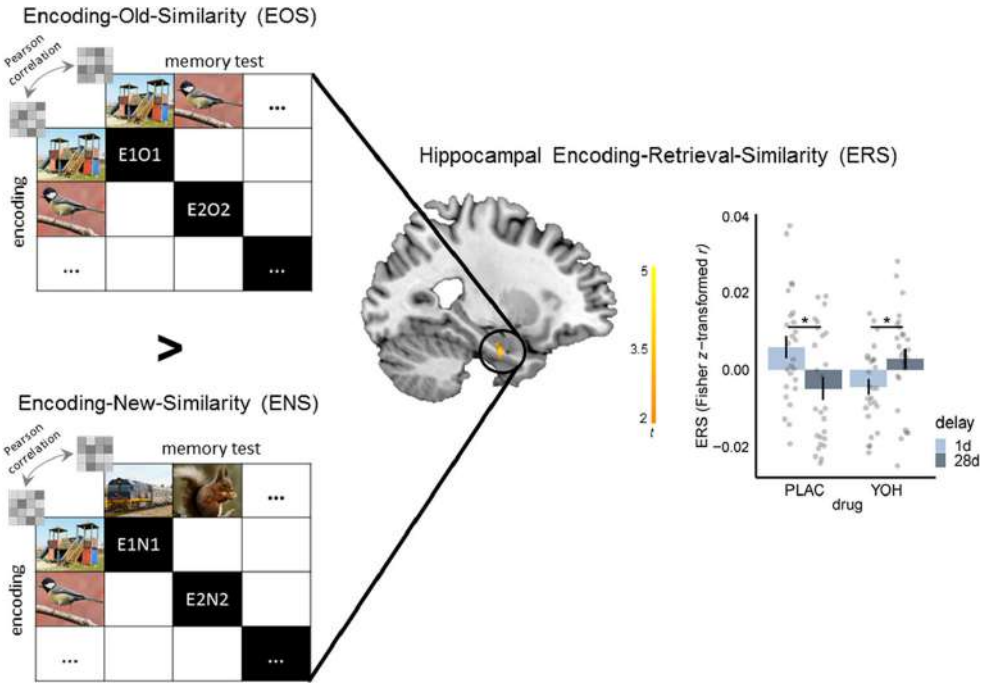

Figure 4. Noradrenergic stimulation increased multivariate memory reinstatement over time. Participants in the placebo group (PLAC) showed a significant decrease in hippocampal pattern reinstatement, as reflected in ERS, from 1d to 28d after encoding, while there was even a significant increase in hippocampal ERS from the 1d to the 28d test in the yohimbine (YOH) group. Visualizations of the ERS results include the t-map for the interaction of drug $\times$ delay, superimposed on a sagittal section of a T1-weighted template image, and the Fisher z-transformed r-values for the significant cluster in the contrast EOS $>$ ENS. Bars represent mean $\pm$ SEM. N = 104 participants. All depicted p-values are two-tailed. *$p < 0.050$. Reprinted from Krenz et al. (2021).

challenge our current understanding of systems consolidation dynamics by showing that memories are not necessarily reorganized from the hippocampus to the neocortex, but that this process can be altered and even reversed.

2.3 Study 3: The nature of memory transformation

Krenz, V., Alink, A., Sommer, T., Roozendaal, B., & Schwabe, L. (2023). Time-dependent memory transformation in hippocampus and neocortex is semantic in nature. *Nature Communications*, 14, 6037. https://doi.org/10.1038/s41467-023-41648-1 – (Appendix B)

2.3.1 Background

The neural reorganization of memory from hippocampal to neocortical regions is expected to be accompanied by a transformation from a detailed episodic memory trace to a less specific memory representation (Nadel & Moscovitch, 1997; Winocur & Moscovitch, 2011; Winocur, Moscovitch, & Bontempi, 2010), with initial evidence pointing to the possibility of a transformation along the hippocampal anterior-posterior axis (Cowan, Liu, et al., 2021; Dandolo & Schwabe, 2018; Tompary & Davachi, 2017). The nature of these qualitative changes over time remains elusive,

particularly whether the generalization of memories over time is semantic in nature or due to a perceptual transformation, with the latter being more in line with the common view that memories fade over time (Cooper & Ritchey, 2019). Here, we aimed to elucidate the nature and neural signature of time-dependent memory transformation. Specifically, we determined whether memories are semantically or perceptually transformed, which neural mechanisms are involved in this process, and whether memories for emotionally negative and neutral material are transformed in a comparable manner over time.

2.3.2 Methods

Fifty-two right-handed young adults participated in a three-day experimental design. On experimental Day 1, participants encoded 30 emotionally negative and 30 neutral scene images over three consecutive runs in an MRI scanner. Participants returned for a recognition test in the MRI scanner 1d or 28d after encoding, with each delay group consisting of 12 female and 12 male participants. Critically, the recognition test included, in addition to original and entirely novel, unrelated items, lures that were either semantically or perceptually related to the old items, probing the nature memory transformation over time. A perceptual transformation would be indicated if, with increasing delay after encoding, perceptually related, but not semantically related, items are endorsed as 'old'. Conversely, a semantic transformation would be indicated if participants endorse semantically related, but not perceptually related, items as 'old'. Participants returned to the lab after at least three and a maximum of eight days after experimental Day 2 for a behavioral task, in which they indicated their individually perceived semantic and perceptual relatedness of the 60 encoded pictures to each of its perceptually related, semantically related, or unrelated lure. Results of this rating task confirmed the finding of a behavioral pilot showing that semantically related lures were perceived as semantically more related to their corresponding original image than perceptually related and entirely novel lures, while perceptually related images were perceived as perceptually related but not semantically related to the corresponding old lure. To examine the neural mechanisms involved in the transformation of memories over time, we leveraged model-based RSAs (Dandolo & Schwabe, 2018; Kriegeskorte et al., 2008; Nili et al., 2014) assessing how the similarity between activation patterns of encoded items and different lure types (semantically related vs. perceptually related vs. unrelated) at memory testing changes in the course of memory transformation. Moreover, we compared encoding-pattern reinstatement, i.e. ERS, along the anterior-posterior hippocampal axis and its association with behavioral memory indicators. We expected that memory would be semantically, but not perceptually transformed, and semanticized memory representations should be reflected in the pHC as well as in prefrontal and posterior parietal cortices previously associated with remote, semanticized memory. Conversely, we expected aHC to represent detailed memory, which may decrease over time.

2.3.3 Results

Over time, participants showed a significant decrease in the correct recognition of original items as 'old' (hits), and this delay-dependent decrease in recognition performance was significantly lower for emotionally negative compared to neutral images (see Figure 5, left panel). Importantly, participants showed a significant time-dependent increase in the endorsement of semantically related lures over time (false alarms, FAs), indicating that remote memories represented the semantic gist of the original memory (see Figure 5, right panel). Importantly, we found no credible evidence for an increase in FAs for lures that were perceptually related to original images. This semantic transformation was more pronounced for emotionally negative compared to neutral items, indicating that stimulus-transient emotional arousal may specifically support memory for the semantic gist of the original memory, at the cost of memory specificity over time.

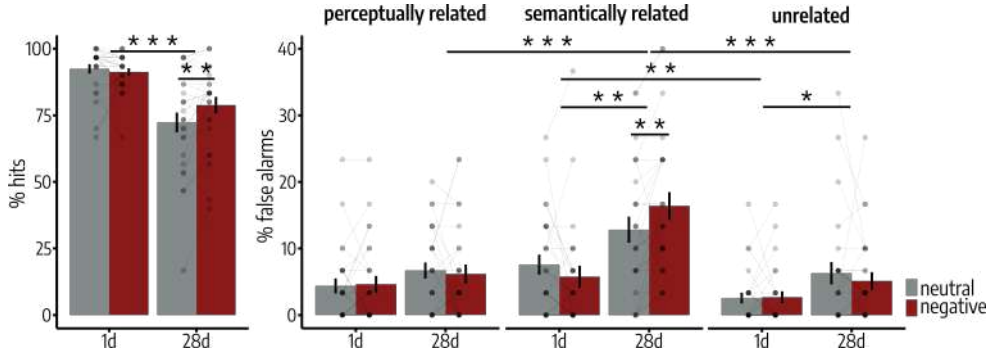

Figure 5. Memories are semantically but not perceptually transformed over time. *Left:* The correct recognition of old items as 'old' significantly decreased from 1d to 28d after encoding. This delay-dependent decrease in hits was significantly higher for emotionally negative compared to neutral images. *Right*: The increase in false alarms (FAs) from 1d to 28d after encoding was significantly higher for lures that were semantically related to the original images, compared to perceptually related or unrelated lures. This semantization of memories over time was significantly higher for emotionally negative compared to neutral items. All $n = 52$ participants. Bars represent mean $\pm$ SEM. Connected dots represent individual data points. All post-hoc tests were applied on estimated marginal means with Šidák correction for multiple comparisons. All reported p-values are two-tailed. *$p < 0.050$; **$p < 0.010$; ***$p < 0.001$. Adapted from Krenz et al. (2023).

On the neural level, the results of our multivariate model-based analyzes indicated that the aHC represents recently encoded events in a detailed manner, including perceptual features, and that these anterior hippocampal representations decrease over time. This analysis did not indicate semantically transformed representations of previously encoded items in either the aHC or the pHC. However, semantically, but not perceptually, transformed pattern representations increased from 1d to 28d in prefrontal (vmPFC) and posterior parietal cortices (precuneus and angular gyrus). Intriguingly, these regions have been repeatedly associated with the representation of remote, schematic memory (Binder & Desai, 2011; Bowman & Zeithamova, 2018; Brodt et al., 2018; Brodt et al., 2016; Frankland & Bontempi, 2005; Frankland et al., 2004; Sekeres et al., 2020; Sommer, 2016; Takashima et al., 2009). Furthermore, encoding-pattern reinstatement analyzes revealed an increase in ERS in the pHC from 1d to 28d after encoding, which was positively associated with FAs for semantically related lures, without a similar association with perceptually related lures. Thus, our memory reinstatement analyzes indicated that the pHC is

associated with the reinstatement of remote memories that may be rather unspecific in nature, representing the semantic, but not perceptual, gist of the original memory.

2.3.4 Conclusion

We show that the transformation of memory over time is semantic, rather than perceptual, in nature and that this semantization of memory over time may be enhanced for emotionally negative compared to neutral material. On the neural level, this semantic transformation was not only linked to the emergence of semantically transformed representations in neocortical areas over time but also to time-dependent changes within the hippocampus, with highly specific pattern representations for encoded events in the aHC that decreased over time while posterior hippocampal encoding-pattern reinstatement was linked to the extent to which remote memories were semantically transformed. These findings indicate that qualitative changes in memory over time, associated with distinct representational changes in the neocortex and within the hippocampus, reflect a semantic transformation, which may promote the integration of memories into abstract knowledge structures.

3 General discussion

Memories evolve over time. Far from being static records, some memories seem to fade away quickly, while others, for instance emotional life events, persist vividly. This evolution of memories, from repeated encoding and immediate retrieval to long-term reorganization and modulation by arousal, is the focus of this dissertation. At the heart of this endeavor is the long-standing debate over the role of the hippocampus in memory over time. The findings presented critically challenge the textbook view of a linear reorganization of memories in their original form, from the hippocampus to the neocortex (Frankland & Bontempi, 2005; McClelland et al., 1995; Squire & Alvarez, 1995), while also inviting a new discourse on a functional differentiation within the hippocampus.

In study 1, we investigated encoding-related dynamics across repetitions and how these relate to the emotional enhancement of immediate free recall. The findings reveal that successful emotional memory formation is linked to persistent (re)activation patterns in attention and cognitive control cortices. This was coupled with transient activation in the anterior MTL (amygdala and aHC), as well as temporofrontal areas, upon initial encounter with an emotional event. Critically, the extent of amygdala activation at first exposure boosted neocortical encoding pattern similarity across repetitions. While corroborating the central role of the amygdala in emotional memory encoding (Dahlgren et al., 2020; Kensinger et al., 2011; LaBar & Cabeza, 2006; Murty et al., 2011; Phelps, 2004), these findings highlight a dynamic interaction between transient amygdala activation and persistent activation patterns in the successful encoding of recurrent emotional events. Furthermore, our findings are consistent with previous research that indicates a progressive activity increase in posterior parietal cortices in the course of repeated encoding (Brodt et al., 2018; Brodt et al., 2016), challenging the traditional view of the neocortex as a slow learner that depends on a consolidation delay (McClelland et al., 1995).

While the first study focused on the memory-enhancing role of stimulus-transient emotional arousal during encoding, emotional arousal often extends into the post-encoding phase, and noradrenergic arousal is a powerful modulator of memory consolidation (Joëls et al., 2011; McGaugh, 2006; McIntyre et al., 2002; Roozendaal & Hermans, 2017; Roozendaal & McGaugh, 2011). The long-term fate of emotional memories, however, has remained elusive. Based on initial findings in rodents (Atucha et al., 2017), we investigated whether noradrenergic arousal may alter the dynamics of systems consolidation over time by employing a pharmacological elevation of post-encoding noradrenergic activity through the α_2-adrenoceptor antagonist YOH, combined with fMRI scanning during both encoding and recognition testing 1d or 28d after learning. Our results reveal that, in contrast to PLAC, post-encoding noradrenergic stimulation leads to an increase in hippocampal activity and multivariate encoding-retrieval pattern similarity, an indicator of episodic memory reinstatement, over time. This increased hippocampal involvement

was accompanied by a time-dependent decrease in neocortical activity, which was linked to a reduction in memory decline over time. These findings demonstrate, for the first time in humans, that systems consolidation can be altered by experimental manipulation such as noradrenergic stimulation shortly after learning, challenging the traditional view of systems consolidation as a progressive linear reorganization of memory from the hippocampus to the neocortex (Frankland & Bontempi, 2005; McClelland et al., 1995; Squire & Alvarez, 1995).

In study 3 our objective was to unravel the nature of memory changes over time, specifically investigating whether these changes are semantic or perceptual in nature. Although existing theories such as TTT (Robin & Moscovitch, 2017b; Sekeres, Winocur, & Moscovitch, 2018; Winocur & Moscovitch, 2011; Winocur, Moscovitch, & Bontempi, 2010; Winocur et al., 2007) imply a semantic transformation over time, previous research has not been able to differentiate between semantic and perceptual memory changes due to the high perceptual similarity of stimulus materials that carry the semantic gist of the original material (Dandolo & Schwabe, 2018). We addressed this challenge by employing a recognition test, administered 1d or 28d after encoding, which included lures that were semantically or perceptually related to the encoded images. Our findings reveal that with an increasing delay between encoding and testing, memories are confused with material that shares the semantic gist of the original, but not with material that is merely perceptually related to original images. This pattern was even more pronounced for emotionally negative compared to neutral images, suggesting that transient emotional arousal at encoding may enhance memory for the semantic gist at the cost of memory specificity over time. Our multivariate fMRI analyses further indicate a memory transformation along the hippocampal long axis, with distinct, recent memory represented anteriorly and the reinstatement of remote memories, representing the semantic gist of the original memory, posteriorly. Moreover, our results indicate the emergence of semanticized memory representations in prefrontal and posterior parietal cortices. These results further underscore the dynamic nature of memory reorganization over time, indicating that memories are not simply fading but semantically transformed over time, and that this semantic transformation is enhanced for emotionally negative memories.

3.1 Modulating memory over time

Throughout the three studies, we consistently observed an arousal-related modulation of memory dynamics. This was true for stimulus-transient emotional arousal, as well as for pharmacologically elevated noradrenergic arousal at initial consolidation. Stimulus-transient emotional arousal enhanced immediate memory (study 1), reduced the decline in memory performance over time (study 2), and facilitated the time-dependent transformation into the semantic gist of the original memory (study 3). These latter findings seemingly challenge the popular belief that emotional memories are exceptionally durable and vivid over time (Brown & Kulik, 1977; Christianson, 1992). Moreover, post-encoding noradrenergic stimulation increased hippocampal and decreased neocortical involvement over time, a pattern previously associated with an increased specificity of remote memory in rodents (Atucha et al., 2017). These seemingly contradictory findings may arise from the differential influence of emotional arousal on memory at encoding and initial

consolidation (Joëls et al., 2011; Quaedflieg & Schwabe, 2018), as well as differences in memory indicators and their measures of memory quality (or lack thereof).

Confidence in or vividness of memories does not necessarily equate to memory specificity (Cooper & Ritchey, 2022; Kensinger, 2009; Neisser & Harsch, 1992; Schmidt, 2004; Schmolck et al., 2000; Talarico & Rubin, 2003). Instead, emotional events that are perceived as subjectively vivid memories often even lack accurate detail (Sharot et al., 2004; Talarico & Rubin, 2003). Such observations led to the proposal that the distinct feature of emotional memory lies in its subjective vividness rather than its factual precision (Dougal & Rotello, 2007; Sharot et al., 2004; Talarico & Rubin, 2003). Other authors (Kensinger, 2009; Kensinger & Schacter, 2006; Kensinger et al., 2007a, 2007b) have argued that there emotional arousal may enhance memory of central elements of an emotional event, i.e. the gist, at the expense of peripheral details. This trade-off has been attributed to arousal-related attentional narrowing at encoding, with a focus on arousing central elements rather than non-arousing peripheral components of an event (Kensinger, 2009; Laney et al., 2004). Previous studies implicate the amygdala in this attentional narrowing towards salient features of emotional events (Adolphs et al., 2005; Kensinger et al., 2011). Our finding of increased amygdala activation at initial exposure to emotionally arousing stimuli (study 1), facilitating sustained superior parietal encoding pattern activation, supports the notion of amygdala-guided attention to salient stimuli.

However, the design of study 1 does not allow inferences on whether enhanced immediate free recall for repeatedly encountered emotional events is due to enhanced memory for the gist or due to a detailed representation of the encoded event. Thus, it remains an intriguing question for future research whether the observed amygdala-SPL dynamic aids in maintaining focused attention on arousal-related central event features over peripheral aspects across repeated encounters, or whether sustained neocortical attention, coupled with decreased amygdala activity over repetitions, may broaden the attentional scope, possibly facilitating encoding of additional, non-central aspects across repeated encounters of the event. Investigating the quality of immediate emotional memory may furthermore elucidate whether the observed decrease in specificity of remote emotional memories (see Figure 5, right panel) emerges over time–possibly due to statistical overlap of repeatedly reactivated memory traces (Nadel & Moscovitch, 1997)–or whether emotional memories are less specific from the start with an increasing reliance on gist over time. The latter assumption aligns with recent data indicating that the gist of a memory may be present from the outset rather than emerge over time (Matorina & Poppenk, 2021) and that memory for emotionally arousing items shows a lower time-dependent decrease than memory for the non-arousing background these items were presented on during encoding (Cox et al., 2023). This reduced decline of the gist of the emotional memory may be facilitated by increased post-encoding elaboration or recapitulation of emotionally arousing details compared to peripheral features (Bowen et al., 2018; Christianson, 1992; Kensinger & Ford, 2020; Steinmetz & Kensinger, 2013). Notably, at 1d after encoding, we observed no significant difference in memory specificity between emotionally negative and neutral items, suggesting that emotional memories may not be less specific than neutral items at this stage and that, instead, differences in memory specificity may evolve over time. However, the high overall memory performance at this time point most likely

reduced the sensitivity to detect nuanced differences in memory quality. This is indicated by a lack of a significant difference in hits for emotionally negative items compared to neutral items in the 1d group, contrary to the well-known memory advantage of emotionally negative material shortly after encoding (Schümann et al., 2018; Talmi, 2013) and our finding of emotionally enhanced immediate free recall.

While transient emotional arousal was associated with a decrease in memory specificity over time, post-encoding noradrenergic arousal led to a time-dependent increase in hippocampal involvement and a decrease in neocortical involvement during remembering. The role of the hippocampus in memory specificity is well established (Winocur & Moscovitch, 2011; Winocur, Moscovitch, & Bontempi, 2010), and findings in rodents (Atucha et al., 2017) indicate that by altering systems consolidation dynamics and maintaining hippocampal involvement over time, post-encoding noradrenergic arousal may enhance memory for contextual details. Interestingly, while stimulus-transient emotional arousal has been proposed to interact with post-encoding arousal to enhance subsequent memory (Roozendaal & Hermans, 2017; Talmi, 2013), our research demonstrates that post-encoding noradrenergic stimulation alters emotional memory dynamics equally for both emotionally negative and neutral stimuli. This finding aligns with previous research suggesting differential mechanisms underlying emotional enhancement due to stimulus-transient arousal and arousal-related modulation of memory consolidation (Schümann et al., 2018), which may also explain the seemingly contradictory effects of transient arousal in facilitating memory transformation in contrast to post-encoding arousal in reversing systems consolidation dynamics. However, while the sensitivity index d', with which we assessed the effect of post-encoding noradrenergic arousal on memory performance, takes into account both correct responses for old items and incorrect responses for novel items, this measure does not allow inferences regarding the effects of post-encoding noradrenergic arousal on memory specificity over time.

Importantly, in our experimental paradigm, noradrenergic stimulation occurred shortly after encoding a mixed list of emotionally negative and neutral stimuli. In a real-life scenario, however, emotional arousal at consolidation typically follows emotionally arousing learning experiences. Therefore, if emotional arousal indeed narrows attention to the central aspects of an experience at the expense of peripheral details (Kensinger, 2009), post-encoding noradrenergic arousal would then affect systems consolidation of those central, arousal-related event features and potentially maintain or even enhance hippocampus-dependency over time for these memory representations. Although the term *gist* is sometimes used interchangeably with *schematic* or *semantic* memory (Winocur & Moscovitch, 2011; Winocur, Moscovitch, & Bontempi, 2010), these central features are inherently tied to a specific episode (see Box 1) and therefore, according to MTT (Nadel & Moscovitch, 1997) and TTT (Robin & Moscovitch, 2017a; Sekeres, Winocur, & Moscovitch, 2018), hippocampus-dependent. Therefore, it is quite plausible that noradrenergic arousal could specifically increase the hippocampus-dependency of the gist of the original memory over time. Intriguingly, recent research suggests that perceived memory vividness may be actually associated with remembering the gist of an experience rather than an episodically rich event (Cooper & Ritchey, 2022). Focused facilitation of central, arousal-related event features, either through

narrowed attention at encoding or an enhanced semantic transformation over time, might explain characteristics of traumatic memory, such as the intrusive, vivid recollection of specific details of a traumatic event coupled with a lack of memory for other aspects (Brewin et al., 2010; Van Der Kolk, 1998). Thus, our findings on arousal-related modulation of memory over time not only give important insights into the dynamic nature of memory over time, but may also facilitate therapeutic approaches in addressing key features of mental disorders associated with emotional memory, such as PTSD.

3.2 Memory transformation along the hippocampal long axis

Our findings show that the hippocampus is not a homogeneous region but that its anterior and posterior poles may serve distinct roles in memory. Specifically, the aHC was involved in successful memory encoding, especially at initial exposure to emotionally negative images (study 1), and in distinct memory representations that included perceptual features and decreased over time (study 3). On the contrary, the pHC was associated with the reinstatement of remote memory that was rather unspecific in nature and linked to the semantic gist of the original event. This distinction is consistent with previous research connecting the aHC to memory encoding (Lepage et al., 1998), emotional enhancement of memory (Murty et al., 2011), and the detection of novel, salient stimuli (Cowan, Fain, et al., 2021; Kafkas & Montaldi, 2018; Ranganath & Rainer, 2003). Furthermore, our results are consistent with studies linking the aHC to detailed, recent memories (Cowan, Liu, et al., 2021; Dandolo & Schwabe, 2018; Hannula et al., 2013; Harand, Bertran, La Joie, et al., 2012) and the pHC to remote, transformed memory representations (Bonnici et al., 2012; Bonnici et al., 2013; Cowan, Liu, et al., 2021; Dandolo & Schwabe, 2018; Tompary & Davachi, 2017).

However, a prominent account (TTT; Robin and Moscovitch, 2017a; Sekeres, Winocur, and Moscovitch, 2018) proposes the exact opposite dynamic, with the aHC supporting gist-like memory and pHC supporting a detailed and perceptually rich memory (Robin & Moscovitch, 2017a; Sekeres, Winocur, & Moscovitch, 2018). According to this account, gist-like memory capabilities are supported by functional connectivity between the aHC and the vmPFC, while the pHC's link to the posterior neocortex is believed to facilitate representations of perceptually rich memories. Indeed, the pHC shows strong functional and structural connectivity to posterior parietal regions, such as the angular gyrus, posterior cingulate cortex, and precuneus (Adnan et al., 2016; Dalton et al., 2022; Frank et al., 2019; Kahn et al., 2008; Tang et al., 2020). However, while previous accounts have mainly focused on long-term memory properties of prefrontal cortices (Frankland & Bontempi, 2005; Robin & Moscovitch, 2017a; Sekeres, Winocur, & Moscovitch, 2018; Winocur & Moscovitch, 2011), emerging evidence highlights the relevance of these posterior parietal regions in schematic, remote memory (Binder & Desai, 2011; Brodt et al., 2018; Brodt et al., 2016; Gutchess & Schacter, 2012; Hebscher et al., 2019; van der Linden et al., 2017). Our findings corroborate this, linking the angular gyrus with a progressive increase in activation over encoding repetitions and with remote, semantically transformed memory. Furthermore, even though the vmPFC may have closer anatomical proximity to the aHC, it is actually the pHC that has been demonstrated to exhibit robust structural and functional connectivity with the vmPFC

(Elliott et al., 2023; Raud et al., 2023), indicating a role of the pHC in the representation of generalized memories. The aHC, on the other hand, receives visual input through its connections with the perirhinal cortex and the fusiform cortex, suggesting its capacity to represent perceptual details (Graham et al., 2010; Smith et al., 2009; Tang et al., 2020).

Evidence of connectivity between the aHC and vmPFC, likely mediated by the entorhinal cortex (Insel & Takehara-Nishiuchi, 2013; Libby et al., 2012), arises primarily from investigations of scene construction, a process that has been repeatedly linked to the aHC (Barry & Maguire, 2019; Poppenk et al., 2013; Zeidman & Maguire, 2016). However, while TTT (Robin & Moscovitch, 2017a; Sekeres, Winocur, & Moscovitch, 2018) predicts that the vmPFC facilitates schema-based construction via the aHC, evidence suggests that connectivity during scene construction is directed from the aHC to the vmPFC rather than the other way around (Campbell et al., 2018; McCormick et al., 2015). This sequence is further supported by rodent research in which activity in the ventral hippocampus preceded that in the mPFC (Place et al., 2016). Therefore, the interaction between the vmPFC and aHC during scene construction could reflect the integration of episodic details from the aHC into the vmPFC, rather than a schema-based construction process (Campbell et al., 2018).

Scene construction is expected to recruit the aHC especially when stimuli are novel, as well as after the early stages of consolidation, while remote memory reconstruction is expected to depend on additional posterior hippocampal involvement (Barry & Maguire, 2019; Barry et al., 2019; Zeidman, Lutti, & Maguire, 2015; Zeidman, Mullally, & Maguire, 2015). These assumptions are consistent with our observations of aHC involvement during encoding of emotionally negative material, which progressively decreased over encoding repetitions (study 1), and with our finding of distinct pattern representations in the aHC that decreased from 1d to 28d after encoding, as well as with the involvement of the pHC in reinstating remote, gist-like memory (study 3). Previous studies have also shown an increase in aHC recruitment (Bosshardt et al., 2005) or a decrease in pHC recruitment (Ritchey et al., 2015; Takashima et al., 2009) after one night of sleep. Critically, while in our design one night of sleep represented recent memory, in these studies one night of sleep was equated with remote memory, resulting in the interpretation that recent and remote memories are represented in the pHC and aHC, respectively (as suggested by TTT; Robin and Moscovitch, 2017a; Sekeres, Winocur, and Moscovitch, 2018). This lack of consensus on the operationalization of recent memory compared to remote memory may thus be a potential contributing factor to the lack of consensus regarding the role of the hippocampal long axis over time.

Although our pattern of results generally supports the notion that the aHC represents specific memories that decrease over time and the pHC represents rather gist-like, remote memories, our findings are not entirely consistent. For instance, while pattern reinstatement in the pHC increased from 1d to 28d after encoding and was associated with memory for the semantic gist of the original event, our model-based analyses did not indicate the emergence of semantically transformed pattern representations in the pHC. However, TTT proposes that memories are transformed along the hippocampal long axis from detailed to gist-like, hippocampal representations are expected to remain episodic in nature, while the neocortex is expected to represent schematic or

semantic memories (Robin & Moscovitch, 2017a; Sekeres, Winocur, & Moscovitch, 2018). Our model focusing on representational pattern similarity between original items and semantically related lures may rather reflect schematic pattern representations. This is supported by the delay-dependent increase in fit of pattern representations in the vmPFC and angular gyrus, both associated with schematic memory (Binder & Desai, 2011; Binder et al., 2009). Although less detailed, gist-based memories should still relate to a specific episode (see Box 1). Our stimulus-specific encoding pattern reinstatement analysis, combined with behavioral indicators of memory specificity, may be more indicative of gist-based memory representation in the pHC.

However, this interpretation does not explain the absence of a delay-dependent decrease in anterior hippocampal encoding-pattern reinstatement, despite our model-based analyses suggesting its involvement in specific pattern representations that decline over time (study 3). This is unexpected, given the well-established role of the aHC in memory encoding (Krenz et al., under peer-review; Langnes et al., 2019, 2020; Lepage et al., 1998; Parsons et al., 2006; Schacter & Wagner, 1999) and scene construction (Zeidman & Maguire, 2016). Notably, scene construction has been specifically associated with the medial section of the aHC (Zeidman & Maguire, 2016), indicating a functional differentiation within the aHC. Accordingly, recent research points to a more complex division of the aHC into medial, lateral, and posterior-anterior sections, along with a distinction between the mHC and pHC (Thorp et al., 2022). The method of hippocampal parcellation, particularly the common practice of merging the body and tail into a single posterior segment (Brunec et al., 2018; Cowan, Liu, et al., 2021; Harand, Bertran, Doidy, et al., 2012; Langnes et al., 2019; Poppenk et al., 2013; Ritchey et al., 2015; Zeidman & Maguire, 2016), can significantly impact the interpretation of hippocampal functions and can lead to an overestimation of posterior hippocampal specificity (Thorp et al., 2022). We employed a tripartite parcellation approach, distinguishing between the hippocampal head (aHC), body (mHC), and tail (pHC), in line with prior research (Chase et al., 2015; Collin et al., 2015; Dandolo & Schwabe, 2018; Fanselow & Dong, 2010; Hannula et al., 2013; Tompary & Davachi, 2017). While this segmentation may have been well suited for identifying generalized patterns in the pHC, the comprehensive coverage of our aHC-segment may have lacked the precision required to discern specific encoding-retrieval pattern representations within more discrete regions of the aHC. Intriguingly, a searchlight analysis in study 2 revealed ERS in a medial section of the aHC that decreased from 1d to 28d after encoding in the PLAC group. Post-encoding noradrenergic stimulation reversed this pattern (see Figure 4). This less constrained searchlight-based methodology potentially allowed the identification of activity in a more circumscribed region within the aHC, namely the medial aHC.

In contrast to the dominant view (Robin & Moscovitch, 2017a; Sekeres, Winocur, & Moscovitch, 2018), which posits that detailed, recent memory is represented in the pHC and remote, gist-like memory in the aHC, our findings align with emerging evidence supporting a reverse course of transformation along the hippocampus, from its anterior to its posterior pole (see Figure2b). Intriguingly, while not aligning with TTT, our proposed anterior-posterior axis corroborates a scene construction account of hippocampal functioning, attributing a critical role in scene construction to the aHC when encountering novel stimuli and at initial stages of systems consolidation, i.e. 1d after encoding, with remote memory reinstatement, i.e. 28d after encoding, involving the pHC

and resulting in less specific memory representations (Barry & Maguire, 2019; Maguire & Mullally, 2013). Achieving a consensus between these perspectives requires the establishment of standards, for instance, regarding the delays to differentiate between recent and remote memories, and the segmentation of the hippocampus. Furthermore, while research employing visual stimuli is largely in line with our findings, most evidence that points to more distinct pHC representations originates from studies focusing on spatial properties of the hippocampus (Collin et al., 2015; Evensmoen et al., 2013, 2015; Javadi et al., 2017; Kjelstrup et al., 2008). Thus, it is possible that the pHC may represent detailed spatial representations in contrast to the aHC, which may preferentially represent details of visual stimuli, in line the suggested key role of the aHC in scene construction (Zeidman & Maguire, 2016). Thus, a conclusive statement regarding hippocampal functioning across different types of learning materials requires complementary investigations of changes in spatial memory representations along the hippocampus over time.

3.3 The state of systems consolidation

The traditional view on systems consolidation holds that experiences are rapidly encoded through hippocampal networks before being gradually transferred to a stable, neocortical storage, where they can reside, principally unchanged, for a lifetime (Frankland & Bontempi, 2005; McClelland et al., 1995; Squire & Alvarez, 1995). We show that this process is much more dynamic than originally assumed. We observed that neocortical representations can rapidly evolve during encoding repetitions, memory reorganization is accompanied by qualitative changes that are semantic in nature, and its course can even be reversed. Critically, these processes depended on the presence of stimulus-transient or post-encoding arousal. Successful encoding and retention of emotional memory, albeit the semantic gist, may be highly adaptive as it aids in the rapid detection of potential threats and guides future behavior (Biderman et al., 2020). While the concept of an adaptive consolidation process is not novel (Cowan, Schapiro, et al., 2021), our findings underscore that consolidation is much more dynamic than previously assumed, as its course can be even reversed. These findings align with a recent proposal (Roüast & Schönauer, 2023), which highlights that memory over time is adaptive, and may be flexibly influenced by environmental factors and emotional arousal, leading to a non-linear process of memory consolidation over time.

Our findings further underscore that the hippocampus is not a homogeneous region but is functionally differentiated along its long axis. Conceptualizations and investigations of memory over time that do not account for this functional differentiation and treat the hippocampus as a whole, may misrepresent the dynamic of memory over time. While our findings of a semantic transformation over time generally align with a trace transformation account (Robin & Moscovitch, 2017a; Sekeres, Winocur, & Moscovitch, 2018), our findings along the hippocampal long axis align more with a scene construction function of the hippocampus (Barry & Maguire, 2019; Hassabis & Maguire, 2007). The latter account allows the integration of our findings indicating a pivotal role of the aHC in encoding novel stimuli and detailed representations after initial systems consolidation by attributing both processes to a single underlying function, namely scene construction (Zeidman, Mullally, & Maguire, 2015). It remains a subject of future research to

investigate whether this process might be indeed based on the rapid decay of hippocampal traces (Barry & Maguire, 2019).

It has been recently proposed that, due to the dynamic nature observed in memory consolidation, the term *systems consolidation* might be misleading as it implies the end of a process (Gilboa & Moscovitch, 2021; Moscovitch & Gilboa, 2022). Roüast and Schönauer (2023) take this point even further by suggesting that the term *consolidation* itself may be a misnomer. Indeed, once consolidated, memories are not as stable as Müller and Pilzecker (1900) proposed: An apparently fixed memory can once again become labile and susceptible to interference (Nadel et al., 2012; Nadel & Hardt, 2011). However, in the absence of post-encoding noradrenergic stimulation, we did observe a decrease in hippocampal involvement and pattern reinstatement over time, accompanied by a time-dependent increase in neocortical involvement, which may indicate a reorganization of memory over time. Moreover, the formation of relatively stable memory traces is well established (Dudai, 2004; Duncan, 1949; Kandel, 2001; Kandel et al., 2014). Ultimately, the challenge may not be in changing the terminology, but in understanding the intricate mechanisms allowing for a continuous, non-linear memory consolidation process within and outside the hippocampus that flexibly adapts to emotional arousal and can even be reversed.

3.4 Future directions

Our findings indicating the reversal of systems consolidation dynamics due to post-encoding noradrenergic stimulation align well with previous findings in rodents (Atucha et al., 2017) and recent accounts highlighting a dynamic, flexible memory consolidation process (Roüast & Schönauer, 2023). However, this finding is highly novel and requires further replication in human participants. To understand how noradrenaline might alter systems consolidation, resting-state fMRI analyses could be employed, focusing on amygdala-hippocampus connectivity during early consolidation when YOH effects are expected to be most pronounced. The challenge here lies in the variability of the onset of YOH action, as evidenced by its 85 minute onset in study 2, in contrast to 40 minutes in a previous study using the same dosage (Kluen et al., 2017). Additionally, the prolonged noradrenergic arousal induced by YOH, lasting at least 35 minutes in our study, complicates pinpointing an exact time frame for connectivity analyses.

Moreover, introducing an additional memory test after noradrenergic stimulation and before sleep could provide additional insights on the trajectory of altered systems consolidation processes. This may elucidate whether changes in systems consolidation due to post-encoding noradrenergic stimulation emerge immediately or whether this effect requires initial systems consolidation during sleep. Given the high memory performance observed in our participants even 28d after encoding, an immediate memory test would require an increased difficulty level to allow meaningful inferences. This could be achieved, for instance, by presenting more stimuli–without repetitions–at encoding or applying a cued recall paradigm instead of a recognition task. Furthermore, testing different stimulus subsets at varied intervals within the same subjects would enhance the study's analytical power and provide insight into individual changes in memory representations over time. Moreover, the observed emotionally enhanced semantic transformation of memories over

time (study 3) and the finding in rodents indicating that noradrenergic arousal after encoding may increase memory specificity over time (Atucha et al., 2017) invite future research on the influence of post-encoding noradrenergic stimulation on memory specificity in humans. Modifying our stimulus design to include original, novel, and semantically related items during recognition testing may offer a comprehensive understanding of the effect of post-encoding noradrenergic arousal on the course of memory transformation over time.

Our finding that systems consolidation is dynamic and can be modulated by post-encoding arousal sets the stage for examining other possible manipulations that could affect systems consolidation dynamics and their interaction with noradrenergic arousal. For instance, encoding items that relate to prior knowledge (Sommer, 2016; van der Linden et al., 2017) or engaging in repeated retrieval (Brodt et al., 2018; Himmer et al., 2019) have been related to the rapid formation of neocortical memory representations. Combining such conditions that accelerate neocortical involvement even before a consolidation delay with post-encoding noradrenergic stimulation may allow critical insights into possible influences on systems consolidation dynamics. For example, it remains unknown whether noradrenergic arousal may also affect such rapidly reorganized memories or if its effect is restricted to memories predominantly dependent on the hippocampus.

Apart from the rapid release of noradrenaline, emotionally arousing experiences induce the delayed release of glucocorticoids, specifically cortisol, which have also been shown to modulate memory consolidation (McGaugh, 2000; Roozendaal & McGaugh, 2011; Schwabe et al., 2012). Interestingly, a recent finding in rodents suggests that while post-encoding noradrenergic stimulation may increase memory specificity (Atucha et al., 2017), cortisol may promote memory generalization after a consolidation delay (Roozendaal & Mirone, 2020). This raises the intriguing possibility that post-encoding cortisol may enhance neural reorganization and semantic transformation, potentially counteracting the effects of noradrenergic arousal over time. Investigating the impact of cortisol during initial consolidation, both independently and in conjunction with noradrenergic stimulation, may provide valuable insights into the influence of both neuromodulators on long-term memory reorganization of emotional experiences.

Study 1 provided valuable information on neural dynamics during repeated exposure to emotional events, showing that amygdala activation at initial encoding boosts subsequent emotional memory through sustained neocortical pattern activity across repetitions. Beyond questions regarding the relation of this dynamic with potential trade-offs due to arousal-related attention narrowing during encoding (Bowen et al., 2018; Kensinger, 2009), this study raises multiple implications for future research. For instance, since memory was tested only once, after completing all encoding repetitions, this study does not allow inferences on which activity changes were attributed to encoding and which to the retrieval of previous repetitions. However, introducing memory tests after each encoding run would very likely affect representations of previously retrieved events (Brodt et al., 2018; Himmer et al., 2019; Karpicke & Roediger, 2008). In addition to repeated retrieval, increasing the temporal delay between learning attempts is well known to increase the learning efficacy (Appleton-Knapp et al., 2005; Feng et al., 2019). Critically, the impact of varying temporal delays, especially those allowing for initial consolidation, on memory

for repeatedly encountered emotional events remains unknown. Investigating repeated emotional encoding after a consolidation delay might offer insight into the emergence of psychopathologies such as complex PTSD, characterized by repeated traumatic events that often occur after considerable temporal delays from each other.

Lastly, while the findings of each study are based on distinct subsets of a single dataset, there is a need for replication in diverse samples to validate these results. Furthermore, our sample only included young adults. Extending this research to different age groups and demographics is crucial to obtaining a more comprehensive understanding of memory dynamics in diverse populations.

3.5 Conclusion

This dissertation focused on elucidating the evolution of memory over time, from its repeated encoding to its systems consolidation and transformation, while considering the influence of emotional arousal on each of these processes. By combining stimulus-transient or pharmacologically elevated emotional arousal with univariate and multivariate pattern analyses of neuroimaging data with varying delays, we demonstrated that memory is not a static entity, but dynamic and influenced by emotional arousal at each stage of its progress.

We show that emotional arousal at encoding facilitates consistent pattern (re)activations in frontoparietal control regions over encoding repetitions. This process is boosted by activation of the amygdala when first encountering an emotional event, which, in turn, enhances subsequent free recall. These findings elucidate the neural dynamics when repeatedly encountering emotional events and invite follow-up studies to investigate the association of this pattern with the quality of the encoded and immediately recalled event.

Furthermore, our findings challenge the textbook view that memories are reorganized from the hippocampus to the neocortex in their original form (Frankland & Bontempi, 2005; McClelland et al., 1995; Squire & Alvarez, 1995). Instead, our results show that systems consolidation is highly dynamic, can be altered, and even reversed by noradrenergic stimulation at initial consolidation. If memories are reorganized, they do not retain their original form or simply decay in perceptual features. Instead, they transform into the semantic gist of the original memory. This process may explain how memories are integrated, in the long run, into semantic knowledge structures. This semantic transformation is further enhanced for emotional memory, indicating that although emotional events are generally perceived to remain more vividly in memory than neutral events (Brown & Kulik, 1977; Christianson, 1992), it may actually be the semantic gist of the emotional event that persists over time.

Our findings also indicate that this memory transformation is observed not only from the hippocampus to the neocortex but also within the hippocampus. In line with recent studies employing multivariate pattern analyses (Cowan, Liu, et al., 2021; Dandolo & Schwabe, 2018; Tompary & Davachi, 2017), our results suggest a transformation from the anterior to the posterior pole of the hippocampus, exactly opposite to the current popular account (Robin & Moscovitch, 2017a; Sekeres, Winocur, & Moscovitch, 2018). These findings invite a new dialogue to establish standards and understand the methodological differences that have led to this inconsistency in

the field. Furthermore, our research suggests that the general focus on the prefrontal cortex in generalized, long-term memory storage should also shift posteriorly. We corroborate emerging research that implicates the posterior parietal cortex as a site of long-term memory representations (Brodt et al., 2018; Brodt et al., 2016), which may rapidly evolve and represent semantically transformed memory (Binder & Desai, 2011; van der Linden et al., 2017; Wagner et al., 2015). With its ability to rapidly form schematic neocortical representations, the posterior parietal cortex may further facilitate the dynamic property of memory over time.

Apart from its high theoretical relevance, our findings also have implications for clinical and legal settings. By recognizing the nuances in how emotional memories are encoded and transformed, clinicians can design more targeted and effective interventions to treat psychopathologies related to aversive memory. This might involve the use of pharmacological agents to modulate noradrenergic systems during the early stages of memory consolidation, potentially reducing the intensity and impact of memories for traumatic events. Furthermore, these findings have important implications for eyewitness memory, suggesting that an arousing experience is more likely to transform into the semantic gist of the original event over time. This transformation can lead to a misattribution of memory vividness to factual precision (Cooper & Ritchey, 2022; Kaplan et al., 2016), a critical consideration in legal contexts. In conclusion, this dissertation considerably advances our understanding of memory over time, laying a foundation for subsequent research and practical applications.

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Appendix: Study 1

A

Krenz, V., Alink, A., Roozendaal, B., Sommer, T., & Schwabe, T. (under peer-review). *Memory boost for recurring emotional events is driven by initial amygdala response promoting stable neocortical patterns across repetitions*.

ABSTRACT

Emotionally arousing events are typically vividly remembered, which is generally adaptive but may contribute to mental disorders such as posttraumatic stress disorder. Previous research on emotional memory focused primarily on events that were experienced only once, leaving the mechanisms underlying the memory of repeatedly encountered emotional events largely unexplored. Here, we aimed to elucidate the brain mechanisms associated with memory for recurring emotional events. Specifically, we sought to determine whether the memory enhancement for recurring emotional events is linked to more variable neural representations, as predicted by the encoding-variability hypothesis, or to more stable representations across repetitions, as suggested by a memory reinstatement account. To investigate this, participants saw repeatedly images of emotionally negative or neutral scenes during three encoding runs in an MRI scanner. Subsequent free recall was, as expected, enhanced for emotional compared to neutral images. Neural data showed that this emotional enhancement of memory was linked to (i) the activation of the amygdala and anterior hippocampus during the initial encounter of the emotional event and (ii) increased neural pattern similarity in frontoparietal cortices across event repetitions. Most importantly, a multilevel moderated mediation analysis revealed that the impact of neocortical pattern stability across repetitions on emotional memory enhancement was moderated by amygdala activity during the initial exposure to the emotional event. Together, our findings show that the amygdala response during the initial encounter of an emotional event boosts subsequent remembering through a more precise reinstatement of the event representation during subsequent encounters of the same event.

SIGNIFICANCE STATEMENT

Despite extensive research on emotional memory, the mechanisms underlying memory formation for recurrent emotional events remain elusive. We show that amygdala and anterior hippocampal activity is most prominent during the initial exposure to an aversive stimulus but decreases markedly with repeated exposure. Neocortical representation patterns of subsequently recalled emotional events, however, are more stable across the repeated encoding of emotional (vs. neutral) events, in line with a memory reinstatement account. Notably, this increased neocortical pattern stability was driven by the amygdala response during the initial exposure to an aversive event. These findings provide novel insights into the mechanisms involved in memory formation for recurrent emotional events, with potential implications for complex PTSD characterized by multiple traumatic exposures.

INTRODUCTION

Emotionally arousing events are often well-remembered (McGaugh, 2006), which aids the avoidance of future threats (Hamann, 2001). However, the persistent, vivid recollection of emotional events may affect mental well-being and contribute to psychopathology (Brewin et al., 2010). Importantly, emotional events may be encountered repeatedly and memories are shaped through repeated (re)encoding processes (Nadel and Moscovitch, 1997; Dudai, 2012). For instance, trauma survivors frequently re-encounter trauma-related stimuli reinstating the original memory (Ehlers and Clark, 2000), and are at an increased risk of re-experiencing similar traumatic incidents (Kessler et al., 2017). While decades of research provided valuable insights into the mechanisms involved in memory formation for emotional events experienced just once (Murty et al., 2011; Dahlgren et al., 2020), the evolution of memory across repeated exposure to the same emotional event remains elusive.

Repeated study is well-known to strengthen memory (Ebbinghaus, 1885). One prominent theory of the enhanced memory after repetition, referred to as encoding variability theory (Estes, 1955; Johnston, 1976), postulates that each time we encounter an event, this event is encoded differentially due to variations in the temporal or spatial encoding context. These variations would multiply the access routes to the memory and hence promote its future recall (Johnston, 1976). Alternatively, each encoding episode may reactivate and thus strengthen the memory representation formed during previous encoding (Thios and D'Agostino, 1976). Extant studies suggested that memory formation is successful when the same neocortical representations are reactivated across subsequent encoding episodes rather than when patterns of activation are more variable across repetitions (Xue et al., 2010, 2013; Feng et al., 2019). Importantly, these studies included only neutral events and, thus, whether the evolution of emotional memory across repeated encoding is based on more stable or more variable (re)activation patterns is completely unknown.

Emotional compared to neutral events recruit specific neural mechanisms that enable their preferential storage in memory. A key role in this process is attributed to the noradrenergic arousal-induced activation of the amygdala, which modulates memory processes in the hippocampus and neocortex (McGaugh, 2000; Fastenrath et al., 2014). This arousal-related mechanism specifically promotes the long-term consolidation of emotional memories (Cahill and McGaugh, 1998; McReynolds and McIntyre, 2012). However, enhanced recall of emotional over neutral events is also evident immediately after encoding, before a consolidation delay (Talmi et al., 2007; Murty et al., 2011; Talmi

and McGarry, 2012; Schümann et al., 2018). This immediate emotional memory enhancement has been attributed to preferential processing and increased attention at encoding, promoting the immediate free recall of these items (Talmi, 2013). Furthermore, the anterior hippocampus, strongly connected to the amygdala (Pitkänen et al., 2000; Richardson et al., 2004; Tillman et al., 2018), has been repeatedly linked to successful emotional memory encoding (Murty et al., 2011). Importantly, both the amygdala (Ranganath and Rainer, 2003) and the anterior hippocampus (Strange et al., 1999; Cowan et al., 2021) have been implicated in novelty detection, which may point to a role of the anterior medio-temporal lobe (MTL) specifically when emotional events are experienced for the first time.

Here, we aimed to elucidate the neural mechanisms underlying memory enhancement for repeatedly encountered emotional events. Specifically, we investigated whether the emotional enhancement of memory is due to more stable or variable neural encoding patterns, and whether these dynamics over repeated encoding are driven by initial anterior MTL responses. To this end, participants encoded images of emotionally negative or neutral scenes in three consecutive runs in an MRI scanner, followed by an immediate free recall test. We expected an emotional memory enhancement associated with enhanced anterior MTL activity at initial encoding and more consistent pattern representations across encoding runs in visual and frontoparietal cortices. Using moderated mediation analyses, we further examined the link between transient anterior MTL involvement and stable neocortical encoding patterns during successful encoding of recurring emotional events.

METHODS

Participants and design

One-hundred-and-nine healthy volunteers (55 males, 54 females, age: M = 24.09 years, SD = 3.92 years) participated in this experiment. Exclusion criteria were checked in a standardized interview and comprised a history of any psychiatric or neurological diseases, medication intake or drug abuse, as well as any contraindications for MRI measurements. All participants provided informed consent before taking part in the experiment and received a monetary compensation for participation. The study protocol was approved by the ethics committee of the Medical Chamber Hamburg (PV5480) and was in accordance with the declaration of Helsinki. Six participants had to be excluded from the analysis because of technical failure (n = 1), missing data for at least one of the experimental tasks (n

= 2) or falling asleep during MRI scanning (*n* = 3), thus resulting in a final sample of 103 right-handed young adults (51 males and 52 females, age: M = 24.08 years, SEM = 0.39 years). A sensitivity analysis using MorePower 6.0 (Campbell and Thompson, 2012) confirmed that this sample size is sufficient to detect a medium-sized effect ($\eta^2 = 0.07$) for a 2 (memory) × 2 (emotion) × 3 (run) interaction with a power of 0.95 ($\alpha = 0.05$).

Experimental procedure

This study is part of a larger project investigating modulators of time-dependent systems consolidation and memory-transformation processes (Krenz et al., 2021, 2023). Therefore, shortly before encoding, participants received orally either placebo or 20mg yohimbine (double-blind), an α2-adrenoceptor antagonist leading to a temporally delayed increase in noradrenergic stimulation. The timing of the drug administration was chosen based on previous studies (Schwabe et al., 2012; Kluen et al., 2017) and the known pharmacodynamics of yohimbine, showing that a significant drug action can be expected about 60 min after drug intake. Our results confirmed that the drug affected neither neural activity during encoding nor immediate memory performance and increased noradrenergic activation only about 30 min after free recall testing (Krenz et al., 2021). Since the drug was not yet effective during encoding and immediate free recall, we collapsed data across the placebo and yohimbine groups for the present analysis.

Participants performed three encoding runs in the MRI scanner. In each run, participants were presented the same 60 scene images (30 emotionally neutral, 30 negative) in random order using MATLAB (The Mathworks, Inc, Natick, US) with the Psychophysics Toolbox extensions (Brainard, 1997), i.e. each image was presented once in each of the three encoding runs. On each trial, an image was presented for 3 s followed by a jittered fixation period of 4 ± 1 s. Participants were instructed to memorize the presented images and informed that there will be a subsequent memory test immediately afterwards. To make sure that participants remained fully attentive throughout the encoding task, they were instructed to press a button as soon as the fixation-cross appeared on the screen.

Immediately after the encoding task, participants completed a free recall task outside the MRI scanner. Here, participants had 15 min to recall as many of the previously encoded stimuli as possible. In order to validate the emotionality of the encoded images, participants rated each stimulus with respect to its valence and arousal on a scale from 0 (‘very negative’/’not arousing’) to 10 (‘very

positive'/'very arousing') in a separate experimental task outside of the MRI. In retrospect, these ratings confirmed that negative images (M = 2.408, SEM = 0.078) were perceived as significantly more negative than neutral ones (M = 5.872, SEM = 0.091; paired *t*-test: $t(102) = 23.367$, $p < 0.001$, Cohen's $d = 4.039$, CI[3.008, 5.071]). Furthermore, negative images (M = 5.950, SEM = 0.135) were associated with significantly higher subjective arousal than neutral ones (M = 2.759, SEM = 0.140; paired *t*-test: $t(102) = 21.676$, $p < 0.001$, Cohen's $d = 2.81$, CI[1.887, 2.675]).

Behavioral Data analysis

To control for attentiveness during encoding and potential influences on subsequent memory effects, missed responses to the fixation cross were analyzed by means of a binomial generalized LMM with the fixed effects of run (run 1 vs. run 2 vs. run 3), subsequent memory (forgotten vs. remembered) and emotion (neutral vs. negative) with a random intercept for participants. The difference in subsequent memory performance depending on stimulus emotionality was analyzed by means of a paired *t*-test.

All statistical analyses were performed with R Version 4.2.2 (https://www.r-project.org/) in RStudio Version 2022.12 (Posit team, 2022). All reported *p*-values are two-tailed with an α-level of 0.05. Mixed model's post-hoc tests (*z*-contrasts) were applied by contrasting EMMs of respective conditions and corrected for multiple comparisons by controlling for the false discovery rate (FDR; Benjamini, 2010) using the R-package emmeans Version 1.7.2 (Lenth et al., 2018).

MRI acquisition

MRI data were acquired using a 3T Prisma Scanner (Siemens, Germany) with a 64-channel head coil. Each MRI session consisted of three functional runs and a magnetic (B0) field map to unwarp the functional images (TR = 634 ms, $TE_1 = 4.92$ ms, $TE_2 = 7.38$ ms, 40 slices, voxel size = $2.9 \times 2.9 \times 3.0$ mm^3, FOV = 224 mm). For the functional scans, T2*-weighted echo planar imaging sequences were used to obtain 2mm thick transversal slices (TR = 2000 ms, TE = 30 ms, flip angle = 60°, FOV = 224). Additionally, a high-resolution T1 weighted anatomical image (TR = 2500 ms, TE = 2.12 ms, 256 slices, voxel size = $0.8 \times 0.8 \times 0.9$ mm^3) was collected.

Preprocessing

All scans underwent the same preprocessing steps using SPM12 (Wellcome Trust Centre for Neuroimaging, London, UK). To allow for magnetic field (T1) equilibration, the first three functional scans were discarded. The images were first realigned and unwarped using the field maps, then coregistered to the structural image followed by a normalization to Montreal Neurological Institute (MNI) space, as implemented in SPM12 (IXI549Space). No smoothing was performed on the echoplanar imaging data that entered the GLM for single-trial univariate and multivariate analyses.

First-level modeling

First-level modeling was applied using SPM12 (Wellcome Trust Centre for Neuroimaging, London, UK). Here, each of the 180 trials of the encoding task were modelled as an individual regressor convolved with a hemodynamic response function along with three run constants in one GLM per subject. A high-pass filter of 128 s was used to remove low-frequency drifts and serial correlations in the time series were accounted for using an autoregressive AR(1)-model.

Single-trial ROI-based analyses

We utilized a single-trial ROI-based analysis approach. Unlike the traditional condition-level, voxel-wise method, this approach enables examining the dynamic in activation (patterns) for each individual stimulus across encoding repetitions while taking into account its emotionality and subsequent memory, within predefined brain regions.

We expected that subsequent memory for negative items would be specifically associated with increased activity in the anterior MTL, i.e. amygdala (McGaugh, 2004; Murty et al., 2011) and anterior hippocampus (Murty et al., 2011; Dandolo and Schwabe, 2018; Cowan et al., 2021), during an early encoding phase (encoding run 1). To assess whether the found effects were indeed specific to the anterior part of the MTL, we additionally examined the mid and posterior hippocampus. Anatomical masks of the anterior, mid and posterior hippocampus (left and right) were derived using the WFU pick-atlas (Lancaster et al., 2000; Maldjian et al., 2003). Anatomical masks for the amygdala were derived from the Harvard-Oxford-Atlas as included in the FMRIB Software Library (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSL) with a probability threshold of 50%, reduced by overlap for the anterior hippocampus mask.

To investigate dynamics of emotional enhancement of memory for recurring events in the neocortex, we divided the cortex into 200 fine-grained regions using a well-established cortical parcellation scheme (Schaefer et al., 2018). While harnessing the benefits of traditional ROI analyses, i.e. increasing statistical power and interpretability by focusing on functionally homogenous regions rather than individual voxels, this parcellation-based approach allows capturing the entirety of the neocortex. This allows a comprehensive examination of activity across encoding runs throughout the neocortex, and thus, along with correcting for multiple comparisons, addresses the complexity of neocortical encoding-related activity more effectively than a limited set of predefined ROIs (Cooper and Ritchey, 2020).

Both, univariate and multivariate data, were analyzed by means of LMMs, fitted using restricted maximum likelihood with a variable intercept for subjects and items in R. In cases of singular fits or convergence issues, where the variance-covariance matrix of the random effects approaches non-invertibility or the optimization algorithm doesn't find optimal parameter estimates, respectively, the respective model was refitted after excluding the random effect causing these estimation difficulties, ensuring a more stable and interpretable fit (Matuschek et al., 2017). Each fixed effect was tested against zero using Satterthwaite's approximation method, which provides reliable estimates of the degrees of freedom in LMMs while minimizing Type 1 error rates (Luke, 2017). To account for multiple comparisons, *p*-values were FDR (Benjamini, 2010) corrected, accounting for the number of ROIs in each analysis. To further ensure the reliability of our results, data were resampled with replacement to create 1000 simulated datasets as implemented in lme4 (Bates et al., 2015), incorporating a seed value for reproducibility. From the distribution of these simulated estimates, we computed 95% confidence intervals, representing a robust range of plausible effect values. Both, bootstrapped confidence intervals and FDR-corrected *p*-values, were taken into account when assessing the statistical significance of an effect at a two-sided α-level of 0.050, aligning with previous recommendations to consider multiple estimates as evidence for an effect (Cumming, 2014; Valentine et al., 2019). Results of fMRI analyses were displayed using BrainNet Viewer (Xia et al., 2013, http://www.nitrc.org/projects/bnv/), where, for visualization purposes, every voxel within a region was allocated the same *t*-statistic, based on this region's fixed effect estimation in the respective LMM.

Univariate analysis

For our univariate analyses, mean single-trial beta series were extracted by averaging across voxels within each ROI per participant and trial. Emotionally-dependent activity changes over encoding runs

in single-trial betas were analyzed by means of trial-wise LMMs with subsequent memory (forgotten vs. remembered), emotion (neutral vs. negative), a linear increase predictor over encoding runs, centered around run 2, and their interactions as fixed effects.

To follow up on interaction effects, we applied post-hoc analyses on the model's EMMs and slope coefficients (EMSs) contrasting remembered > forgotten items. In this context, EMM and EMS represent the predicted activity at each level of emotion and run and the change in activity over repeated encoding for each level of emotion, respectively, while adjusting for the level of each predictor, capturing emotion-specific changes across encoding repetitions in activity associated with successful memory encoding. To account for multiple comparisons in our post-hoc analyses, *p*-values of resulting contrast estimates were further FDR-corrected (Benjamini, 2010), as implemented in the R-package emmeans (Lenth et al., 2018).

Multivariate analysis

While our univariate analyses allowed investigating dynamic changes over repeated encoding underlying emotional enhancement of memory, we further applied multivariate pattern analyses probing stable (vs. variable) representation pattern activations over repeated exposure underlying successful emotional memory encoding. For this, single-trial first-level betas at encoding were transformed into *t*-statistics to increase the reliability of the measured activation patterns by normalizing for noise (Walther et al., 2016). Data were then subjected to representational similarity analyses (RSAs; Kriegeskorte et al., 2008) using custom scripts in MATLAB (The Mathworks, Inc, Natick, US). Specifically, we computed item-wise encoding pattern similarity (Xue et al., 2010, 2013; Feng et al., 2019) within each ROI and subject, by correlating activation patterns of an item in a specific run with activation patterns of the same item in a subsequent encoding run (see Figure 4a). The resulting Pearson's *r*-values were further Fisher *z*-transformed and averaged over run comparisons before statistical analyses in R were conducted. Fisher *z*-transformed *r*-values were analyzed by means of item-wise LMMs with the factors subsequent memory (forgotten vs. remembered), emotion (neutral vs. negative) and their interactions as fixed effects and a random intercept of subject and item. Post-hoc analyses were conducted by computing the model's EMMs contrasting remembered > forgotten items. Resulting EMMs thus represent encoding pattern similarity associated with successful encoding of emotionally negative or neutral items.

Previous work suggests that successful memory encoding is associated with stable pattern representations during repeated encoding as an indicator of a consistent reactivation of neural activations across study episodes (Xue et al., 2010, 2013; Feng et al., 2019). Thus, we expected pattern similarity at encoding to be positively associated with memory encoding and that pattern similarity for subsequently remembered items should be increased for emotionally negative items, particularly in frontoparietal neocortical regions associated with attentional and cognitive control processes which may enhance immediate emotional memory enhancement (Talmi, 2013). As we expected the anterior MTL to be primarily involved in the initial, yet transient, enhancement of emotional memory formation, we did not expect stable encoding-pattern representations in this region.

Multilevel moderated mediation analysis

In a final step, we analyzed whether initial MTL engagement may modulate neocortical pattern stability linked to emotional memory enhancement. We specifically focused on the modulating role of univariate encoding activation in the left amygdala and right anterior hippocampus at run 1, which our univariate analyses identified as highly impactful in the successful encoding of emotional memories (see Figure 2), and the mediating role of stable encoding patterns in regions associated with emotional memory enhancement as identified in our multivariate analysis (OFC, ACC, STS, SPL, postcentral sulcus; see Figure 4b). Given the hierarchical structure of our data—with items nested in subjects—we employed a multilevel moderated mediation approach utilizing the R-packages mediation (Tingley et al., 2014) and lme4 (Bates et al., 2015). This entailed fitting two models: (i) an LMM estimating the mediator (encoding pattern similarity in Fisher transformed *r*) as a function of the predictor (emotion: neutral vs. negative), the moderator (anterior MTL activity), their interaction, and the random intercept of participants; (ii) a generalized LMM predicting the outcome variable (subsequent memory: forgotten vs. remembered), based on the interaction between emotion (neutral vs. negative) and anterior MTL activity, the interaction between encoding pattern similarity and anterior MTL activity, and the random intercept of participants. Continuous variables were subject-mean centered before entering the models as predictors. Mediator and outcome model fits were then combined to estimate the indirect effect, i.e. influence of emotion on subsequent memory via encoding pattern similarity ($a_1 \times b$ in Figure 5), and the direct effect of emotion on subsequent memory when controlling for both the mediator and moderator (c_1'). For this, a quasi-Bayesian Monte Carlo method with a total of 5000 simulations including a predefined seed was applied, offering a robust estimation of the direct effect by

approximating the distribution of the indirect effect (Tingley et al., 2014). This approach allows evaluating conditional indirect and direct effects under different levels of the moderator (Tingley et al., 2014). To follow up on a numeric change in the indirect effect from low (-1 SD) over average to high (+1 SD) levels of the moderator and a significant indirect effect (FDR-corrected for the total number of ROIs) for at least one of the moderator levels, we further estimated the index of moderated mediation (Hayes, 2015). In the context of a moderated mediation, the indirect effect ω of a predictor on an outcome through a mediator can be expressed as $\omega = a_1 b + a_2 b W$, where the intercept $a_1 b$ represents the indirect effect when the moderator (W) equals zero and the slope $a_2 b$ quantifies the change in the indirect effect as a linear function of the moderator, i.e. the index of moderated mediation (Hayes, 2015). Thus, in our analysis, the index of moderated mediation is reflected by the product of the moderated effect of the predictor on the mediator (emotion × anterior MTL activity on encoding similarity; a_2) and the mediator's effect on the outcome when controlling for the effect of the predictor (main effect encoding similarity on subsequent memory; b). For rigorous statistical inference, we applied bias-corrected bootstrap confidence intervals, drawing 10000 samples from the original dataset to construct a reliable distribution of the index of moderated mediation, following previous recommendations (Hayes, 2015).

Data accessibility

The behavioral and fMRI data generated in this study are provided at: http://doi.org/10.25592/uhhfdm.13783.

Code accessibility

Custom code used to model and analyze the data is available at: https://zenodo.org/doi/10.5281/zenodo.10210565.

RESULTS

Emotional enhancement of immediate free recall

To elucidate the neural evolution of emotional memory enhancement across repeated encoding sessions, 103 participants saw 30 emotionally negative and 30 neutral scene images across three consecutive runs in the MRI scanner (see Figure 1a). To control for attentiveness during encoding,

participants were asked to respond with a button press as soon as a fixation cross appeared on the screen. On average, participants missed responding to only 0.809% (SEM = 0.176%) of the fixation crosses, indicating an overall high attentiveness during the encoding task. While missed responses increased over encoding runs (main effect run: β = 0.540, CI[0.164, 0.914], z = 2.816, p < 0.001), the overall number of missed trials per run remained very low throughout the task (run 1: M = 0.485%, SEM = 0.114%; run 2: M = 0.841%, SEM = 0.271%; run 3: M = 1.100%, SEM = 0.286%). Moreover, misses and, by implication, participant's attentiveness immediately before stimulus presentation, did not differ between subsequently remembered and forgotten trials (all $|\beta|$ < 1.613, all p > 0.107), nor between emotionally negative and neutral images (all $|\beta|$ < 1.051, all p > 0.293). In the free recall test immediately after encoding, participants recalled significantly more negative (M = 60.680%, SEM = 1.708%) than neutral items (M = 43.592%, SEM = 1.743%; paired t-test: $t(102)$ = 13.736, p < 0.001, Cohen's d = 0.976, CI[0.805, 1.146]; see Figure 1b), thus demonstrating the well-known emotional enhancement of immediate memory (Talmi et al., 2007; Murty et al., 2011; Talmi and McGarry, 2012; Schümann et al., 2018).

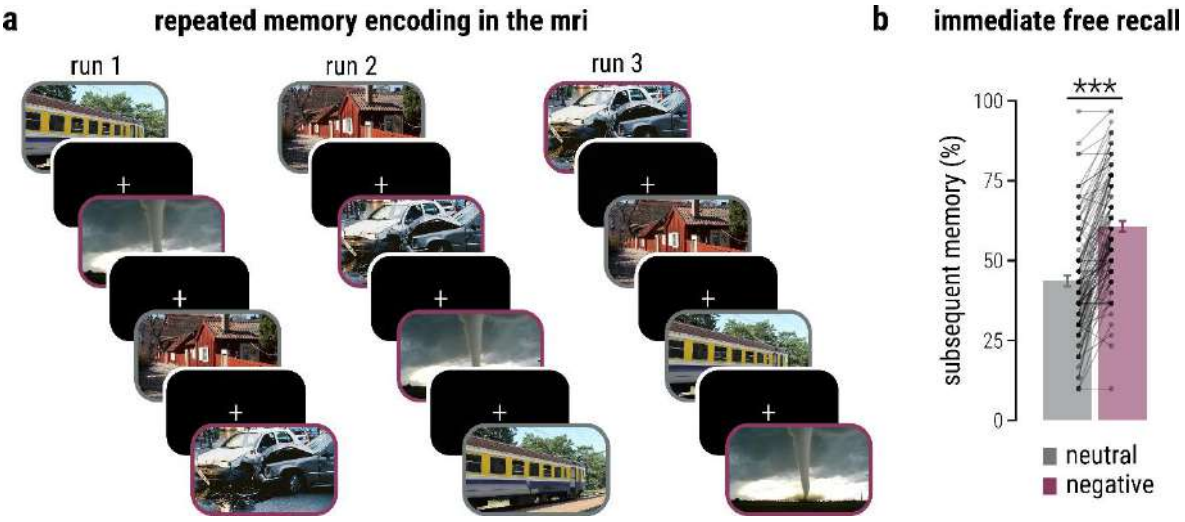

Figure 1. Encoding task and subsequent free recall performance. a Participants repeatedly encoded images that were either emotionally neutral or emotionally negative in three consecutive runs in an MRI scanner. All included images are licensed under Creative Commons BY-SA license: image of train is courtesy of John Samuel (https://bit.ly/3SkVjma; changed), image of tornado is courtesy of Justin Hobson (https://bit.ly/3SbJTkK; changed), image of buildings is courtesy of Holger Ellgaard (https://tinyurl.com/4cybwv2f; changed), image of car crash is courtesy of Dino Kužnik (https://bit.ly/3SodgAx; changed). **b** Shortly after encoding, participants were asked to freely recall all of the previously presented images. Subsequent memory was significantly higher for emotionally negative compared to neutral items (two-tailed paired t-test: p < 0.001; n = 103). Connected dots represent the percentage of remembered items per participant and emotion; bars represent mean percentage of remembered items per emotion ± SEM. ***p < 0.001.

Trajectory of anterior medial temporal lobe involvement across repetitions distinguishes memory formation of emotional and neutral events

To examine the neural mechanisms involved in the evolution of enhancement of memory for recurring emotional events, we analyzed activation changes over multiple encoding runs for both emotionally negative and neutral scene images, taking into account subsequent memory of the specific item. We expected that subsequently enhanced memory for negative compared to neutral items would be associated with activity in the anterior MTL, specifically the amygdala (McGaugh, 2004; Murty et al., 2011; Dahlgren et al., 2020) and the anterior portion of the hippocampus (Murty et al., 2011) during the first exposure to an emotionally negative item, i.e. in encoding run 1 (Ranganath and Rainer, 2003; Cowan et al., 2021).

Analyzing encoding-related activity on a single-trial level by means of an LMM with a predictor modeling a linear increase over encoding runs and the factors emotion (neutral vs. negative) and subsequent memory (forgotten vs. remembered), showed a significant run × emotion × memory interaction in the left amygdala (β = -0.090, CI[-0.156, -0.017], t(18350.200) = -2.478, p_{corr} = 0.040) and the right anterior hippocampus (β = -0.080, CI[-0.151, -0.013], t(18363.510) = -2.328, p_{corr} = 0.040).

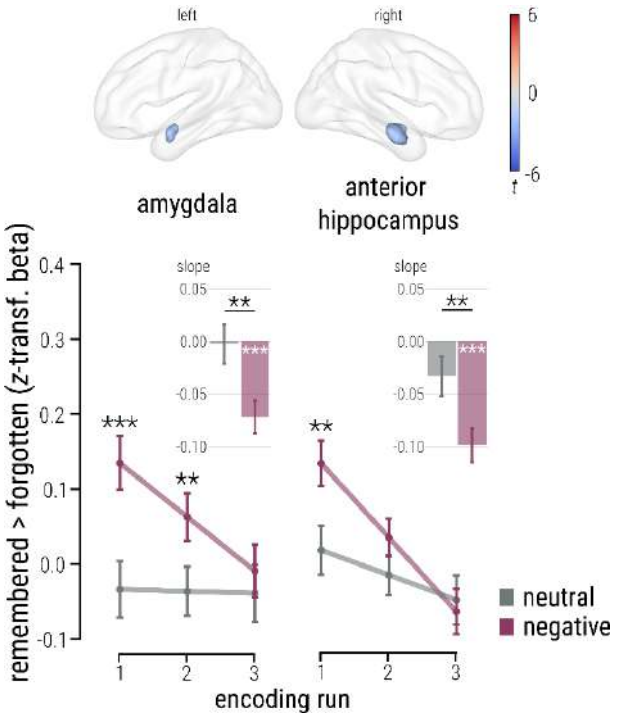

Figure 2. Transient anterior medial temporal lobe (MTL) involvement in encoding of recurring emotional events. While both amygdala and anterior hippocampus activity at initial encoding was associated with subsequent memory of emotional (vs. neutral) events, anterior MTL involvement in emotional memory encoding significantly decreased over repetitions (linear mixed models, run × emotion × memory, both p_{corr} = 0.040). During the final encoding run, no association between

subsequent emotional (vs. neutral) memory and anterior MTL activation was evident. These findings indicate that the emotional enhancement of memory is linked to rapid anterior MTL recruitment when an emotional stimulus is encountered for the first time, but that anterior MTL decreases over repeated exposures. Connected dots depict the estimated marginal means for the contrast 'remembered > forgotten' per level of emotion and run ± SE; bars represent estimated marginal slopes for the same contrast per level of emotion ± SE. All n = 103. Reported p-values are two-tailed and FDR-corrected for multiple comparisons while accounting for number of regions of interest in this analysis (p_{corr}). ***p < 0.001; **p < 0.010.

To disentangle this three-way interaction in the amygdala and anterior hippocampus, we applied post-hoc analyses on the model's estimated marginal means (EMMs) and slope coefficients (estimated marginal slopes, EMSs) contrasting remembered > forgotten items. In this context, EMM and EMS values represent the predicted anterior MTL activity at each level of emotion (neutral vs. negative) and run (run 1 vs. run 2 vs. run3) and the change in anterior MTL activity over repeated encoding for each level of emotion, respectively, capturing emotion-specific changes across repeated exposures in anterior MTL activity associated with successful memory encoding. As shown in Figure 2, these analyses demonstrated that subsequently remembered emotional items were associated with a significantly higher anterior MTL activity compared to neutral items during initial exposure, i.e. run 1 (interaction contrasts; amygdala: EMM = 0.169, CI[0.084, 0.253], t(182.172) = 3.933, p < 0.001; anterior hippocampus: EMM = 0.116, CI[0.044, 0.188], t(376.749) = 3.158, p = 0.005). Anterior MTL activity, however, did not significantly differ between emotionally negative and neutral images at the last exposure, i.e. run 3 (all |EMM| < 0.030, all p > 0.486). Accordingly, both anterior MTL regions showed a significant decrease in activity for emotionally negative items (paired contrasts; amygdala: EMS = -0.072, CI[-0.108, -0.037], t(18350.218) = -4.547, p < 0.001; anterior hippocampus: EMS = -0.099, CI[-0.135, -0.063], t(18363.538) = -6.178, p < 0.001), which was significantly higher compared to neutral items (interaction contrasts; amygdala: EMS = -0.069, CI[-0.117, -0.021], t(18350.215) = -2.832, p = 0.005; anterior hippocampus: EMS = -0.066, CI[-0.114, -0.017], t(18363.516) = -2.654, p = 0.008). No significant change in anterior MTL activity over runs was observed for emotionally neutral items (paired contrasts: all |EMS| < 0.034, all p > 0.078). These findings indicate that emotional enhancement of immediate memory is linked to increased anterior MTL recruitment specifically during the first exposure to an emotional item. With repeated exposure, anterior MTL involvement decreased. For neutral items that were subsequently remembered, anterior MTL activity remained rather stable across repeated item presentations.

To assess whether our findings are specific to the anterior part of the MTL, we additionally analyzed activity in the mid and posterior part of the hippocampus, again by means of LMMs with a predictor modeling a linear increase over runs and the factors subsequent memory (forgotten vs. remembered), emotion (neutral vs. negative) and their interaction. This analysis indicated that bilateral posterior hippocampal activity was overall positively associated with successful memory formation (paired contrasts; left: EMM = 0.044, CI[0.074, 0.013], t(7455.599) = 2.826, p = 0.005; right: EMM = 0.039, CI[0.07, 0.009], t(6878.434) = 2.551, p = 0.011; main effect memory, left: β = 0.047, CI[0.005, 0.090], t(11249.719) = 2.245, p_{corr} = 0.0496; right: β = 0.053, CI[0.014, 0.094], t(10643.403) = 2.512, p_{corr} = 0.048), yet did not differ between emotional and neutral items (memory × emotion: all $|\beta|$ < 0.028, all p_{corr} > 0.796) and did not significantly change over runs (memory × run: all $|\beta|$ < 0.045, all p_{corr} > 0.315; run × emotion × memory: all $|\beta|$ < 0.021, all p_{corr} > 0.749). No effects were significant in the mid part of the MTL (all $|\beta|$ < 0.059, all p_{corr} > 0.151).

Opposite dynamics of anterior and posterior neocortical cortices across repetitions for emotional and neutral events

In a next step, we investigated the dynamics of neocortical activity during repeated encoding of emotionally negative and neutral images by segmenting the cortex into 200 fine-grained parcellations (Schaefer et al., 2018). This method, focusing on functionally homogeneous regions over individual voxels or a limited set of neocortical regions of interest while correcting for multiple comparisons, allows a comprehensive analysis of activation dynamics over recurring emotional events throughout the entire neocortex.

Analyzing encoding-related activity on a single-trial level by means of an LMM with a predictor modeling a linear increase over encoding runs and the factors emotion (neutral vs. negative) and subsequent memory (forgotten vs. remembered) revealed an initial enhancement of activity associated with emotional (vs. neutral) memory formation in the right inferior frontal gyrus (IFG; interaction contrast: EMM = 0.116, CI[0.040, 0.191], t(291.589) = 3.024, p = 0.008; run × emotion × memory: β = -0.110, CI[-0.169, -0.038], t(18340.610) = -2.970, p_{corr} = 0.047) and bilateral anterior temporal cortices (interaction contrasts; peak in left anterior superior temporal sulcus, STS: EMM = 0.160, CI[0.088, 0.233], t(343.210) = 4.352, p < 0.001; peak in right temporal pole: EMM = 0.219, CI[0.148, 0.29], t(400.730) = 6.043, p < 0.001; run × emotion × memory, left: β = -0.140, CI[-0.207, -0.073], t(18330.090) = -3.940, p = 0.008; right: β = -0.110, CI[-0.174, -0.042], t(18340.840) = -3.010,

p_{corr} = 0.047; see Figure 3). With repeated exposure, activity associated with successful emotional memory encoding decreased in both anterior temporal cortices (left: EMS = -0.157, CI[-0.193, -0.122], t(18330.126) = -9.941, p < 0.001; right: EMS = -0.095, CI[-0.130, -0.059], t(18340.890) = -5.916, p < 0.001) and the IFG (EMS = -0.036, CI[-0.072, -0.0001], t(18340.631) = -2.247, p = 0.049), whereas no significant activity changes over runs were observed for emotionally neutral images (all |EMS| < 0.025, all p > 0.193; paired contrasts). Contrasting the activity change over runs for emotional and neutral images, confirmed that subsequent emotional compared to neutral memory was associated with a significantly higher decrease over encoding repetitions in both, anterior temporal cortices (left: EMS = -0.133, CI[-0.181, -0.085], t(18330.071) = -5.436, p < 0.001; right: EMS = -0.117, CI[-0.166, -0.069], t(18340.82) = -4.755, p < 0.001) and the IFG (EMS = -0.053, CI[-0.101, -0.005], t(18340.614) = -2.146, p = 0.032; interaction contrasts). Consequently, at the time of the final encoding run, encoding-related activity in the IFG (EMM = 0.010, p = 0.796) and right anterior temporal lobe (EMM = -0.016, p = 0.655) did not significantly differ between emotional and neutral images, while it was even reduced for emotionally negative compared to neutral images in the left anterior temporal cortex (EMM = -0.106, CI[-0.178, -0.033], t(344.068) = -2.867, p = 0.007; interaction contrasts). Notably, both the anterior temporal lobe and right IFG have previously been recognized for their pivotal role in memory processes, particularly in semantic control (Patterson et al., 2007; Ralph et al., 2017) and emotional enhancement of memory (Dolcos et al., 2004; Ritchey et al., 2011; Weintraub-Brevda and Chua, 2018), respectively. Our findings point to a transient role of these anterior temporo-frontal regions in emotional memory encoding, with a heightened encoding-related activity for emotional events, specifically during initial exposure, mirroring our results in the anterior MTL. A mid-central cluster showed a similar pattern of results, with a significantly higher decrease in activity over runs for recurrent emotional (peak in the mid cingulate cortex, paired contrast: EMS = -0.035, CI[-0.071, -0.0001], t(18334.427) = -2.25, p = 0.049) compared to neutral images (paired contrast: EMM = 0.0236, p = 0.203; interaction contrast: EMS = -0.059, CI[-0.107, -0.011], t(18334.391) = -2.427, p = 0.015; run × emotion × memory: β = -0.120, CI[-0.188, -0.051], t(18334.46) = -3.37, p_{corr} = 0.026), however, without significant activity differences between negative and neutral items at run 1 (EMM = 0.062, p = 0.128), run 2 (EMM = 0.003, p = 0.900), and run 3 (EMM = -0.056, p = 0.128).

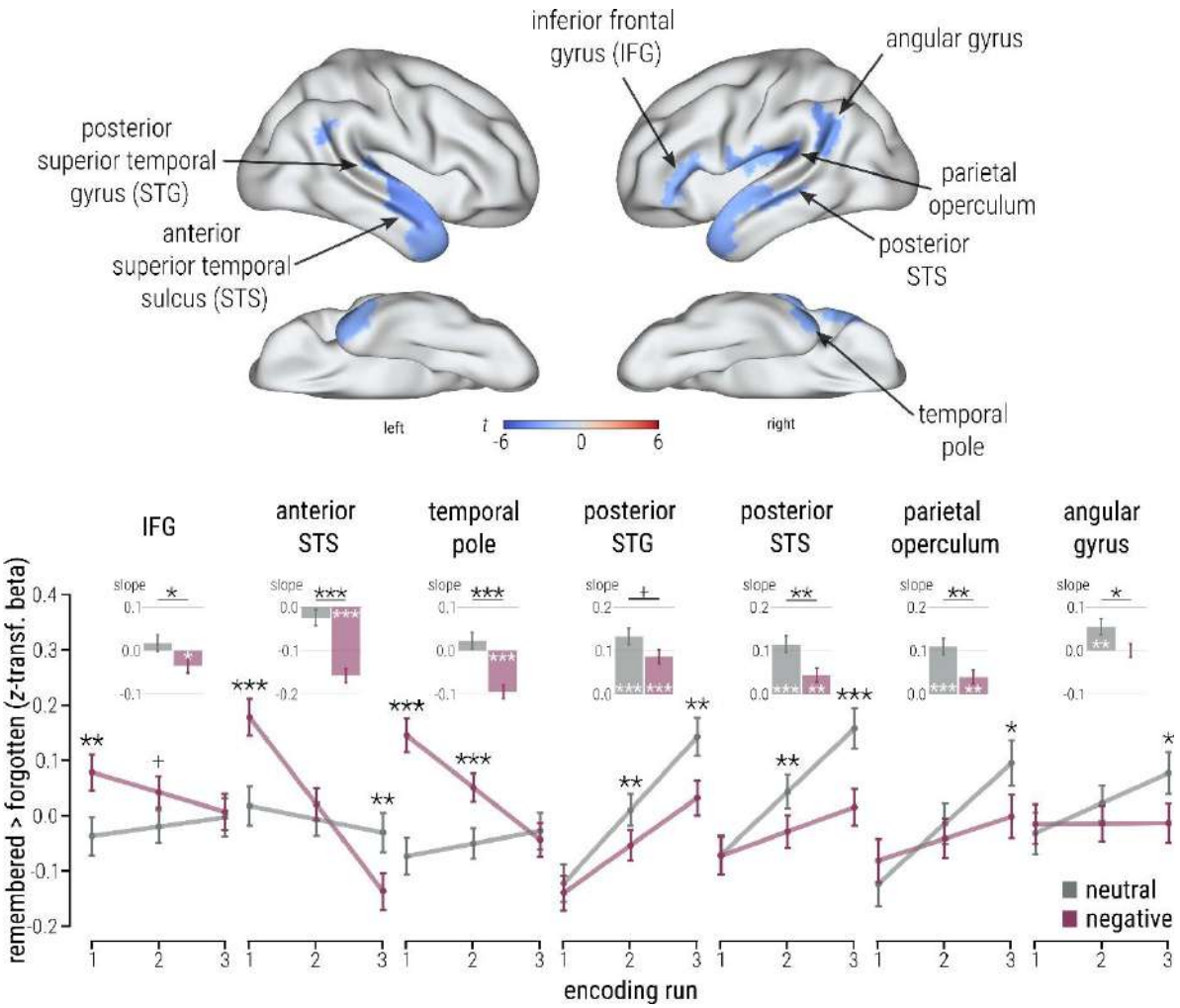

Figure 3. Differential neocortical trajectories for repeated exposure to emotional and neutral events. Bilateral anterior temporo-frontal activity during initial exposure was associated with subsequent memory for emotional (vs. neutral) events, with decreasing involvement across encoding runs (linear mixed models, LMMs, run × emotion × memory: IFG: p_{corr} = 0.047; anterior STS: p_{corr} = 0.008; temporal pole: p_{corr} = 0.047). Conversely, posterior temporal and parietal corices were associated with subsequent memory after several encoding runs, specifically for emotionally neutral events (LMMs, posterior STG: p_{corr} = 0.021; posterior STS: p_{corr} = 0.039; parietal operculum: p_{corr} = 0.001; angular gyrus: p_{corr} = 0.021). These findings highlight the rapid, yet transient engagement of anterior temporo-frontal cortices in emotional memory encoding, whereas successful encoding of neutral events may require multiple exposures and rely on posterior neocortical areas. Connected dots depict the estimated marginal means for the contrast 'remembered > forgotten' per level of the predictors emotion and run ± SE; bars represent estimated marginal slopes for the same contrast per level of emotion ± SE. All n = 103. Reported p-values are two-tailed and FDR-corrected for multiple comparisons accounting for the number of regions of interest in this analysis (p_{corr}). ***p < 0.001; **p < 0.010; **p < 0.050; ^{+}p < 0.060.

While these data indicated that anterior neocortical regions were more strongly involved in successful emotional memory encoding at initial encounter, and that this involvement in successful emotional memory encoding decreased with repeated exposure, posterior neocortical areas showed a markedly different pattern. In the posterior temporal cortex, there was no significant difference in activation between negative and neutral events at initial exposure (run 1, peak in the left posterior

superior temporal gyrus, STG: EMM = -0.017, p = 0.602; peak in the right posterior STS: EMM = -0.002, p = 0.964; interaction contrasts). However, at final exposure (run 3), both posterior temporal cortices showed a marked increase for emotionally neutral compared to negative events (interaction contrasts, left: EMM = -0.110, CI[-0.175, -0.045], t(718.708) = -3.330, p = 0.003; right: EMM = -0.143, CI[-0.211, -0.075], t(496.588) = -4.118, p < 0.001; run × emotion × memory, left: β = -0.120, CI[-0.192, -0.06], t(18321.820) = -3.510, p_{corr} = 0.021; right: β = -0.110, CI[-0.181, -0.046], t(18346.77) = -3.200, p_{corr} = 0.039). Here, successful memory formation was associated with a significant increase in activation over runs, specifically for emotionally neutral images (paired contrasts; left: EMS = 0.132, CI[0.091, 0.174], t(18321.725) = 7.103, p < 0.001; right: EMS = 0.114, CI[0.073, 0.156], t(18346.776) = 6.154, p < 0.001), and, to a significantly lesser degree (interaction contrast; right: EMS = -0.071, CI[-0.118, -0.023], t(18346.776) = -2.893, p = 0.004), for emotionally negative images (paired contrasts; left: EMS = 0.086, CI[0.050, 0.121], t(18321.77) = 5.43, p < 0.001; right: EMS = 0.044, CI[0.009, 0.079], t(18346.776) = 2.786, p = 0.005). A right perisylvian cluster (peak in the parietal operculum; run × emotion × memory: β = -0.16, CI[-0.224, -0.091], t(18328.32) = -4.55, p_{corr} = 0.001) showed a similar pattern of results, with successful memory encoding being associated with a significant increase over encoding runs, which was significantly higher for emotionally neutral (paired contrast: EMS = 0.109, CI[0.069, 0.150], t(18328.271) = 6.017, p < 0.001) compared to negative images (paired contrast: EMS = 0.040, CI[0.005, 0.074], t(18328.379) = 2.582, p = 0.010; interaction contrast: EMS = -0.070, CI[-0.116, -0.023], t(18328.307) = -2.919, p = 0.004).

In the inferior PPC, specifically within the bilateral angular gyrus, we observed a significant activation increase over runs for emotionally neutral items (paired contrasts, left: EMS = 0.064, CI[0.022, 0.106], t(18352.785) = 3.433, p = 0.001; right: EMS = 0.054, CI[0.013, 0.096], t(18359.129) = 2.938, p = 0.007) that was significantly higher compared to negative events (interaction contrasts, left: EMM = -0.081, CI[-0.129, -0.033], t(18352.776) = -3.302, p = 0.001; right: EMS = -0.054, CI[-0.101, -0.006], t(18359.143) = -2.213, p = 0.027), which did not significantly change over encoding runs (paired contrasts: all p > 0.290; run × emotion × memory, left: β = -0.129, CI[-0.190, -0.057], t(18352.820) = -3.470, p_{corr} = 0.021; right: β = -0.130, CI[-0.198, -0.058], t(18359.16) = -3.660, p_{corr} = 0.017). Accordingly, in the final encoding run, the right angular gyrus displayed a significantly higher activity for emotionally neutral events compared to negative events that were subsequently recalled (EMM = -0.091, CI[-0.162, -0.020], t(362.745) = -2.506, p = 0.038). Intriguingly, the angular gyrus has previously been implicated in the rapid formation of memory representations across repeated

encoding (Brodt et al., 2016). Our findings thus indicate memory formation in the angular gyrus for emotionally neutral events but less so for negative events over repeated exposure.

Together, our univariate analyses across the neocortex suggest a differential pattern of anterior and posterior neocortical involvement over repeated exposure to emotional compared to neutral events. While anterior temporo-frontal areas were associated with successful emotional memory encoding at initial exposure, posterior temporal and parietal cortices were involved in neutral memory formation after several encoding runs. Notably, no region showed an initial prioritization of emotionally neutral over negative memories or significantly higher activation for emotionally negative items during final exposure.

Successful emotional memory encoding is associated with stable neocortical pattern representations across repetitions

Whereas our analyses so far have focused on the dynamics of univariate, trial-wise anterior MTL and neocortical activity during recurring exposure to emotionally negative vs. neutral images, previous research suggested that successful encoding of episodic memory (of neutral events) may be associated with a consistent reactivation of neural representations across encoding episodes (Xue et al., 2010, 2013; Feng et al., 2019). Whether the reinstatement of representational patterns during encoding is altered for emotional information, and hence associated with a subsequent emotional enhancement of memory, remains unknown. Thus, in a next step, we applied a multivariate item-wise similarity analysis by correlating encoding patterns of items in a specific encoding run with the encoding patterns of the same item during a subsequent encoding run (see Figure 3a). Based on previous literature (Murty et al., 2011; Cowan et al., 2021) and the results of our univariate analyses suggesting a transient role of the anterior MTL in emotional memory formation, we did not expect stable encoding patterns in the anterior MTL. Accordingly, amygdala and anterior hippocampal pattern stability across runs was neither linked to emotional enhancement of memory (memory × emotion: all $|\beta| < 0.005$, all $p_{corr} > 0.568$) nor to overall memory (main effect memory: all $|\beta| < 0.002$, all $p_{corr} > 0.970$). Similarly, no such observation was observed in the mid or posterior hippocampus (main effect memory: $|\beta| < 0.003$, all $p_{corr} > 0.565$; memory × emotion: all $|\beta| < 0.004$, all $p_{corr} > 0.673$).

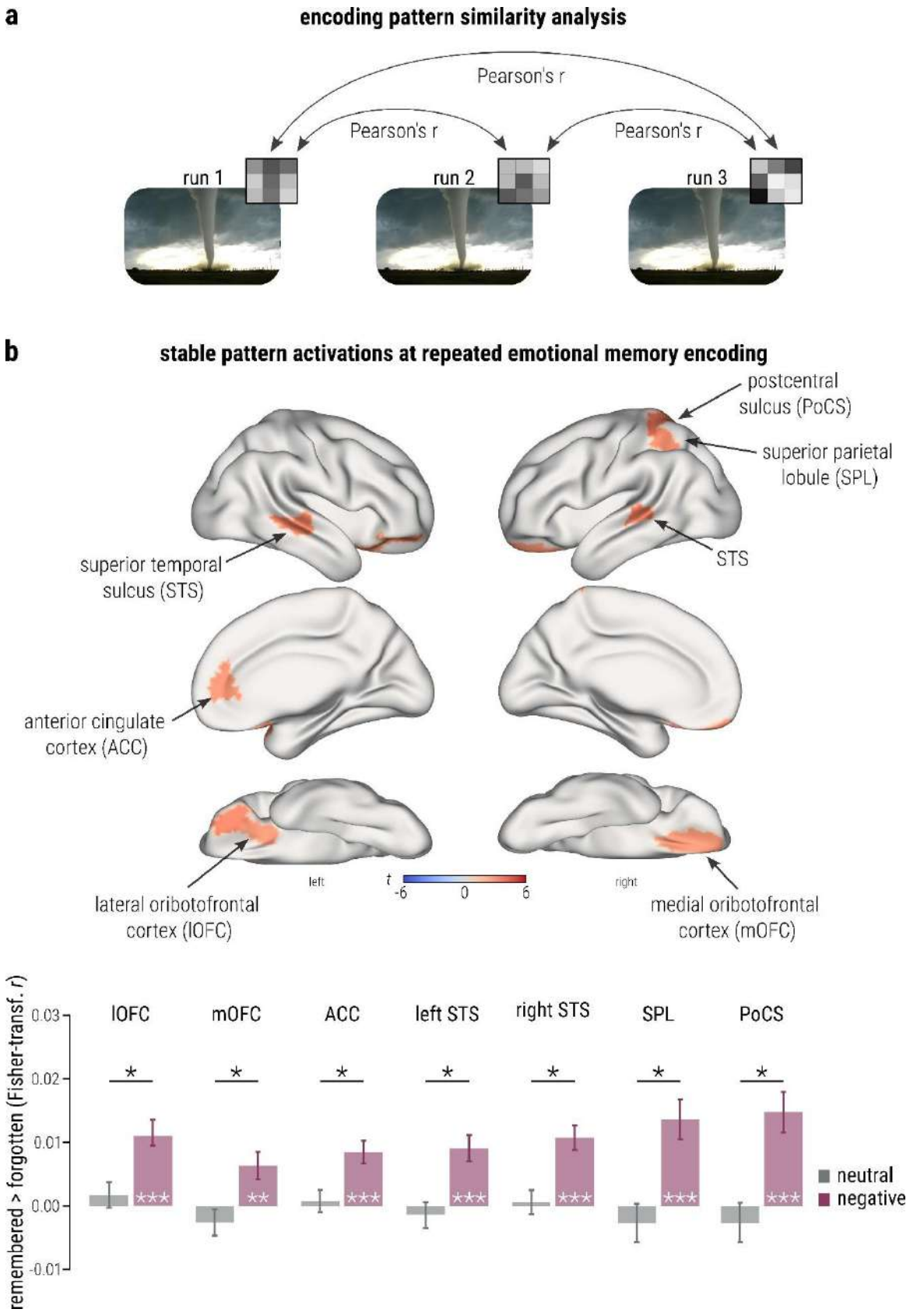

Figure 4. **Pattern stability across repeated encoding associated with subsequent emotional memory enhancement. a** To assess stable activation patterns across repeated emotional memory encoding, we correlated encoding patterns of items in a specific encoding run with the encoding patterns of the same item during a subsequent encoding run. Depicted image is licensed under Creative Commons (CC-BY-SA) license and is courtesy of Justin Hobson (https://bit.ly/3SbJTkK;

changed). **b** Subsequent emotional (vs. neutral) memory was associated with consistent activation patterns over repeated encoding runs in prefrontal (lOFC: p_{corr} = 0.019; mOFC: p_{corr} = 0.048) and posterior neocortical areas (left STS: p_{corr} = 0.043; right STS: p_{corr} = 0.010; SPL: p_{corr} = 0.010; PoCS: p_{corr} = 0.010; memory × emotion, linear mixed models). These findings highlight stable activation patterns over repeated encoding in neocortical regions associated with attention and cognitive control processes that contribute to emotional enhancement of immediate subsequent memory. Bars represent estimated marginal means for the contrast 'remembered > forgotten' per level of the predictor emotion ± SE. All n = 103. Reported p-values are two-tailed and FDR-corrected for multiple comparisons, accounting for the number of regions of interest in this analysis (p_{corr}). ***p < 0.001; **p < 0.010; *p < 0.010.

In contrast to MTL encoding pattern similarity, neocortical pattern similarity across repeated encoding runs was significantly involved in successful encoding of emotionally negative images. Specifically, recall of emotional compared to neutral images was associated with significantly higher pattern stability in the medial prefrontal cortex, including the perigenual anterior cingulate cortex (ACC; memory × emotion: β = 0.008, CI[0.003, 0.013], t(4803.245) = 3.139, p_{corr} = 0.043), left lateral orbitofrontal cortex (OFC; peak, memory × emotion: β = 0.010, CI[0.004, 0.016], t(5114.366) = 3.492, p_{corr} = 0.019) and right medial OFC (memory × emotion: β = 0.009, CI[0.004, 0.014], t(6135.003) = 3.068, p_{corr} = 0.048). Notably, both the ACC and OFC have been previously implicated in emotion control processes (Etkin et al., 2011; Sakata et al., 2019) which may promote the successful encoding of emotionally arousing events. Post-hoc analyses confirmed that, in both of these regions, successful emotional memory formation was associated with consistent pattern representations over repeated encoding runs (ACC: EMM = 0.008, CI[0.005, 0.012], t(3994.984) = 4.737, p < 0.001; left OFC: EMM = 0.012, CI[0.008, 0.016], t(4414.477) = 5.624, p < 0.001; right OFC: EMM = 0.006, CI[0.002, 0.011], t(6147.45) = 2.99, p = 0.003). For neutral events, there was no significant involvement of pattern stability in these prefrontal areas in successful memory encoding (all |EMM| < 0.003, all p > 0.206; paired contrasts).

Moreover, subsequent memory was associated with a significantly higher encoding similarity for emotionally negative compared to neutral images in the posterior section of left (memory × emotion: β = 0.010, CI[0.005, 0.016], t(4851.661) = 3.677, p_{corr} = 0.012) and right temporal cortices (memory × emotion: β = 0.010, CI[0.005, 0.016], t(4664.417) = 3.794, p_{corr} = 0.010). Although this appears to mirror our univariate findings of more stable activations for successfully encoded emotionally negative compared to neutral events in posterior temporal cortices, it is crucial to note that regions exhibiting a significant effect in our univariate analyses did not overlap with regions showing a significant encoding pattern stability, thus ruling out that our multivariate findings might be driven by

univariate activation differences. Successful encoding of emotional (vs. neutral) images was further associated with significantly more stable pattern representations in posterior parietal regions, such as the right postcentral gyrus (memory × emotion: β = 0.017, CI[0.009, 0.026], t(5822.193) = 4.002, p_{corr} = 0.010) and right superior parietal lobule (SPL, peak: memory × emotion: β = 0.010, CI[0.005, 0.016], t(4664.417) = 3.794, p_{corr} = 0.010). Notably, the SPL, as part of the dorsal attentional network (Corbetta and Shulman, 2002; Corbetta et al., 2008; Spreng et al., 2013), is expected to foster perceptual attentional processes that support emotional memory formation (Sestieri et al., 2017). The postcentral sulcus, interconnected with the frontoparietal control network (Vincent et al., 2008), on the other hand, is expected to support memory encoding by consistent evaluation of the familiarity of the presented material (Sestieri et al., 2017). Notably, our results did not indicate any statistically significant association between more dissimilar, i.e. more variable, encoding patterns and subsequent memory for emotionally negative nor neutral images.

Thus, results of our multivariate analyses suggest that successful encoding of emotional events is associated with stable pattern representations over encoding runs in prefrontal and posterior parietal areas which have been previously linked to attentional and cognitive control processes. These findings align with previous work suggesting a crucial role of cognitive factors, such as heightened attention to emotionally negative material during encoding (Talmi, 2013), in the emotional enhancement of immediate memory.

Amygdala activity at first exposure modulates emotional memory enhancement via neocortical pattern stability over repetitions

As a final step, we analyzed whether anterior MTL engagement at initial exposure, i.e. encoding run 1, influences immediate emotional memory enhancement via stable neocortical pattern activations over encoding repetitions. To this end, we employed a multilevel moderated mediation analysis with the predictor emotion (neutral vs. negative), the outcome variable subsequent memory (forgotten vs. remembered), the mediator encoding pattern similarity, and the moderator anterior MTL (left amygdala or right anterior hippocampus) activity at encoding run 1. This approach involved (i) an LMM estimating the mediator as a function of the predictor, the moderator, and their interaction, (ii) a generalized LMM predicting the outcome by means of the predictor and mediator, both interacting with the moderator, (iii) evaluating the moderated mediation by assessing conditional indirect effects at

different levels of the moderator (Tingley et al., 2014; Hayes, 2015), and (iv) inference statistical testing of the linear change of conditional indirect effects as a linear function of the mediator—the index of moderated mediation (Hayes, 2015)—via bias-corrected bootstrap confidence intervals (as recommended by Hayes, 2015).

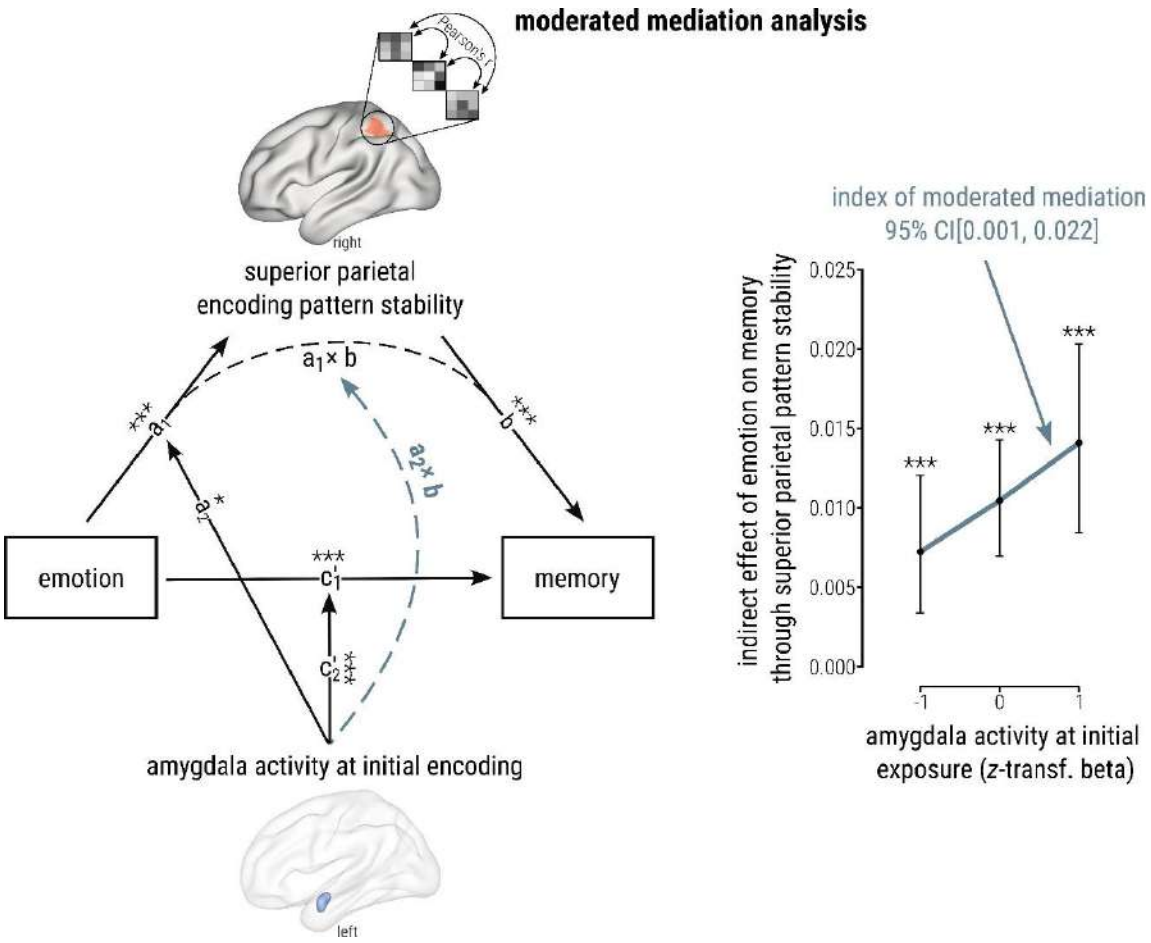

Figure 5. Amygdala activity at first exposure boosts subsequent emotional memory via neocortical encoding pattern stability. *Left panel:* Multilevel moderated mediation analyses revealed a significant mediation of emotional memory enhancement through superior parietal encoding pattern stability (indirect effect, $a_1 \times b$: $p_{corr} < 0.001$; direct effect, path c_1': $p_{corr} < 0.001$). *Right panel:* The indirect effect of emotion on subsequent memory through stable neocortical encoding patterns was significantly facilitated by amygdala activity during initial stimulus exposure, as indicated by the index of moderated mediation ($a_2 \times b$). These findings underscore the pivotal role of rapid amygdala engagement in emotional memory encoding and its interaction with the SPL in facilitating memory for recurring emotional events. Inference statistical testing of the index of moderated mediation based on bias-corrected, bootstrapped confidence interval (as recommended by Hayes, 2015). Points represent conditional indirect effects at low (-1SD), mean, and high (+1SD) levels of the moderator ± SE. Regression line illustrates the index of moderated mediation as the linear change in the indirect effect as a function of the moderator. All n = 103. Reported p-values are two-tailed and FDR-corrected for multiple comparisons, accounting for the number of regions of interest in this analysis (p_{corr}). ***p < 0.001, *p < 0.050.

This analysis revealed a direct link between amygdala activity at initial exposure and consistent pattern (re)activations over repeated encoding facilitating emotional enhancement of immediate free recall. When controlling for the influence of the moderator (initial amygdala activity), encoding pattern stability in the SPL significantly mediated emotional enhancement of subsequent memory (indirect effect, $a_1 \times b$ in Figure 5: β = 0.010, CI[0.007, 0.014], p_{corr} < 0.001). When controlling for this indirect effect through SPL encoding pattern stability (and the moderator), the direct effect of emotion on memory remained significant (c_1' in Figure 5: β = 0.156, CI[0.133, 0.180], p_{corr} < 0.001), suggesting a partial mediation by consistent encoding patterns in the SPL. Critically, the extent of amygdala activation at initial encoding significantly moderated this relationship (index of moderated mediation, $a_2 \times b$: β = 0.013, CI[0.001, 0.022]; see Figure 5, right panel), with higher amygdala activity (*z*-transformed beta = 1) enhancing the indirect effect of emotion on memory via SPL pattern stability (compared to lower levels of initial amygdala activity; indirect effect: β = 0.014, CI[0.008, 0.020], p_{corr} < 0.001; direct effect: β = 0.186, CI[0.152, 0.219], p_{corr} < 0.001). Conversely, if amygdala activity during initial exposure was relatively low (*z*-transformed beta = -1), emotional memory enhancement through stable posterior encoding patterns was reduced (indirect effect: β = 0.007) but still significant (CI[0.003, 0.012], p_{corr} < 0.001; direct effect: β = 0.125, CI[0.092, 0.159], p_{corr} < 0.001). These results suggest that amygdala activation, when first encountering an emotional stimulus, may boosts memory for this stimulus by persistent superior parietal (re)activation patterns during subsequent exposures.

DISCUSSION

This study aimed to elucidate the neural mechanisms underlying memory formation for recurrently encountered emotional events. Our findings reveal that successful emotional memory formation is linked to persistent (re)activation patterns in neocortical attention and cognitive control regions, coupled with transient activation in anterior MTL and temporo-frontal regions upon first encountering an emotional event. Critically, the extent of amygdala activation during this first exposure facilitated emotional memory enhancement via neocortical encoding pattern stability.

The observed elevation in amygdala and anterior hippocampal activity during the first exposure to an emotional event corroborates previous findings, underscoring the pivotal role of these regions in detecting novel, salient stimuli (Ranganath and Rainer, 2003; Cowan et al., 2021) and

emotional memory encoding (Murty et al., 2011; Dahlgren et al., 2020). Rapid detection of emotionally salient events is crucial for survival in potentially threatening situations and has been predominantly linked to the amygdala (LeDoux & Phelps, 2008). Notably, our findings demonstrate a dynamic involvement of the anterior MTL in successful emotional encoding, with an activation decrease over repeated exposures. This dynamic dovetails with the adaptive response of the anterior MTL during emotional learning (Büchel and Dolan, 2000; Yin et al., 2018). Moreover, this trajectory of a decrease in anterior MTL (amygdala and anterior hippocampus) activity across repetitions was mirrored by anterior temporal areas and the right IFG, which have been linked to attention allocation based on stimulus salience (Corbetta et al., 2008), emotional memory enhancement (Dolcos et al., 2004; Ritchey et al., 2011; Weintraub-Brevda and Chua, 2018), novelty detection (Ranganath and Rainer, 2003), and semantic memory (Patterson et al., 2007; Binder and Desai, 2011; Ralph et al., 2017). These areas may promote efficient encoding of novel, emotionally salient information by anchoring it to existing knowledge frameworks (Prince et al., 2007; Irish and Piguet, 2013; Sommer, 2016). In sharp contrast to the trajectory in anterior temporo-frontal regions, our results indicate that successful encoding of recurring neutral events is marked by increasing involvement of posterior temporal and parietal cortices associated with semantic processes (Patterson et al., 2007; Binder and Desai, 2011; Liebenthal et al., 2014; Ralph et al., 2017). The increased engagement of angular gyrus over repeated exposure aligns with previous finding associating this region with cortical memory formation in the course of repeated spatial learning (Brodt et al., 2016). While the angular gyrus has been repeatedly associated with memory retrieval (Sestieri et al., 2017), it is likely to reflect more generalized, schema-based memories (Binder et al., 2009; Wagner et al., 2015; van der Linden et al., 2017). Thus, in the absence of emotional salience, memory formation may rely on multiple encoding repetitions, potentially leading to more generalized memory representations (Nadel and Moscovitch, 1997; van der Linden et al., 2017; Hebscher et al., 2019). Our data suggest that this repetition-based memory formation in posterior parietal areas such as the angular gyrus may be slowed down for emotionally negative events, potentially in order to keep more specific representations of these events.

While our trial-wise univariate analyses focused on dynamic activation changes, our multivariate encoding similarity analysis allowed us to probe the stability (vs. variability) of activation patterns across repeated encoding runs. Previous findings (Xue et al., 2010, 2013; Feng et al., 2019) indicated that successful memory formation for neutral events is associated with the consistent reinstatement of similar representation patterns over repeated encoding, rather than an increased

dissimilarity over repeated encoding as suggested by encoding-variability accounts (Estes, 1955; Bower, 1972; Johnston, 1976). Here, we show that this pattern stability across repeated encoding runs is even enhanced for emotional compared to neutral events, particularly in prefrontal regions such as the ACC and OFC. These persistent prefrontal activation patterns may reflect the involvement of these regions in facilitating attention to emotional stimuli (Seeley et al., 2007; Pourtois et al., 2013), which, in turn, may enhance subsequent memory for emotional events (Kensinger, 2009; Mather and Sutherland, 2011; Pourtois et al., 2013). Accordingly, successful encoding of emotional (compared to neutral) images was furthermore associated with more consistent activation patterns in the SPL, likely reflecting sustained perceptual attention to emotionally negative events (Corbetta and Shulman, 2002; Corbetta et al., 2008; Spreng et al., 2013).

Intriguingly, the results of our multilevel moderated mediation analysis indicate that the amygdala's transient response at initial event exposure may boost subsequent memory for emotionally salient information via persistent superior parietal (re)activation patterns across recurring exposures. This finding is consistent with previous reports suggesting that the amygdala guides perceptual attention to emotionally salient information through interactions with frontoparietal attention cortices (Liberzon et al., 2003; Lim et al., 2009, 2009; Mather and Sutherland, 2011; Pourtois et al., 2013). Thus, these results support previous accounts suggesting that emotional enhancement of immediate memory may be mediated by cognitive factors such as increased perceptual attention to emotionally salient information (Pourtois et al., 2013; Talmi, 2013), while highlighting the modulation of this process by amygdala activation at initial exposure. This dynamic may be highly adaptive as it, on the one hand, ensures sustained attention to and, consequently, memory of emotionally salient events (Pourtois et al., 2013), while allowing the amygdala to reset and allowing the response to potential novel, emotionally salient information. Notably, while previous accounts implicated increased involvement in visual cortices during emotional memory encoding (Mather and Sutherland, 2011; Pourtois et al., 2013), neither our univariate nor our multivariate analyses indicated beneficial activation (patterns) in such regions during successful encoding of emotional (compared to neutral) images across repeated encoding runs.

To conclude, our findings shed light on the dynamic interplay between transient amygdala activation and persistent neocortical activation patterns in the successful encoding of recurring emotional events. Moreover, our data indicate distinct trajectories of neocortical activity over encoding

repetitions of emotional and neutral events with a diminishing engagement in anterior temporo-frontal regions for emotionally salient stimuli and a progressive increase in posterior temporal and parietal activation for neutral events. Beyond their relevance for our understanding of the evolution of emotional memory across repeated encoding, these findings might have implications for the development of novel interventions for disorders such as complex posttraumatic stress disorder, that are characterized by recurring traumatic events and the debilitating memories thereof.

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Appendix: Study 2

B

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Noradrenergic arousal after encoding reverses the course of systems consolidation in humans

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It is commonly assumed that episodic memories undergo a time-dependent systems consolidation process, during which hippocampus-dependent memories eventually become reliant on neocortical areas. Here we show that systems consolidation dynamics can be experimentally manipulated and even reversed. We combined a single pharmacological elevation of post-encoding noradrenergic activity through the α_2-adrenoceptor antagonist yohimbine with fMRI scanning both during encoding and recognition testing either 1 or 28 days later. We show that yohimbine administration, in contrast to placebo, leads to a time-dependent increase in hippocampal activity and multivariate encoding-retrieval pattern similarity, an indicator of episodic reinstatement, between 1 and 28 days. This is accompanied by a time-dependent decrease in neocortical activity. Behaviorally, these neural changes are linked to a reduced memory decline over time after yohimbine intake. These findings indicate that noradrenergic activity shortly after encoding may alter and even reverse systems consolidation in humans, thus maintaining vividness of memories over time.

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With time, episodic memories may undergo a neural reorganization. Specifically, the temporally graded amnesia in patients such as H.M. and neuroimaging findings suggested that memories are initially critically dependent on the hippocampus but, over time, relocated to neocortical areas during a process of systems consolidation[1–6]. This time-dependent neural reorganization of the memory trace may be accompanied by a semantization[7,8], and hence areas implicated in semantic memory, such as the ventromedial prefrontal cortex (vmPFC) and the inferior frontal gyrus (IFG)[5,9,10], are prime candidates for neocortical storage sites. Although this semantization over time may be adaptive in that it promotes the building of abstract knowledge structures[10,11], keeping specific and vivid memories may be particularly important for emotionally arousing events. However, whether the dynamics of systems consolidation may be shaped by environmental conditions, such as emotional arousal, remains unknown.

Stress and emotional arousal are powerful modulators of memory[12–16]. Extensive evidence demonstrates that arousal-induced noradrenergic activation of the basolateral amygdala (BLA) modulates neuroplasticity processes in other brain regions[17–20]. Most studies investigating noradrenergic arousal effects on memory have focused on episodic or contextual memories that depend on the hippocampus[21]. Surprisingly, however, the long-term fate of such memories and potential changes in systems consolidation processes remained completely unclear. A recent study in rodents provided first evidence that noradrenergic arousal shortly after encoding may prolong hippocampal involvement in long-term memory and hence alter systems consolidation[22]. This study showed that the administration of norepinephrine into the BLA shortly after training on an inhibitory avoidance discrimination task resulted in significantly increased episodic-like memory after a delay of 28d, compared to a saline administration. Even more strikingly, this study indicated that norepinephrine after encoding did not only maintain hippocampal dependency of memory after 28d but even led to an increased hippocampal dependency of memory over time, suggesting not only that systems consolidation processes can be experimentally manipulated, but that noradrenergic activation during initial consolidation might even reverse systems consolidation dynamics. Whether noradrenergic arousal can influence the dynamics of systems consolidation of memories in humans remains completely unknown.

In the present experiment, we aimed to unravel the impact of noradrenergic stimulation on systems consolidation and long-term memory maintenance in humans. To this end, participants encoded a series of pictures in an MRI scanner. Participants received orally either a placebo (PLAC) or the α_2-adrenoceptor antagonist yohimbine (YOH) shortly before encoding. Immediate free recall was tested to ensure that initial memory encoding was comparable between groups. Critically, in order to probe time-dependent systems consolidation, delayed memory performance was tested either 1d or 28d after encoding, again in an MRI scanner, which enabled us to directly assess changes in the neural architecture of memory from encoding to test using univariate as well as multivariate functional MRI (fMRI) analyses. We predicted that YOH administration would enhance memory performance after 28d and decelerate or even reverse systems consolidation, as reflected by an increased hippocampal but reduced neocortical, in particular vmPFC and IFG, involvement. Moreover, leveraging multivariate pattern analysis for the assessment of encoding-retrieval similarity, we hypothesized that the representational pattern of memories at the remote test should become even more similar to the pattern at encoding, when noradrenergic stimulation was elevated after encoding.

As predicted, we show here that increased noradrenergic arousal shortly after encoding critically altered the systems consolidation dynamics. Whereas participants in the PLAC group show the expected systems consolidation process, with decreased hippocampal and increased neocortical activity over time, this process is reversed in the YOH group. Participants treated with YOH show increased hippocampal and reduced neocortical activity from 1d to 28d after encoding. Moreover, hippocampal encoding-retrieval similarity decreases from the 1d to the 28d test in the PLAC group but even increases in the YOH group. These neural changes are accompanied by a reduced decline of memory over time in participants that had received YOH. Together, these findings show that noradrenergic arousal shortly after encoding may not only alter but even reverse the dynamics of systems consolidation over time.

Results

Effective manipulation of arousal after encoding. To determine the effect of post-encoding noradrenergic arousal on time-dependent systems consolidation in humans, we used a two-day fully crossed between-subjects design with the factors drug (PLAC vs. YOH) and delay (1d vs. 28d), resulting in four experimental groups: 1d/PLAC, 28d/PLAC, 1d/YOH, and 28d/YOH. On the first experimental day, participants ($n = 104$) received orally either a PLAC or 20 mg of the α_2-adrenoceptor antagonist YOH right before they entered the MRI for encoding. The dosage and timing of drug administration was chosen based on the known pharmacodynamics of YOH[23,24], in order to achieve increased noradrenergic arousal shortly after the encoding session, i.e. during initial consolidation. To track the action of the drug, blood pressure was measured before and at six different time points (35, 55, 70, 85, 100, and 115 min) after drug administration. The efficacy of drug manipulation was tested using mixed-model ANOVAs with the between-subjects factors drug and delay and the within-subject factor time. Groups had comparable blood pressure before the drug administration (all $t < -0.61$, all $p > 0.242$, all $d < 0.12$). We found a significant drug × time interaction for both systolic ($F_{5.12,501.39} = 14.86$, $p < 0.001$, $\eta_p^2 = 0.13$) and diastolic ($F_{5.25,514.73} = 9.36$, $p < 0.001$, $\eta_p^2 = 0.09$) blood pressure (Fig. 1B). Importantly, even directly after encoding (and before the immediate free recall test) there was no effect of YOH on blood pressure (all $t < -1.06$, all $p > 0.111$, all $d < 0.32$), indicating that YOH was not yet effective during encoding. YOH did, however, increase both systolic and diastolic blood pressure from 85 min after drug administration until the end of day 1 (systolic: all $t > 2.89$, all $p < 0.005$, all $d > 0.57$; diastolic: all $t > 2.93$, all $p < 0.005$, all $d > 0.58$), thus showing the action of the drug shortly after encoding.

Successful memory encoding. Within 5 min after drug administration, participants encoded 60 pictures (30 neutral, 30 emotionally negative) in the MRI scanner, each presented once in each of three consecutive runs. To control for alertness during encoding, participants were instructed to respond to the fixation cross shown between trials with a button press. On average, participants missed only 1.44 (SD = 3.20) responses across all trials and runs, without any differences between groups (all $\beta < 0.54$, $p > 0.187$), suggesting that participants of all four groups remained attentive throughout the encoding task.

To further control for potential group differences in initial encoding, we asked participants to recall as many of the pictures as possible immediately after the encoding session. In this immediate free recall test, participants recalled on average 31.38 (SD = 9.58) of the 60 previously presented items. Although the

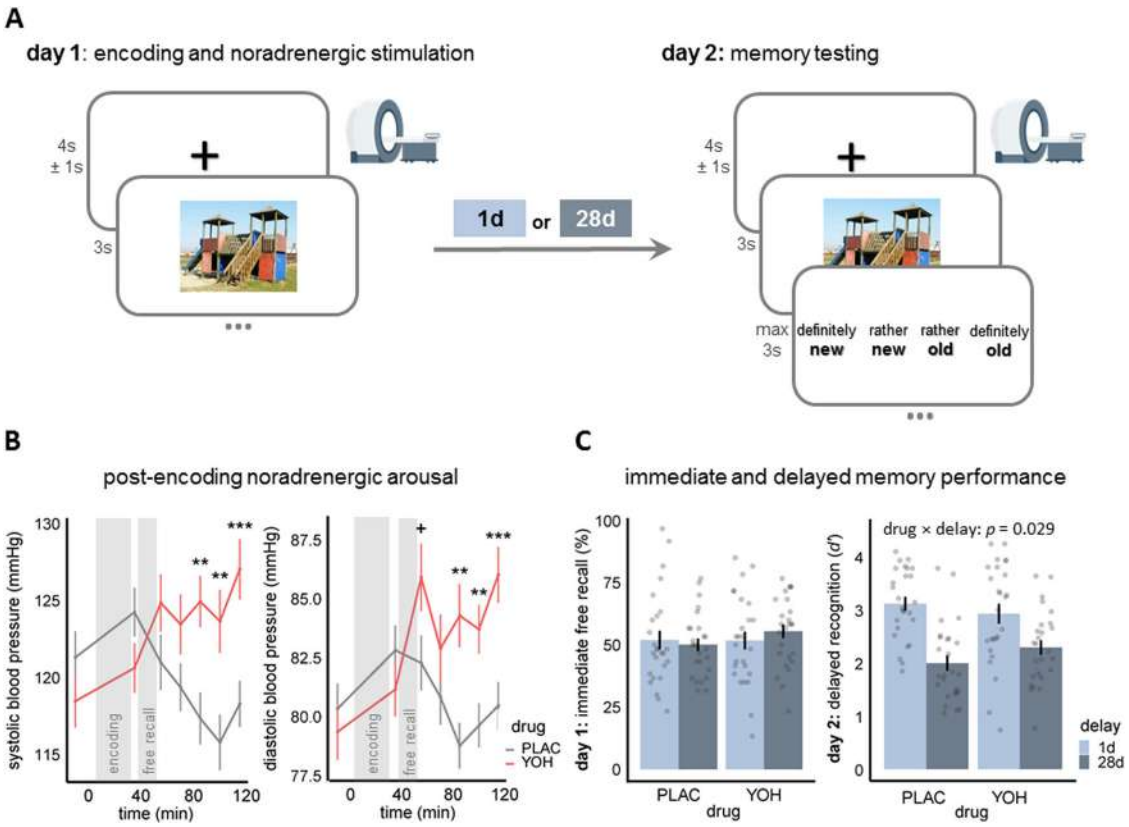

Fig. 1 Experimental design, physiological, and behavioral results. A Participants were tested on two experimental days: day 1, stimulus encoding and pharmacological manipulation of post-encoding noradrenergic activity and day 2, memory recognition. Both encoding and test took place in the MRI scanner. Critically, to investigate time-dependent consolidation processes, the memory test took place either 1d or 28d after encoding. The image of the playground is licensed under Creative Commons License; courtesy of Tomasz Sienicki (https://commons.wikimedia.org/wiki/File:Playground_29_ubt.JPG; image unchanged). **B** Effective manipulation of noradrenergic arousal after encoding: While groups did not differ at baseline (all $p > 0.242$, two-tailed Welch's *t*-tests) or shortly after encoding (all $p > 0.111$, two-tailed Welch's *t*-tests), participants of the yohimbine (YOH) group had significantly higher systolic (all $p < 0.005$, two-tailed Welch's *t*-tests) and diastolic (all $p < 0.005$, two-tailed Welch's *t*-tests) blood pressure from 85 min after drug intake until the end of experimental day 1 (drug × time: all $p < 0.001$, mixed ANOVAs). **C** A generalized linear mixed model (LMM) with the between-factors drug and delay and the within-factor emotion revealed no group-difference in immediate free recall performance on day 1, suggesting that encoding was comparable in the four groups. However, while memory performance significantly decreased from 1d to 28d after encoding (main effect delay: $\beta = -1.12$, $p < 0.001$, LMM), post-encoding noradrenergic arousal reduced this time-dependent memory decline (drug × delay: $\beta = 0.64$, $p = 0.029$, LMM): The YOH group showed a significantly smaller decrease in memory performance from 1d to 28d than the placebo (PLAC) group. All $n = 104$ participants. Bars represent mean ± SEM. Source data are provided as Source data file. $^{**}p < 0.010$; $^{***}p < 0.001$.

delay to the recognition test should not be relevant for performance immediately after encoding, we ran a trial-wise binomial generalized linear mixed model (LMM) with drug (PLAC vs. YOH), delay (1d vs. 28d) and emotion (neutral vs. negative) and their interactions as fixed effects and the random intercept of participants and stimuli to not only assess potential drug effects on encoding but to also rule out potential differences between the 1d- and 28d-groups in initial encoding. This analysis showed a significant effect of the factor emotion ($\beta = 0.68$, $p < 0.001$, $z = 3.1$; supplementary Fig. 1), indicating overall higher free recall performance for emotionally negative compared to neutral stimuli. Critically, there was no effect of drug ($p = 0.499$), delay ($p = 0.403$) or drug × delay ($p = 0.281$), showing that the drug administration did not influence initial memory encoding and that the four groups had comparable memory performance shortly after stimulus encoding (Fig. 1C).

Noradrenergic stimulation reduces time-dependent memory decline. To examine the impact of noradrenergic stimulation on time-dependent changes in memory, we tested participants' memory in a recognition test that took place either 1d or 28d after encoding, again in the MRI scanner. Before this recognition test, groups had comparable blood pressure, confirming that the drug was not active at the time of memory testing (all $F_{1,100} < 1.02$, all $p > 0.386$, $\eta_p^2 < 0.02$).

Overall, participants correctly recognized 85.11% (SD = 13.21%) of the old items (hits) and incorrectly classified only 4.21% (SD = 6.36%) of the new pictures as old (false alarms), demonstrating a high memory performance in the recognition test. Participants' intact memory for the learned items was further confirmed by the sensitivity index d', which takes the individual response bias into account[25] and likewise indicated that memory performance was overall high (mean $d' = 2.59$, SD = 0.89). To test for time-dependent effects of noradrenergic stimulation on memory performance, d'-values were analyzed by means of an LMM with drug (PLAC vs. YOH), delay (1d vs. 28d), emotion (neutral vs. negative) and their interactions as fixed effects and the random intercept of participants. This analysis showed, as expected, that memory performance was lower at 28d than 1d after encoding ($\beta = -1.12$, 95%-*CI*[−1.53,−0.72], $t_{125.82} = -5.43$, $p < 0.001$). This time-dependent decrease in d' was smaller for

negative compared to neutral pictures (emotion × delay: $\beta = 0.42$, 95%-*CI*[0.14, 0.70], $t_{100} = 2.98$, $p = 0.003$; supplementary Fig. 2). Most importantly, there was a significant drug × delay interaction ($\beta = 0.64$, 95%-*CI*[0.06, 1.21], $t_{125.82} = 2.18$, $p = 0.029$), showing that the memory decline from 1d to 28d was weaker in the YOH group than in the PLAC group (Fig. 1C), irrespective of the emotionality of the encoded stimuli (drug × delay × emotion: $\beta = -0.31$, $p = 0.124$).

Participants' responses in the recognition test included ratings of confidence (Fig. 1A). An additional trial-wise generalized LMM on confidence for hits with drug (PLAC vs. YOH), delay (1d vs. 28d), emotion (neutral vs. negative) and their interactions as fixed effects and the random intercept of participants and stimuli revealed, as expected, a decrease in confidence in the 28d group, compared to the 1d group ($\beta = -1.91$, $p < 0.001$, $z = -5.98$). This decrease in confidence in recognizing old items was significantly lower for emotionally negative stimuli (emotion × delay: $\beta = 0.70$, $p = 0.007$, $z = 2.69$), but not influenced by noradrenergic stimulation (drug × delay: $\beta = 0.63$, $p = 0.151$, $z = 1.44$). No other main or interaction effects reached significance in this analysis (all $p > 0.110$). Moreover, in an additional analysis we weighted participants' responses by the level of confidence. This analysis indicated, as before, a significant decrease in memory performance in the 28d-group relative to the 1d-group (main effect delay: $\beta = -1.25$, 95%-*CI*[−1.68,−0.82], $t_{123.33} = -5.71$, $p < 0.001$). This time-dependent decrease in memory was again significantly lower in the YOH group than in the PLAC group (drug × delay: $\beta = 0.62$, 95%-*CI*[0.01,1.22], $t_{123.33} = 1.98$, $p = 0.0495$). Note that in none of these analyses the interaction drug × delay × emotion approached statistical significance (all $p > 0.094$).

Finally, although our study did not focus on potential differences between men and women and was not sufficiently powered to detect such effects, in light of findings suggesting sex differences in the impact of arousal or stress mediators on memory[26], we exploratively analyzed potential sex differences. Including the factor sex into the above LMM did not reveal a significant main effect of sex ($\beta = 0.07$, $p = 0.820$) nor any interactions with any other factors (all $p > 0.384$), suggesting that the effect of post-encoding noradrenergic arousal on memory performance over time was comparable in men and women.

Noradrenergic stimulation increases hippocampal but decreases neocortical contributions to remote memory. To determine the influence of post-encoding noradrenergic activation on systems consolidation, we measured BOLD-activity during both encoding and recognition testing after 1d and 28d, respectively. Our neural analyses focused mainly on the hippocampus, which had been at the center of the research on systems consolidation[1–6]. Our univariate fMRI analysis revealed a significant drug × delay interaction for hippocampal activity for old vs. new pictures (SVC peak-level: x = 22, y = −38, z = 4, $t = 3.31$, p(FWE) = 0.036, k = 10). As shown in Fig. 2A, while hippocampal activity for old (vs. new) pictures tended to be reduced 28d relative to 1d after encoding in the PLAC group ($t_{49.70} = 1.75$, $p = 0.086$, $d = 0.49$), hippocampal activity significantly increased 28d vs. 1d after encoding in participants who had received YOH ($t_{45.05} = -3.54$, $p < 0.001$, $d = 0.98$). Moreover, at the 28d test, hippocampal activity was significantly higher in the YOH than in the PLAC group ($t_{48.24} = 2.53$, $p = 0.015$, $d = 0.70$).

While we predicted a time-dependent decrease in hippocampal activation in the PLAC group, we analyzed also activity in the IFG and vmPFC, two neocortical regions that are known to be of particular relevance for remote, semantic memory[5,9,10] and in which thus activity might increase over time. In sharp contrast to the pattern observed in the hippocampus, the IFG showed a significant increase for old (vs. new) pictures from 1d to 28d in the PLAC group ($t_{43.16} = -3.61$, $p < 0.001$, $d = 1.00$), whereas there was no such increase in IFG activity in participants who had received YOH ($t_{46.37} = 0.50$, $p = 0.620$, $d = 0.14$; drug × delay, SVC peak-level: x = −44, y = 32, z = 12, $t = 4.01$, p_{corr}(FWE) = 0.042, k = 62; Fig. 2B). Interestingly, activation of the IFG was negatively correlated with memory performance expressed as sensitivity index *d'* across groups ($t_{102} = -2.22$, $r = -0.21$, $p = 0.029$; Fig. 2C), suggesting that the decline of memory performance over time was directly associated with the increased IFG involvement in memory. This correlation remained significant after removing outliers, which were defined in accordance to Tukey's method[27]. There were no effects of drug × delay in the vmPFC or in an exploratory whole-brain analysis.

While the previous analysis focused on brain activity for old vs. new items during memory testing, in a next step we analyzed changes in brain activity from the last run of encoding to recognition testing either 1d or 28d later. By taking explicitly the activity at encoding into account, this analysis provides insights into dynamic changes in memory-related activity over time and its modulation by noradrenergic arousal. We focused specifically on changes relative to activity in the last run of the encoding task since this run reflected not only encoding activity but due to the preceding stimulus presentations also immediate memory-related activity. We found a significant drug × delay interaction for recognition vs. encoding for the IFG (SVC peak-level: x = −48, y = 34, z = 12, $t = 5.6$, p_{corr}(FWE) < 0.001, k = 842; whole-brain peak-level: x = −48, y = 34 z = 12, $t = 5.6$, p(FWE) = 0.002, k = 45). As displayed in Fig. 2D, while the PLAC group showed a significant increase in IFG activity from encoding to retrieval at 1d vs. 28d ($t_{47.02} = -4.71$, $p < 0.001$, $d = 1.31$), in the YOH group there was even a decrease in IFG activity from encoding to retrieval with increasing retention delay ($t_{44.86} = 2.69$, $p = 0.010$, $d = 0.75$). Interestingly, an exploratory whole-brain analysis also revealed a significant drug × delay interaction for recognition vs. encoding in the same direction for the precuneus (drug × delay, whole-brain peak-level: x = −4, y = −50, z = 46, $t = 5.21$, p(FWE) = 0.009, k = 27), showing a significant increase in activity after a short compared to a long retention delay in the PLAC group ($t_{48.69} = -3.56$, $p < 0.001$, $d = 0.99$), in line with recent findings that identified the precuneus as a site for neocortical long-term storage[28,29], but a significant decrease in activity for the YOH group ($t_{47.12} = 3.95$, $p < 0.001$, $d = 1.10$). No drug × delay interactions were observed for the vmPFC or the hippocampus in this analysis.

An additional analysis of potential group differences during the final encoding run did not indicate a main effect of drug, neither in any of our a-priori defined regions of interest (ROIs) nor in an exploratory whole-brain analysis, thus providing further evidence that the drug administration left the encoding activity itself unaffected and that YOH was active only after encoding, in line with our autonomic measures.

Noradrenergic stimulation reverses the time-dependent changes in IFG-hippocampus connectivity. In a next step, we performed a psychophysiological interaction (PPI) analysis to test whether the functional connectivity of the hippocampus with the IFG during the recognition task changed as a function of time and noradrenergic stimulation. Using the IFG as seed, this analysis showed that hippocampal-IFG connectivity was significantly increased at 28d relative to 1d after encoding in the PLAC group ($t_{42.94} = -3.08$, $p = 0.004$, $d = 0.85$), whereas there was even a significant decrease ($t_{45.78} = 2.40$, $p = 0.020$, $d = 0.67$) in hippocampal-IFG functional connectivity at 28d vs. 1d in the

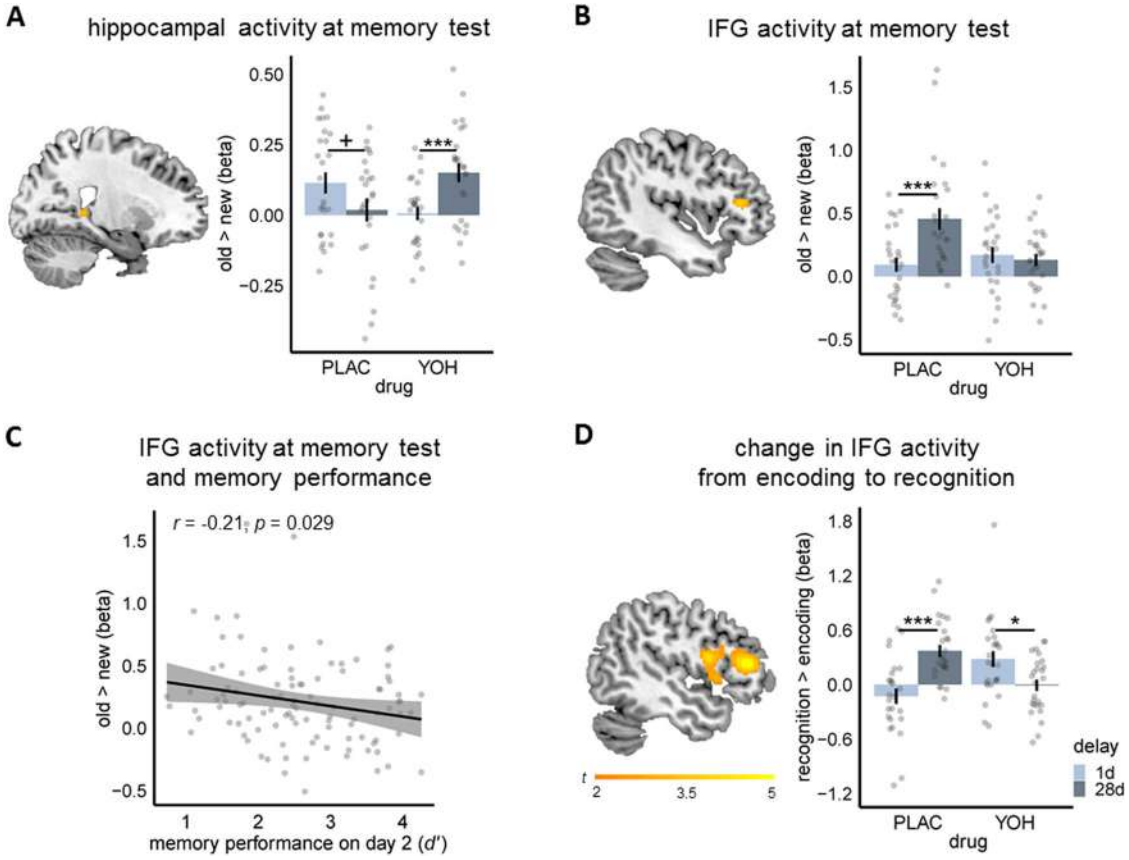

Fig. 2 Noradrenergic stimulation increases hippocampal but decreases neocortical contributions to remote memory. A While hippocampal activity tended to decrease from 1d relative to 28d in the placebo (PLAC) group ($p = 0.086$, two-tailed Welch's t-test), there was even a significant increase in hippocampal activity during memory testing from 1d to 28d in the yohimbine (YOH) group ($p < 0.001$, two-tailed Welch's t-test; drug × delay, SVC peak level: x = 22, y = −38, z = 4, p(FWE) = 0.036, mixed ANOVA). **B** Conversely, inferior frontal gyrus (IFG) activity increased significantly from 28d relative to 1d in the PLAC group ($p < 0.001$, two-tailed Welch's t-test) but not in the YOH group ($p = 0.620$, two-tailed Welch's t-test; SVC peak-level: x = −44, y = 32, z = 12, p_{corr}(FWE) = 0.042, mixed ANOVA). **C** Pearson correlation analysis indicated that IFG activity at 28d-delayed memory test was negatively associated with memory performance on day 2. Note that this correlation remained significant after removing outliers from the analysis. **D** Moreover, while there was a significant increase in IFG activity from encoding to memory testing at the 28d vs. 1d-delayed test in the PLAC group ($p < 0.001$, two-tailed Welch's t-test), there was even a significant decrease in IFG activity from encoding to retrieval with increasing retention delay in the YOH group ($p = 0.010$, two-tailed Welch's t-test; drug × delay, SVC peak-level: x = −48, y = 34, z = 12, p_{corr}(FWE) < 0.001, mixed ANOVA). Bonferroni correction was applied for the number of regions of interest in each analysis. All $n = 104$ participants. Visualizations show t-maps for the interesting contrasts superimposed on sagittal sections of T1-weighted template images and beta-values for the significant cluster. Bars represent mean ± SEM. Source data are provided as Source data file. $^{+}p < 0.100$; $^{*}p < 0.050$; $^{***}p < 0.001$.

YOH group (drug × delay, SVC peak-level: x = −22, y = −40, z = −2, $t = 3.77$, p(FWE) = 0.009, k = 10; Fig. 3). As an increase in hippocampal-IFG connectivity has been linked with the generation of semantic associations[30], this finding further indicates that noradrenergic activation after encoding may reverse systems consolidation processes.

Noradrenergic stimulation increases pattern reinstatement in the hippocampus over time. Successful remembering has been associated with the reinstatement of brain activity present during encoding at test[2,31–33]. To determine the influence of norepinephrine and time on the reactivation of encoding-related activation patterns during memory testing, we assessed in a final step Encoding-Retrieval-Similarity (ERS) as a multivariate measure of trial-specific episodic reinstatement[34–39] applying a searchlight-based representational similarity analysis (RSA) approach[40–42]. Because a decrease in memory reinstatement is thought to reflect a more abstract memory representation and that the episodic details of a specific memory are not successfully retrieved[43], we expected a decrease in similarity between activation patterns during encoding and memory testing, i.e. ERS, during the course of systems consolidation. We computed the ERS by contrasting the pattern similarity between the same items during the final run of the encoding task and during the recognition task (encoding-old-similarity, EOS) with the similarity between pattern representations during the final run of the encoding task and corresponding new items on the recognition task (encoding-new-similarity, ENS). To disentangle memory reinstatement, i.e. ERS, from pattern similarity resulting from mere perceptual processes, we focused on group differences in the differential value of EOS vs. ENS. As shown in Fig. 4, we found a significant decrease in hippocampal ERS from 1d to 28d in the PLAC group ($t_{49.90} = 2.66$, $p = 0.010$, $d = 0.74$) while hippocampal ERS significantly increased over time in the YOH group ($t_{46.66} = -2.22$, $p = 0.031$, $d = 0.62$; drug × delay, SVC peak-level: x = −26, y = −10, z = −26, $t = 4.19$, p(FWE) = 0.007, k = 20). This finding indicates the expected time-dependent decrease in reinstatement of encoding-related hippocampal pattern representations, implying a decrease in successful retrieval of episodic

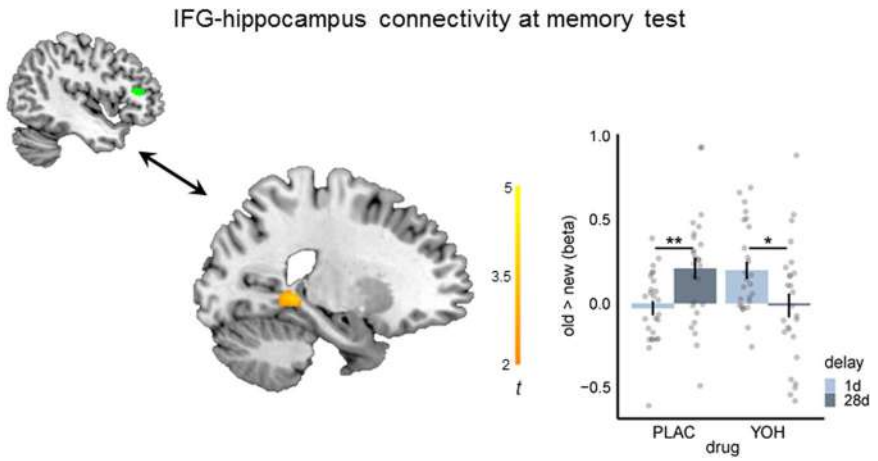

Fig. 3 Noradrenergic stimulation reverses the time-dependent changes in IFG-hippocampus functional connectivity. Psychophysiological interaction analysis indicated that while the connectivity between the inferior frontal gyrus (IFG) and hippocampus increased in the placebo (PLAC) group from 28d relative to 1d ($p = 0.004$ two-tailed Welch's t-test), there was even a decrease in IFG-hippocampus connectivity at 28d compared to memory testing after 1d in the yohimbine (YOH) group ($p = 0.020$, two-tailed Welch's t-test; drug × delay, SVC peak-level: x = −22, y = −40, z = −2, p(FWE) = 0.009, mixed ANOVA; $n = 104$ participants). Bonferroni correction was applied for the number of regions of interest in each analysis. The seed-region in the IFG (green), retrieved from the drug × delay interaction of the univariate analysis (peak: x = −50, y = 34, z = 12; k = 62), and the significant cluster in the hippocampus (orange) are superimposed on sagittal slices of T1-weighted template images. Distribution of beta-values for the significant cluster is presented for the contrast old > new. Bars represent mean ± SEM. Source data are provided as Source data file. *$p < 0.050$, **$p < 0.010$.

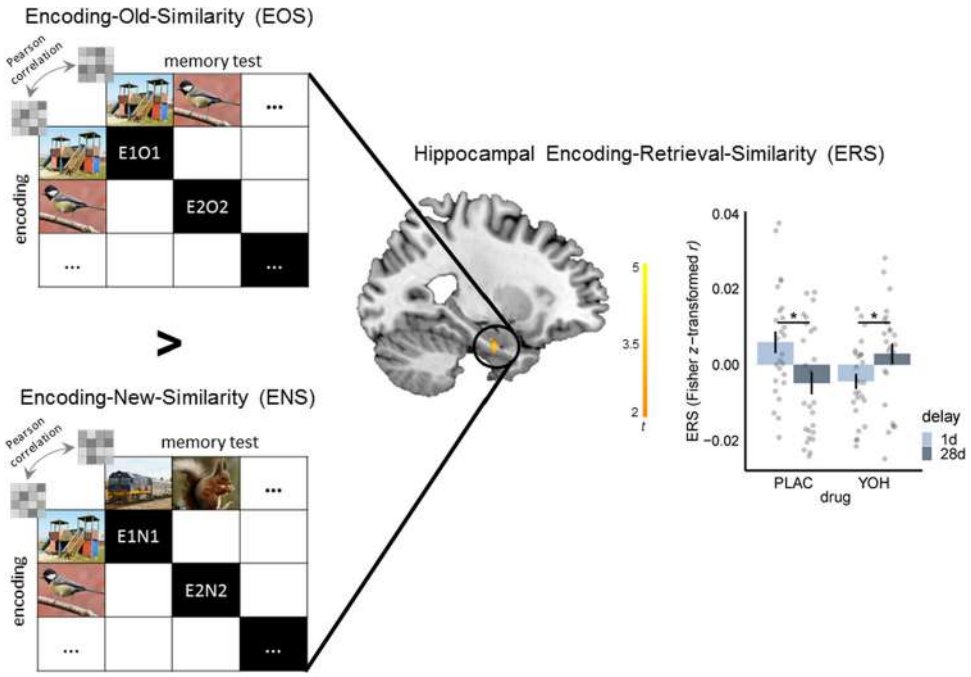

Fig. 4 Multivariate encoding-retrieval-similarity (ERS) analysis. Participants of the placebo (PLAC) group showed a significant decrease in hippocampal pattern reinstatement, as reflected in ERS, from 28d relative to 1d ($p = 0.010$, two-tailed Welch's t-test), while there was even a significant increase in hippocampal ERS from the 1d to the 28d test in the yohimbine (YOH) group ($p = 0.031$, two-tailed Welch's t-test; drug × delay: SVC peak-level: x = −26, y = −10, z = −26, mixed ANOVA; $n = 104$ participants). Bonferroni correction was applied for the number of regions of interest in each analysis. All images are licensed under Creative Commons License; image of the playground courtesy of Tomasz Sienicki (https://commons.wikimedia.org/wiki/File:Playground_29_ubt.JPG; image unchanged); image of the bird courtesy of Francis C. Franklin (https://commons.wikimedia.org/wiki/File:Great_tit_side-on.jpg; image unchanged); image of the train courtesy of DBZ2313 (https://commons.wikimedia.org/wiki/File:Locomotive_NR27_hauling_Indian_Pacific_train_(cropped).jpg; image unchanged); and image of the squirrel courtesy of Peter Timing (https://commons.wikimedia.org/wiki/File:Squirrel_posing.jpg; image unchanged). Visualizations of the ERS results include the t-map for drug × delay superimposed on a sagittal section of a T1-weighted template image and the Fisher z-transformed r-values for the significant cluster in the contrast EOS > ENS. Bars represent mean ± SEM. Source data are provided as Source data file. *$p < 0.050$.

details of individual memories[43] in the PLAC group. The YOH group, in turn, showed even the opposite course with increased similarity between hippocampal patterns representations during encoding with activation patterns at memory testing after 28d vs. 1d, again indicating a reversal in systems consolidation dynamics by post-encoding noradrenergic stimulation.

In addition to the analysis of trial-unique pattern reinstatement, we also analyzed the influence of noradrenergic stimulation on cross-trial ERS, representing general memory-related activity rather than the reinstatement of individual memories. Again, we found a significant decrease in ERS from 1d to 28d for the PLAC group ($t_{49.94} = 2.63$, $p = 0.011$, $d = 0.73$) and a significant time-dependent increase in the YOH group ($t_{47.83} = -2.05$, $p = 0.046$, $d = 0.58$) for the hippocampus (drug × delay, SVC peak-level: x = −24, y = −6, z = −26, $t = 3.21$, p(FWE) = 0.011, k = 22). No significant effects were found for the IFG or vmPFC nor on the whole-brain level in these analyses. The absence of a drug × delay interaction effect on the ERS in neocortical areas might be due to the fact these areas seem to be less involved in the retrieval or reinstatement of specific memory details[32], other than the hippocampus which is thought to play a key role in reconstructing the original memory representation during recall[32] and in coding contextual information such as space and time[44].

Exploratory analyses of posterior areas. Given the result of our exploratory whole-brain analysis indicating a time-dependent increase in precuneal activity from encoding to memory testing, which was reversed by noradrenergic stimulation, and due to recent findings indicating an important role of posterior neocortical areas for long-term memory-storage[28,29], we performed additional exploratory analyses including the precuneus, retrosplenial cortex (anatomically defined as Brodmann areas 29 and 30) and the posterior cingulate gyrus representing the posterior parietal cortex (PPC)[45] as well as the angular gyrus. This analysis yielded an interaction of drug × delay for the angular gyrus (SVC peak-level: x = −62, y = −54, z = 22, t = 3.75, p_{corr}(FWE) = 0.020, k = 96) with a significant increase in activity from encoding to memory testing in the PLAC group ($t_{45.88} = -2.51$, $p = 0.016$, $d = 0.70$), but—in line with our results in the IFG—a significant decrease in activity in the angular gyrus in the YOH group ($t_{49.82} = 2.41$, $p = 0.020$, $d = 0.67$; see Supplementary Fig. 3A). Apart from this interaction in the angular gyrus and of the above-mentioned effect in the precuneus (drug × delay, SVC peak-level: x = −4, y = −50, z = 46, t = 5.21, p_{corr}(FWE) < 0.001, k = 877; see Supplementary Fig. 3B), there were no effects of drug × delay in other PPC-areas. Beyond these changes in precuneal and angular gyral activity from encoding to memory testing, there were no further effects of drug × delay in the tested posterior areas, neither in our univariate or connectivity analyses during memory testing, nor in the multivariate ERS-analyses.

Discussion

The time-dependent redistribution of memory traces from the hippocampus to neocortical areas, referred to as systems consolidation, has been in the spotlight of memory research for decades[1–6]. Systems consolidation may be highly adaptive in that it aids the building of abstract, generalized knowledge structures but may become detrimental for memories of important events that need to be remembered in detail. Recent evidence suggests that systems consolidation might be more dynamic than initially thought[28,29]. However, whether the systems consolidation process can be experimentally manipulated and shaped by conditions such as emotional arousal remained unclear. Here, we asked whether noradrenergic stimulation shortly after encoding may modulate the systems consolidation process. We show that pharmacologically enhanced noradrenergic activity shortly after encoding reduces the time-dependent decline of memory performance and, more importantly, increases hippocampal but decreases neocortical involvement in memory from 1d to 28d after encoding. Furthermore, multivariate ERS analysis revealed that while reactivation of hippocampal encoding patterns decreased over time in the PLAC group, after YOH intake there was even a time-dependent increase in the reactivation of hippocampal encoding patterns at the delayed test. Importantly, our autonomic and neuroimaging data indicate that the initial encoding was left unaffected by the drug and groups were comparable in immediate free recall performance, thus confirming that the observed long-term effects were due to altered consolidation processes. Together, these findings show that noradrenergic stimulation during initial consolidation may have long-lasting effects on human memory by reversing time-dependent neural reorganization processes and, therefore, critically challenge our current understanding of systems consolidation dynamics.

Our behavioral data dovetail with previous research demonstrating enhanced memory for emotionally arousing events and a pivotal role of norepinephrine in this emotional memory enhancement[1–6,46]. By explicitly targeting time-dependent changes in memory over an interval of 28d, we show that the decline in memory performance that was observed for neutral stimuli over time was significantly decelerated for emotional stimuli. Interestingly, however, the beneficial effect of YOH on long-term memory performance was comparable for neutral and emotional items suggesting that the impact of post-encoding noradrenergic stimulation is not biased by stimulus-related arousal.

Most importantly, our neural data revealed that noradrenergic stimulation after encoding critically alters the known dynamics of the systems consolidation process. In the PLAC group, hippocampal activity decreased from 1d to 28d after encoding, as predicted by the systems consolidation theory[1–6]. Likewise, ERS, an indicator of episodic memory reinstatement[34–39], decreased significantly in the hippocampus over time in the PLAC group, suggesting that the hippocampal activity patterns became more distinct from the encoding-related patterns as time after encoding proceeded. The decrease in hippocampal involvement in memory was paralleled by a time-dependent increase in the IFG, a region implicated in remote, semantic memory[5,9,10], and this increase in IFG activity was directly correlated with reduced memory performance. Moreover, there was a time-dependent increase in the functional connectivity between IFG and hippocampus in the PLAC group, which has been linked to the generation of semantic associations in previous research[30]. Critically, noradrenergic stimulation after encoding markedly altered all of these time-dependent neural changes. For hippocampal activity, there was not only no decrease but even an increase from 1d to 28d after encoding. Similarly, hippocampal activity patterns during recognition testing resembled the encoding-related patterns even more at the 28d- vs. 1d-delayed test in the YOH group. Conversely, while activity in neocortical areas implicated in semantic memory (i.e. IFG)[9] or long-term storage per se (i.e., precuneus and angular gyrus in exploratory analyses)[28,29] increased over time in the PLAC group, this neocortical activity was even decreased in the 28d- vs. 1d-delayed test in the YOH group. Furthermore, the time-dependent increase in IFG-hippocampus connectivity was not found when participants received YOH before encoding. Together, this pattern of results strikingly mirrors recent findings in rats[22] and indicates that noradrenergic stimulation after encoding may not only decelerate but even reverse systems consolidation and maintain long-term hippocampus-dependent memory performance.

Our results indicate that—other than classically assumed—memories might not necessarily become hippocampus

independent over time but that environmental factors such as post-encoding arousal may actually increase hippocampus dependency over time, in line with the view that the hippocampus might be continuously required for the retrieval of specific encounters[6,7,47]. Our findings further align with a recently proposed neuromodulation theory suggesting that activation of the locus coereleus-norepinephrine system during post-encoding periods of consolidation amplifies the preferential processing of salient event features of emotional stimuli[46] and the finding that increased post-encoding amygdala-hippocampal-cortical resting state functional connectivity relates to behavioral negative memory bias and the degree of pattern reinstatement after 1d[48]. At the same time, the present findings emphasize the impact of post-encoding noradrenergic arousal on long-term memory, irrespective of valence or arousal of the encoded stimuli.

How may post-encoding noradrenergic stimulation alter systems consolidation? It is well established that the BLA is critically involved in arousal-related changes of memory, which then modulates neuroplasticity processes in memory storage sites such as the hippocampus[49–53]. Direct support for a critical role of the amygdala in the norepinephrine-related modulation of systems consolidation comes from the above-mentioned rodent study suggesting a reversal of systems consolidation, as indicated by opposite changes in DNA methylation and expression of critical memory-associated genes in the hippocampus and neocortex[22]. Specifically, norepinephrine-injection into the BLA shortly after learning was associated with a time-dependent decrease in DNA methylation and increase in transcriptional activation of *Reln* in the hippocampus, compared to saline. As this gene has been shown to increase synaptic plasticity by increasing long-term potentiation[54] and to support the development of synapses in the hippocampus[55] and its demethylation and transcriptional activation has previously been associated with memory formation[56], such epigenetic mechanisms are likely underlying the reversing effect of post-encoding noradrenergic arousal on the course of systems consolidation. Based on these data, it is tempting to speculate that a noradrenergic arousal-related recruitment of the amygdala during initial consolidation may have resulted in a distinct anchoring of memory traces in the hippocampus leading to an increased connectivity between those brain regions, presumably through epigenetically driven transcriptional changes in memory-related genes which may be actively maintained[22]. At the same time, the burst in noradrenergic stimulation might have led to a break between the pass-off of the short-term synaptic consolidation mode in the hippocampus into a systems consolidation mode, keeping memories in the hippocampus. In the present study, we did not find evidence for an involvement of the amygdala in the norepinephrine-driven reversal of systems consolidation. The absence of such evidence, however, might be due to methodological limitations of task-related fMRI. In particular, noradrenergic stimulation was elevated after encoding, when fMRI was not measured any more, and the putative amygdala modulation of memory most likely took place during a loosely defined window of early consolidation that is difficult to target with fMRI. Future studies might use post-encoding resting-state scans to investigate the potential role of the amygdala and its connectivity with the hippocampus or prefrontal areas in norepinephrine-driven changes in early consolidation.

Although YOH administration led to increased hippocampal involvement in memory after 28d, at the 1d interval YOH appeared to be associated with even reduced hippocampal activity compared to PLAC. This pattern of results is also remarkably similar to the above-mentioned findings in rodents indicating reduced hippocampal activity at a short retention interval[22]. Post-encoding noradrenergic stimulation thus seems not only to decelerate but to reverse systems consolidation and the reduced hippocampal involvement at short delays may be owing to a restructuring that promotes memory maintenance in the long run.

Both, the present study and the antecedent rodent study[22] probed systems consolidation by contrasting recent, i.e., 1d or 2d, respectively, with remote, i.e. 28d old, memories. Although the parallels between the results of these studies are striking, it is important to note that due to the differential lifespan of rodents and humans the temporal dynamics of systems consolidation might differ between species. In both, rodents and humans, the exact time course of systems consolidation is not well understood[57,58]. While we did find a time-dependent memory reorganization from hippocampal to neocortical areas in the PLAC group after 28d, which was reversed by noradrenergic arousal shortly after encoding, this does not necessarily imply that the systems consolidation process was completed at that time point. It has been argued that systems consolidation might continue for months, years or even decades[58]. Thus, although the 28d old memories investigated here may be considered as remote memories, these memories might not be fully consolidated. Future studies are required to determine how post-encoding noradrenergic arousal influences hippocampal and neocortical contributions to remembering at even later stages of the life of a memory. Another possible limitation refers to the modelling of our imaging data based on the item category regardless of the participants' memory responses. This procedure was chosen because of the overall very high memory performance, specifically in our 1d group, resulting in a low number of false alarms and misses. Future studies on the neural basis of time-dependent changes in memory should employ a design that increases the variability in memory performance, for instance by increasing the number of the to-be-encoded stimuli. Furthermore, as prior work on stress and memory has shown quadratic relationships between post-encoding stress hormone administration and subsequent memory[26] and it is generally assumed that arousal exerts quadratic effects on cognitive functions[59], future studies should include different dosages of YOH to further elucidate noradrenergic arousal effects on changes of memory over time.

To conclude, the present study shows that noradrenergic arousal shortly after learning reverses systems consolidation in humans in the sense that it does not only maintain but even increase hippocampal involvement in memory over time and, in parallel, reduces the neocortical contribution and the related time-dependent decline in memory performance. Thus, noradrenergic arousal shortly after encoding does not only prevent the classical systems consolidation process but seems to induce an alternative, reversed consolidation process, in which hippocampal memory involvement is strengthened and neocortical involvement lessened. These findings demonstrate that a fundamental characteristic of memory is much more dynamic than traditionally thought and sensitive to modulation by environmental factors such as arousal. This mechanism could explain the long-term vividness characteristic for memories of emotionally arousing events[16].

Methods

Participants and design. One-hundred-and-nine healthy volunteers (55 males, 54 females, age: M = 24.09 years, SD = 3.92 years) participated in this experiment. Exclusion criteria were checked in a standardized interview and comprised a history of any psychiatric or neurological diseases, medication intake or drug abuse, kidney- and liver-related diseases, body-mass index below 19 or above 26 kg/m², diagnosed cardiovascular problems as well as any contraindications for MRI measurements or YOH intake. Participants were asked to refrain from physical exercise, caffeine, alcohol, and fatty meals within the two hours before the experiment. All participants provided informed consent before taking part in the experiment and received a monetary compensation for participation. The study protocol was approved by the ethics committee of the Medical Chamber Hamburg (PV5480) and was in accordance with the declaration of Helsinki. The Medical

Chamber Hamburg designated this study to be a basic experimental study in humans and it was not designated to be a clinical trial.

Five participants had to be excluded from the analysis because of technical failure ($n = 1$), missing data for day 2 ($n = 1$) or falling asleep during at least one of the MRI sessions ($n = 3$), thus resulting in a final sample of 104 right-handed young adults (52 men and 52 women, age: M = 24.12 years, SD = 3.92 years). This final sample size is in line with other fMRI studies on the effect of stress or stress mediators on memory[24,60] and an a-priori power calculation with G*Power[61] suggested that this sample size is sufficient to detect a medium-sized effect with a power of 0.80.

We used a fully crossed, placebo-controlled, double-blind, between-subjects design with the factors delay (1d vs. 28d) and drug (PLAC vs. YOH) in which participants were pseudo-randomly assigned to one of four groups, each including 13 men and 13 women.

Experimental procedure. All testing took place in the afternoon or the early evening (between 1 and 6 pm). After providing informed consent, participants completed the Trier Inventory for the Assessment of Chronic Stress (TICS)[62], the Beck Depression Inventory (BDI-II)[63], and the State-Trait Anxiety Inventory (STAI)[64]. At the beginning of the second experimental day (either 1d or 28d after day 1), participants also filled out the Pittsburgh Sleep Quality Index (PSQI)[65] extended by questions regarding the duration and quality of sleep in the last 24 hours. Groups did not differ in any of these parameters (see Supplementary Results).

Drug administration and manipulation check (day 1): depending on the experimental group, participants received orally either a PLAC or 20 mg YOH, an α_2-adrenoceptor antagonist leading to increased noradrenergic stimulation. PLAC and YOH pills were indistinguishable and the experimenter was not aware of participants' group assignment, thus ensuring double-blind testing. The timing and dosage of YOH administration were chosen in accordance with previous studies[23,24] and based on the known pharmacodynamics of YOH showing that a significant drug action can be expected about 60 min after drug intake. We administered the drug immediately before encoding, in order to ensure the action of the drug shortly after encoding, i.e. during initial consolidation. To assess the efficacy of the pharmacological manipulation and the timing of the drug action, we measured systolic and diastolic blood before drug administration (baseline), immediately after encoding and before the free recall task (35 min), immediately after the free recall task (55 min), and another four times every 15 min during a resting phase (70 min, 85 min, 100 min, 115 min after drug administration), in which participants read handed out magazines. Furthermore, we assessed blood pressure before memory testing on day 2 to rule out any group differences in noradrenergic arousal before memory testing.

Memory encoding (day 1): on the first experimental day, participants performed three encoding runs in the MRI scanner. In each run, participants encoded the same 60 stimuli (30 emotionally negative, 30 neutral; for details see supplementary material) presented in random order using MATLAB (The Mathworks, Inc, Natick, US) with the Psychophysics Toolbox extensions[66], i.e., each picture was presented three times across the encoding session. On each trial, a picture was presented for 3 s followed by a jittered fixation period of 4 ± 1 s. Participants were instructed to memorize the presented pictures and informed that there will be a subsequent memory test. To make sure that participants remained fully attentive throughout the encoding task, they were instructed to press a button each time the fixation cross appeared. Immediately after the encoding task, participants completed a free recall task outside the MRI. Here, participants had 15 min to name as many stimuli in as much detail as possible, while an experimenter ticked off the correct stimuli from a list.

Memory test (day 2): Depending on the experimental condition, participants returned to the lab either 1d or 28d after day 1. On this second experimental day, participants performed a recognition task in the MRI, which was separated into three consecutive runs. During the memory test, participants saw the 60 pictures that were presented on day 1 (old) and 60 new pictures (as well as additional items that are beyond the scope of the present manuscript and will be reported elsewhere). Each picture was presented for 3 s and participants were requested to indicate via button press whether the shown picture had been presented on day 1 or not using a four-point scale ("definitely new", "rather new", "rather old", "definitely old"). Between trials, a jittered fixation cross was presented for 4 s ± 1 s. Finally, participants rated, outside the scanner, the arousal and valence of each stimulus shown in the recognition task on two separate 10-point Likert scales (see Supplemental material).

Analysis of behavioral and physiological data. Behavioral and physiological data analyses were performed with R version 4.0.2 (https://www.r-project.org/). Blood pressure was analyzed by means of mixed model ANOVAs with the between factors drug (PLAC/YOH) and delay (1d/28d) and the within factor time (baseline or 35 min/55 min/70 min/85 min/100 min/115 min after drug intake). In case of violated sphericity, as indicated by Mauchly's test, Greenhouse-Geisser corrected degrees of freedom and p-values are reported.

To control for attentiveness throughout the encoding task, the number of missed responses was analyzed by means of an LMM using the lme4-package[67] including delay (1d vs. 28d), drug (PLAC vs. YOH) and run (run1 vs. run2/run3) and their interactions as fixed effects and the random intercept of participants. The probability to remember items in the immediate free recall test was analyzed on a single-trial level by means of a binomial generalized LMM. Again, this model included drug (YOH vs. PLAC), delay (1d vs. 28d), emotion (negative vs. neutral) and their interaction as fixed effects as well as the random intercept of participants and stimuli. Analysis of memory performance focused on the sensitivity index d'[25]. D'-values were also further analyzed by means of an LMM. This model included drug (YOH vs. PLAC), delay (1d vs. 28d), emotion (negative vs. neutral) and their interactions as fixed effects and the random intercept of participants. All reported p-values are two-tailed. Post-hoc t-test were applied with Welch's correction. To further investigate whether participants' confidence in recognizing old items differed depending on stimulus emotionality, delay or drug, confidence for hits was analyzed by means of a trial-wise generalized LMM with drug (PLAC vs. YOH), delay (1d vs. 28d), emotion (neutral vs. negative) and their interactions as fixed effects and the random intercept of participants and stimuli. Furthermore, in an additional analysis, we weighted participants' responses by the level of confidence before computing d' and again, analyzed this by means of an LMM with drug (YOH vs. PLAC), delay (1d vs. 28d), emotion (negative vs. neutral) and their interactions as fixed effects and the random intercept of participants. Finally, to rule out potential effects of sex differences on our results, we exploratively analyzed (unweighted) d' by means of an LMM with the factors drug (YOH vs. PLAC), delay (1d vs. 28d), emotion (negative vs. neutral) and sex (female vs. male) and their interactions as fixed effects and the random intercept of participants.

MRI data acquisition, preprocessing, and analysis. MRI data were acquired using a 3T Prisma Scanner (Siemens, Germany) with a 64-channel head coil. Each MRI session consisted of three functional runs and a magnetic (B0) field map to unwarp the functional images (TR = 634 ms, TE_1 = 4.92 ms, TE_2 = 7.38 ms, 40 slices, voxel size = 2.9 × 2.9 × 3.0 mm^3, FOV = 224 mm). For the functional scans, T2*-weighted echo planar imaging sequences were used to obtain 2 mm thick transversal slices (TR = 2000ms, TE = 30 ms, flip angle = 60°, FOV = 224). Additionally, a high-resolution T1 weighted anatomical image (TR = 2500 ms, TE = 2.12 ms, 256 slices, voxel size = 0.8 × 0.8 × 0.9 mm^3) was collected at the end of the MRI session of day 2.

To allow for magnetic field (T1) equilibration, the first three functional scans were discarded. The images were first realigned and unwarped using the field maps, then coregistered to the structural image followed by a normalization to Montreal Neurological Institute (MNI) space, as implemented in SPM12 (IXI549Space). For the univariate analysis, the images were additionally smoothed with an 8 mm full-width half-maximum Gaussian kernel.

Preprocessing and analysis of the fMRI data was performed using SPM12 (Wellcome Trust Centre for Neuroimaging, London, UK). Multivariate analysis was applied using custom scripts in MATLAB (The Mathworks, Inc, Natick, US). Results of all neural analyses were considered significant at a family-wise error (FWE) corrected threshold of $p < 0.050$. To test our hypotheses, we performed ROI analyses with a-priori defined ROIs using SVC ($p < 0.050$, FWE corrected) with an initial threshold of $p < 0.005$ uncorrected. We corrected for the number of ROIs in the specific analysis by applying Bonferroni correction. In additional exploratory whole-brain analyses, we used an initial significance threshold of $p < 0.050$ FWE-corrected and a 10-voxel extend. The resulting estimates were extracted using the MarsBar Toolbox (http://www.mrc-cbu.cam.ac.uk/Imaging/marsbar.html) to further inspect interaction effects by post-hoc t-tests and correlate the neural activity in the relevant ROIs with the sensitivity index d' as a behavioral indicator of memory performance in R.

ROI definition: The anatomical mask for the hippocampus was derived from the Harvard-Oxford subcortical atlas using a probability threshold of 50%. For the IFG and vmPFC, a sphere with 20 mm radius was used that was centered on the peak voxel (x = −50, y = 16, z = 12) derived from 386 imaging studies reporting "IFG" and on the peak voxel (x = −2, y = 46, z = −8) derived from 199 imaging studies reporting "vmPFC", respectively, as determined by meta-analyses conducted on the neurosynth.org platform (status 26/02/2021).

Univariate fMRI analysis: Due to the overall very high memory performance resulting in a low number of misses and false alarms in many participants, we modelled our imaging data based on stimulus category and chose a correlative approach to link these data to behavioral memory performance. On the first level, the functional MRI data were analyzed using general linear modeling (GLM) as implemented in SPM12. For the univariate analysis, the model included one regressor per run and per emotion for the encoding task (6 regressors) and one regressor per emotion and stimulus category for the recognition task (8 regressors) as well as 6 run constants as regressors of no interest. The resulting 20 regressors were convolved with the canonical hemodynamic response function. A high-pass filter of 128 s was used to remove low-frequency drifts and serial correlations in the time series were accounted for using an autoregressive AR(1)-model.

To assess the effect of YOH on the time-dependent change of hippocampal and prefrontal memory dependency, a flexible factorial model (SPMs non-sphericity correction for violation of the i.i.d.-assumption) with the two between-subject factors delay (1d vs. 28d) and drug (YOH vs. PLAC) and the within-subject factor picture type (new vs. old) was applied. As a-priori ROIs, we focused on the hippocampus in the interaction testing for a higher increase for YOH (vs. PLAC)

from 1d to 28d and expected a higher time-dependent increase for PLAC (vs. YOH) in the IFG and vmPFC for old vs. new stimuli.

Additionally, we assessed the influence of group on the increase in BOLD-activity during the same set of stimuli from day 1, specifically the final encoding run, to day 2 by conducting a flexible factorial model with the two between-subject factors delay (1d vs. 28d) and drug (YOH vs. PLAC) and the within factor task (encoding vs. recognition). As a-priori ROIs, we focused on the hippocampus in the interaction testing for a higher time-dependent increase for YOH (vs. PLAC) and expected a higher time-dependent increase for PLAC (vs. YOH) in the IFG and vmPFC for recognition vs. encoding.

Functional Connectivity Analysis: In addition, psychophysiological interaction (PPI) analyses, as implemented in SPM12, were conducted to assess the functional coupling of the hippocampus and the IFG. To this end, the first eigenvariate of the activity time course of the relevant ROI for old pictures and new pictures were extracted and included as seed in the PPI. We used the significant clusters in the hippocampus (peak: $x = 22$, $y = -38$, $z = 4$; $k = 10$) and the IFG (peak: $x = -50$, $y = 34$, $z = 12$; $k = 62$) in the interesting interaction of the univariate group-level analysis as seed. A first-level model was set up including the seed, a vector coding the contrast of interest as well as an interaction term, computed as the element by element product of the first two regressors. The resulting interaction contrasts were then analyzed on the second-level to test whether the functional connectivity between hippocampus and IFG differed depending on delay and noradrenergic stimulation and whether the picture was old or new. For the IFG-seed, we used the hippocampus as an a-priori ROI. Using the hippocampus as a seed, a-priori ROIs were the vmPFC and the IFG.

Multivariate Analysis: RSA using a spherical searchlight approach[40–42] was used to assess ERS as a measure of trial-specific episodic reinstatement[34–39]. For this multivariate analysis, each individual trial of the encoding and recognition task was modelled as an individual regressor convolved with a hemodynamic response function along with six session-constants in one GLM per subject using SPM12. No smoothing was performed on the echoplanar imaging data that entered the GLM. To increase the reliability by normalizing for noise[68], the resulting beta-values were further transformed into *t*-statistics. We then applied a whole-brain searchlight-analysis in which a sphere with a 3-voxel-radius was centered on every voxel of the brain and subjected the resulting set of voxels to an RSA. Please note that our main findings remained largely unaffected when using a 5-voxel radius of the searchlight sphere. We hereby computed the similarity (Pearson's *r*) between pattern responses during the final run of encoding on experimental day 1 and during old items in the recognition task on day 2 (encoding-old-similarity, EOS) and between pattern responses during the final run of encoding and the corresponding (matched by valence and the occurrence of animals, humans or objects; old and new items were furthermore roughly matched by the first author and an independent rater based on their subjective experience of scene complexity and number of details) new items of the recognition task (encoding-new-similarity, ENS). The resulting *r*-maps were further Fisher *z*-transformed and subjected to a flexible factorial model with the two between-subject factors delay (1d vs. 28d) and drug (YOH vs. PLAC) and the within-subject factor similarity (EOS vs. ENS). We further focused on the differential value of EOS vs. ENS, as an indicator of memory reinstatement, i.e. ERS. In addition to trial-specific pattern-reinstatement, we also assessed cross-trial ERS by correlating pattern responses during encoding trials with patterns of all non-corresponding old (EOS) vs. new trials (ENS) of the recognition task. As a-priori-ROIs, we focused on the hippocampus testing for a significantly higher delay-dependent increase in YOH (vs. PLAC) in ERS and expected a significantly higher delay-dependent increase in PLAC (vs. YOH) for the IFG and vmPFC in ERS.

Reporting summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

The behavioral, autonomic, and fMRI data generated in this study are provided at Github: https://github.com/valentinakrenz/NorSysCons[69]. Source data are provided with this paper.

Code availability

Custom code used to analyze and model the data is available at Github: https://github.com/valentinakrenz/NorSysCons[69].

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Author contributions

L.S. and B.R. designed research; V.K. performed research; V.K., T.S., and A.A. analyzed data; and V.K., T.S., A.A., B.R., and L.S. wrote the paper.

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SUPPLEMENTARY INFORMATION

Noradrenergic arousal after encoding reverses the course of systems consolidation in humans

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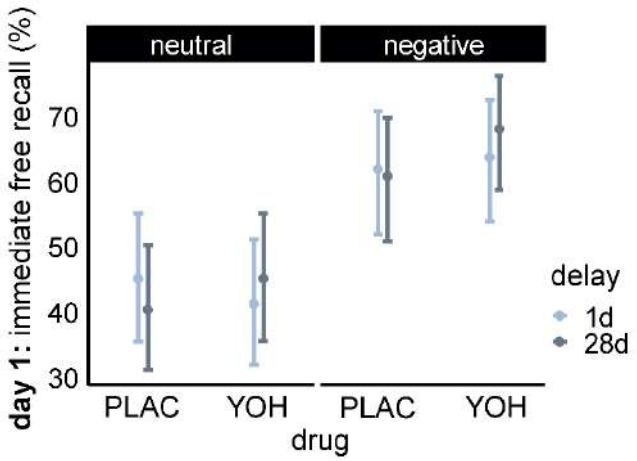
Supplementary methods

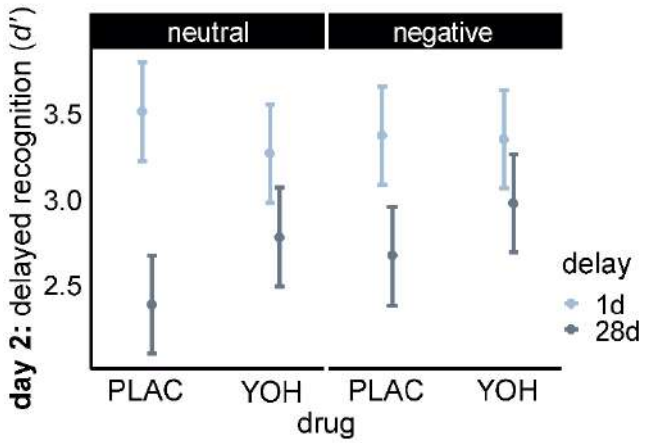
Stimulus material. We used 120 pictures of scenes and objects as stimulus material (as well as 120 additional stimuli which will be analyzed elsewhere), taken from the International Affective Picture System[1] and open internet platforms. Half of the pictures contained emotionally negative scenes or objects while the other half contained neutral contents. At the end of the experiment, participants rated all pictures with respect to picture valence and arousal on a scale from 0 (“very negative”/”not arousing”) to 10 (“very positive”/”very arousing”). As expected, negative pictures were rated as significantly more negative (M=2.52, SD=0.69) than neutral pictures (M=5.62, SD = 0.81; paired *t*-test: t_{103}=24.41, p<0.001, d=2.39). Furthermore, negative pictures (M=5.70, SD=1.30) were rated as more emotionally arousing than neutral pictures (M=2.74, SD=1.45; paired *t*-test: t_{103}=-23.03, p<0.001, d=2.26).

Supplementary results

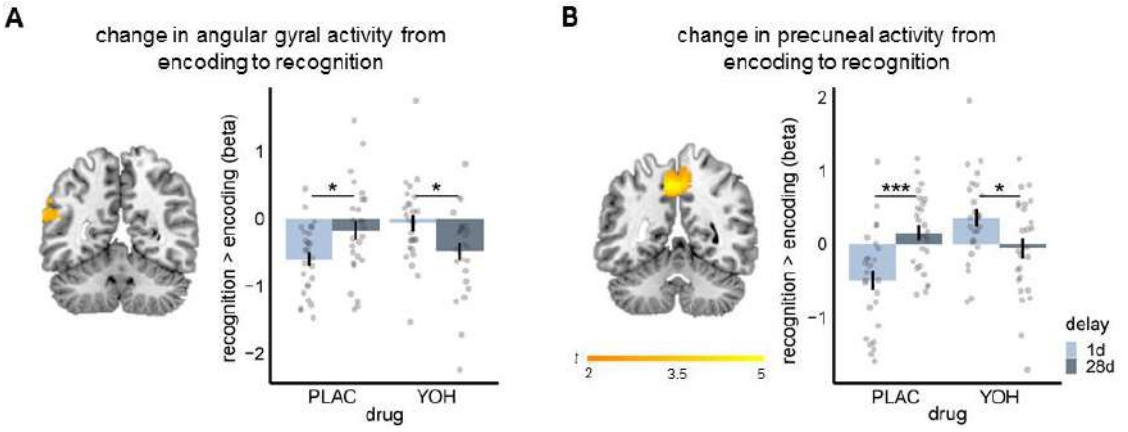
Control Variables. The four experimental groups did not differ in subjective chronic stress levels, depressive mood, state or trait anxiety, sleep quality or quantity in the time between encoding and recognition testing (all F<2.53, all p>0.061, see supplementary table 1).



Supplementary figure 1. Predicted probability to remember items in the free recall task. Emotionally negative items were remembered significantly more likely than emotionally neutral ones (main effect emotion: β=1.98, z=3.1, p=0.001, generalized linear mixed model; n=104 participants). No differences were found between groups in this task indicating that yohimbine (YOH vs. placebo (PLAC)) did not influence memory during encoding. Bars represent predicted means with 95%-CIs. Source data are provided as Source Data file.



Supplementary figure 2. Predicted memory performance during delayed recognition testing. The time-dependent decrease in memory performance from the 1d- to the 28d-delayed test (β=-1.12, 95%-*CI*[-1.12,-0.72], $t_{125.82}$=- 5.43, p<0.001, linear mixed model (LMM); n=104 participants) was significantly lower for emotionally negative than neutral items (emotion×delay: β=0.42, 95%-*CI*[0.14, 0.70], t_{100}=2.98, p=0.003, LMM). Most importantly, the memory decline with increasing delay was weaker in the yohimbine (YOH) group than in the placebo (PLAC) group (drug×delay: β=0.64, 95%-*CI*[0.06, 1.21], $t_{125.816}$=2.18, p=0.029, LMM) irrespective of the emotionality of the encoded stimuli (drug×delay×emotion: β=-0.31, p=0.124, LMM). Bars represent predicted means with 95%-CIs. Source data are provided as Source Data file.



Supplementary figure 3. Noradrenergic stimulation decreases contribution for exploratory posterior regions over time. A While there was a significant increase in angular gyral activity from encoding to memory testing at the 28d vs. 1d delayed test in the placebo (PLAC) group ($t_{45.88}$=-2.51, p=0.016, d=0.70, two-tailed Welch's t-test), there was even a significant decrease in angular gyral activity from encoding to retrieval with increasing retention delay in the yohimbine (YOH) group (drug×delay: SVC peak-level: x=-62, y=-54, z=22, t=3.75, p_{corr}(FWE)=0.020, k=96; $t_{49.82}$=2.41, p=0.020, d=0.67, mixed ANOVA). **B** As in our exploratory whole-brain analysis, focusing on the precuneus as ROI revealed an interaction of drug×delay (SVC peak-level: x=-4, y=-50, z=46, t=5.21, p_{corr}(FWE)<0.001, k=877, mixed ANOVA) with a significant increase from 1d to 28d delayed test in the PLAC group ($t_{46.76}$=-3.82, p<0.001, d=1.06, two-tailed Welch's t-test), but a significant decrease in precuneal activity for the YOH group ($t_{49.30}$=2.34, p=0.02, d=0.65, two-tailed Welch's t-test).
All n=104 participants. Bonferroni Correction was applied for number of regions of interest in each analysis. Visualizations show t-maps for the interesting contrasts superimposed on sagittal sections of T1-weighted template images and beta-values for the significant cluster. Bars represent mean ± SEM. Source data are provided as Source Data file. ^{+}p<0.100; **p<0.010; ***p<0.001

Supplementary table 1. Control variables.

Variable	PLAC		YOH	
	1d	28d	1d	28d
depressive mood (BDI-II)	4.23 (0.72)	3.77 (0.74)	6.69 (0.92)	4.81 (0.83)
state anxiety (STAI-S)	32.92 (0.67)	34.77 (1.43)	35.62 (1.25)	34.19 (1.16)
trait anxiety (STAI-T)	33.19 (1.16)	32.77 (1.44)	33.31 (1.25)	34.96 (1.27)
subjective chronic stress (TICS)	10.88 (1.06)	12.73 (1.21)	15.35 (1.53)	14.23 (1.57)
sleep quality (PSQI)				
global score (last 28d)	4.23 (0.39)	4.92 (0.53)	4.42 (0.43)	4.68 (0.53)
sleep quality (last 24h)	1.69 (0.12)	1.92 (0.12)	2.04 (0.20)	1.96 (0.15)
sleep latency (last 24h)	7.44 (0.22)	7.21 (0.26)	7.54 (0.33)	7.39 (0.24)

Data represents mean (SEM). Source data are provided as Source Data file.

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Appendix: Study 3

C

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Time-dependent memory transformation in hippocampus and neocortex is semantic in nature

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Check for updates

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Memories undergo a time-dependent neural reorganization, which is assumed to be accompanied by a transformation from detailed to more gist-like memory. However, the nature of this transformation and its underlying neural mechanisms are largely unknown. Here, we report that the time-dependent transformation of memory is semantic in nature, while we find no credible evidence for a perceptual transformation. Model-based MRI analyses reveal time-dependent increases in semantically transformed representations of events in prefrontal and parietal cortices, while specific pattern representations in the anterior hippocampus decline over time. Posterior hippocampal memory reinstatement, in turn, increases over time and is linked to the semantic gist of the original memory, without a statistically significant link to perceptual details. These findings indicate that qualitative changes in memory over time, associated with distinct representational changes in the neocortex and within the hippocampus, reflect a semantic transformation, which may promote the integration of memories into abstract knowledge structures.

Episodic memory changes over time. Converging lines of evidence from lesion studies in rodents[1,2], human neuroimaging studies[3–5] or studies in amnesic patients[6,7] indicate that episodic memories undergo a time-dependent neural reorganization. While memories are initially dependent on the hippocampus, they become more dependent on neocortical structures, such as the ventromedial prefrontal cortex (vmPFC)[8–10], inferior frontal gyrus (IFG)[4,5], anterior cingulate cortex (aCC)[2,11–13], angular gyrus and precuneus[14,15], as time after encoding proceeds. Whether remote memories become entirely independent of the hippocampus is still debated[16–18] and, intriguingly, initial evidence points to the possibility of a time-dependent reorganization of memories within the hippocampus, from anterior to parietal parts[19,20]. Critically, the neural reorganization of memory is thought to be accompanied by a transformation from a detailed episodic memory trace to a more gist-like representation[16,17]. Such qualitative changes over time are a fundamental aspect of memory and may promote the building of abstract knowledge networks[4]. Moreover, they have highly relevant implications, for instance, for eyewitness testimony or the generalized memory for aversive events in mental disorders.

The nature of these qualitative changes of memories over time remains, however, elusive. One possible mechanism is a perceptual transformation, in which a detailed, perceptually rich episodic trace evolves over time into a less specific trace that contains knowledge of general perceptual features of the original event (e.g. 'I remember the painting contained a lot of red and brown'). Indeed, the hippocampus is critically implicated in remembering perceptual details[21] and the perceptual transformation perspective may be close to the common view that memories fade away and simply lose (perceptual) detail over

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time[22]. Alternatively, with time, memories may not be just a perceptually degraded version of the original trace but become semantically transformed into representations that carry the semantic gist, with only minimal (detailed or generalized) perceptual information (e.g. 'I remember the painting showed an apple on a table'). This semantization of memories over time may provide a better explanation of how episodic experiences are integrated into abstract knowledge structures than a mere decay of (perceptual) features of a memory trace. While prominent theoretical accounts appear to favor the semantic transformation view[16,17], there is a lack of clear empirical evidence for a semantic transformation of memory over time. Paradigms used in previous studies on time-dependent memory transformation in humans or rodents involved tests of transformation that were both semantically and perceptually similar to the original event and could thus not distinguish between different mechanisms of transformation. Thus, whether the transformation of memory over time is perceptual or semantic in nature (or both) remains unclear.

In the present experiment, we aimed at elucidating the nature and neural signature of time-dependent memory transformation. Specifically, we sought to determine whether there is a semantic or a perceptual transformation of the original memory over time. Moreover, because emotional arousal has been shown, on the one hand, to enhance memory for the gist of the event at the cost of reduced memory for peripheral features[23–25] but, on the other hand, to increase memory specificity in the long-run[2,26], we further tested whether the nature of memory transformation over time, as well as its neural underpinnings, would differ depending on the level of emotionality of the encoded material. To this end, we tested participants' recognition memory for emotionally neutral and negative pictures either 1d or 28d after encoding. As the neural reorganization of memories can be expected to be much further progressed 28d compared to 1d after encoding[2,19], varying the delay between encoding and recognition testing allowed probing time-dependent memory transformation. Critically, this recognition test included, in addition to initially encoded and entirely new pictures, also lures that were either perceptually or semantically related to the original stimuli. Encoding as well as memory testing took place in an MRI scanner, enabling us to analyze time-dependent changes in the reinstatement of encoding patterns and the specificity of memory representations during memory testing by leveraging multivariate fMRI-analysis approaches. A perceptual transformation would be indicated if, with increasing delay after encoding, perceptually related, but not semantically related, items are endorsed as 'old'. Conversely, a semantic transformation would be indicated if participants endorse semantically related, but not perceptually related, items as 'old'.

Here, we show that episodic memories are semantically transformed over time, while we obtain no credible evidence for a perceptual transformation. This time-dependent semantization of memories was further enhanced for emotionally negative compared to neutral stimuli. At the neural level, the time-dependent transformation of memories was reflected in semantic, gist-like representations of remote memories in prefrontal as well as parietal neocortical storage sites. The anterior hippocampus was associated with distinct representations of encoded events that declined with increasing delay after encoding. Posterior hippocampal memory reinstatement increased over time and was associated with less specific memory representations that were linked to the semantic gist of the original memory, again without evidence for a reliable effect of the perceptual gist.

Results

To elucidate whether episodic memories are semantically or perceptually transformed over time and whether this process is equally evident for emotionally neutral compared to negative pictures, we performed a 3-day study: Day 1—encoding of emotionally neutral or negative pictures in the MRI scanner; Day 2 (either 1d or 28d after Day 1)—recognition testing in the MRI scanner; Day 3—individual assessment of the semantic and perceptual relatedness of the stimulus material. In order to dissociate semantic and perceptual mechanisms of time-dependent memory transformation, the recognition test included, in addition to original and entirely novel items, items that were either perceptually or semantically related to the original pictures. Each originally encoded picture corresponded precisely to one semantically related, one perceptually related and one unrelated picture, matching the original picture in terms of the level of emotionality and other relevant features (see methods section). The semantic and perceptual relatedness of each originally encoded item to their corresponding semantically related, perceptually related, or unrelated lure was tested in an independent behavioral pilot study ($n = 32$ participants), which confirmed that semantically related items were rated as significantly more semantically related but significantly less perceptually related to the original items than perceptually related items (see Supplementary Fig. 1).

On the first experimental day, 52 healthy, right-handed young adults (26 females, 26 males, age: $M = 24.29$ years, SEM = 0.55 years) encoded 60 pictures (30 emotionally neutral, 30 emotionally negative) in an MRI scanner, each presented for 3 s in each of three consecutive runs (see Fig. 1). To control for alertness during encoding, participants were instructed to respond with a button press as soon as a fixation cross appeared between trials. On average, participants missed only 1.48 (SEM = 0.43) responses across all trials and runs, indicating that participants were attentive during encoding, without statistically significant differences between 1d- and 28d-groups (main effect delay: $F(1, 50) = 1.46$, $p = 0.233$, $\eta_p^2 = 0.03$, 95% Confidence Interval: [9e−05, 0.18]; delay × run: $F(1.87, 93.71) = 0.84$, $p = 0.429$, $\eta_p^2 = 0.02$, 95% Confidence Interval: [0.001, 0.12]; mixed ANOVA). To ensure that the 1d- and 28d-groups did not differ in initial encoding, we asked participants to recall as many of the pictures as possible immediately after the encoding session. In this immediate free recall test, participants recalled on average 50.99% (SEM = 2.21%) of the 60 previously encoded items. A mixed ANOVA with the between-subjects factor delay (1d vs. 28d) and the within-subject factor emotion (neutral vs. negative) did not indicate a statistically significant difference between delay groups in immediate memory performance (main effect delay: $F(1, 50) = 0.17$, $p = 0.678$, $\eta_p^2 = 0.003$, 95% Confidence Interval: [2e−05, 0.11]; delay × emotion: $F(1, 50) = 1.13$, $p = 0.293$, $\eta_p^2 = 0.02$, 95% Confidence Interval: [6e−05, 0.16]). As expected, participants recalled significantly more negative ($M = 58.78\%$, SEM = 2.30%) than neutral pictures ($M = 43.21\%$, SEM = 2.49%; main effect emotion: $F(1, 50) = 69.33$, $p = 5e{-}11$, $\eta_p^2 = 0.58$, 95% Confidence Interval: [0.42, 0.72]; Supplementary Fig. 2), indicating an enhancement of immediate memory performance due to the emotionality of the encoded material, in line with previous reports[27,28].

Memories are semantically transformed over time

On experimental Day 2 (either 1d or 28d after initial encoding), participants underwent a recognition test in which they were instructed to indicate for each of the presented pictures, whether the picture had been presented on Day 1 ('old') or not ('new'). Critically, this recognition test included, in addition to original and entirely novel, unrelated items, lures that were either semantically or perceptually related to the old items, thus enabling us to examine the nature of time-dependent memory transformation. As expected, the hit rate was significantly higher in the 1d-group ($M = 91.86\%$, SEM = 1.12%) than in the 28d-group ($M = 75.58\%$, SEM = 2.45%; main effect delay: $F(1, 50) = 20.72$, $p = 3e{-}05$, $\eta_p^2 = 0.29$, 95% Confidence Interval: [0.11, 0.49]; Fig. 2a and Supplementary Table 1). Notably, this delay-dependent decrease in memory performance was dependent on the emotionality of the stimuli (emotion × delay: $F(1, 50) = 9.23$, $p = 0.004$, $\eta_p^2 = 0.16$, 95% Confidence Interval: [0.02, 0.36]; main effect emotion: $F(1, 50) = 4.52$, $p = 0.038$, $\eta_p^2 = 0.08$, 95% Confidence

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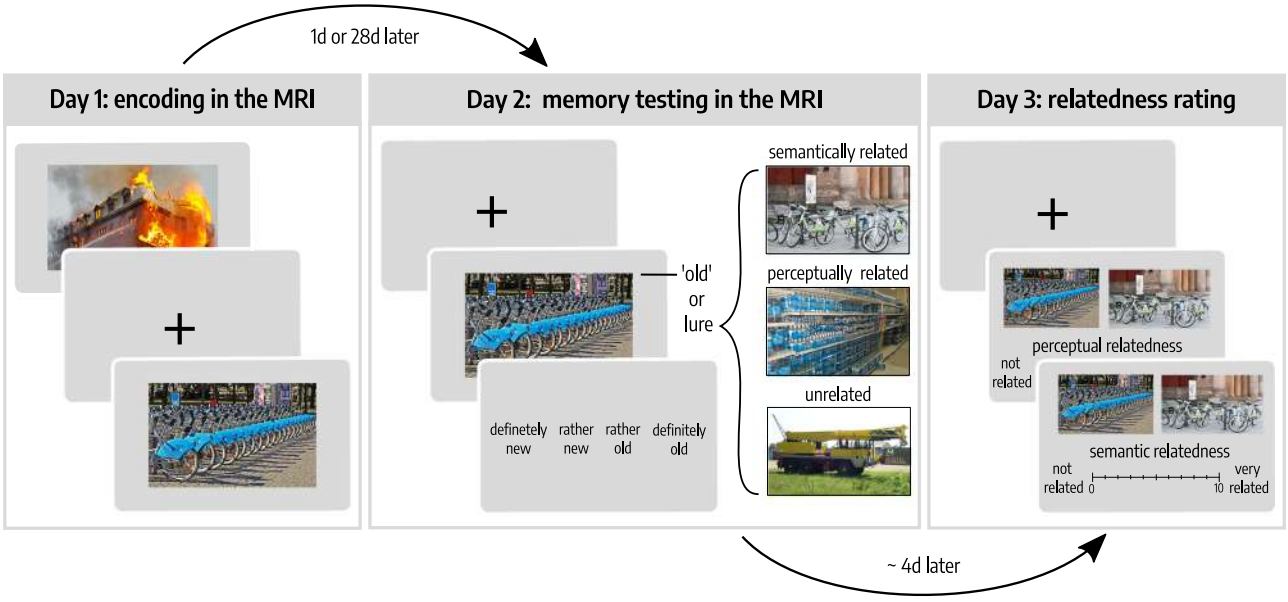

Fig. 1 | Experimental paradigm. On the first experimental day (Day 1), participants encoded 30 emotionally neutral and 30 negative pictures, each presented once in each of three consecutive runs. After a delay of 1d or 28d (Day 2), participants were presented with the encoded pictures, lures that were perceptually or semantically related to the old pictures or entirely novel, unrelated material in a recognition test. Both encoding and memory testing were conducted in an MRI scanner. On the third experimental day (Day 3), participants rated the individually perceived semantic and perceptual relatedness between each old image and their corresponding semantically related, perceptually related or unrelated lure. All depicted images are licensed under Creative Commons BY-SA License: image representing emotionally negative item at encoding (fire) is courtesy of Sylvain Pedneault (https://commons.wikimedia.org/wiki/File:Fire_inside_an_abandoned_convent_in_Massueville,_Quebec,_Canada.jpg; edited), image representing 'old' item is courtesy of W. Bulach (https://commons.wikimedia.org/wiki/File:00_2141_Bicycle-sharing_systems_-_Sweden.jpg; edited), image representing 'semantically related' item is courtesy of Matti Blume (https://commons.wikimedia.org/wiki/File:Bike_share_2019,_Berlin_(P1080139).jpg; edited), image representing 'perceptually related' item is courtesy of Ivy Main (https://fi.m.wikipedia.org/wiki/Tiedosto:Bottled_water_in_supermarket.JPG; edited), image representing 'unrelated' item is courtesy of Hannes Drexl (https://commons.wikimedia.org/wiki/File:Autokran_Seite.jpg?uselang=de; unchanged).

Interval: [0.002, 0.27]): the decrease in hits for the 28d- compared to the 1d-group was significantly lower for emotionally negative compared to emotionally neutral pictures (interaction contrast: $t(50) = 3.04$, $p = 0.004$, $d = 0.40$, 95% Confidence Interval = [0.14, 0.66]). Accordingly, the hit rate for negative pictures after 28d was significantly higher than for neutral pictures (paired t-test: $t(50) = -3.65$, $p = 6e{-}04$, $d = -0.66$, 95% Confidence Interval = [−1.01, −0.31]), while there was no statistically significant difference in the hit rate for emotionally negative and neutral pictures when tested 1d after encoding (paired t-test: $t(50) = 0.64$, $p = 0.522$, $d = 0.14$, 95% Confidence Interval = [−0.28, 0.56]). The latter finding may be owing to the overall very high memory performance on the recognition test 1d after encoding.

To assess the nature of memory transformation over time, the key question of this study, we analyzed participants' false alarms (FAs) to unrelated (i.e., entirely novel), semantically related and perceptually related lures by means of a mixed ANOVA with the between-subjects factor delay (1d vs. 28d) and the within-subject factors emotion (neutral vs. negative) and lure type (unrelated vs. semantically related vs. perceptually related). This analysis showed a time-dependent increase in FA rates depending on the lure type (delay × lure type: $F(1.55, 77.43) = 9.33$, $p = 7e{-}04$, $\eta_p^2 = 0.16$, 95% Confidence Interval: [0.05, 0.32]; main effect lure type: $F(1.55, 77.43) = 42.90$, $p = 2e{-}11$, $\eta_p^2 = 0.46$, 95% Confidence Interval: [0.32, 0.60]; main effect delay: $F(1, 50) = 6.79$, $p = 0.012$, $\eta_p^2 = 0.12$, 95% Confidence Interval: [6e−03, 0.29]). As shown in Fig. 2a, a striking increase in the FA rate for the 28d- compared to the 1d-group was observed selectively for semantically related lures (two-sample t-test: $t(50) = -3.32$, $p = 0.002$, $d = -1.09$, 95% Confidence Interval = [−1.73, −0.45]), which was significantly higher than for perceptually related (interaction contrast: $t(50) = -4.29$, $p = 2e{-}04$, $d = -0.58$, 95% Confidence Interval = [−0.85, −0.32]; two-sample t-test: $t(50) = -1.22$, $p = 0.226$, $d = -0.26$, 95% Confidence Interval = [−0.69, 0.16]) or entirely novel, unrelated lures (interaction contrast: $t(50) = -2.68$, $p = 0.030$, $d = -0.47$, 95% Confidence Interval = [−0.82, −0.13]; two-sample t-test: $t(50) = -3.32$, $p = 0.002$, $d = -1.09$, 95% Confidence Interval = [−1.73, −0.45]). Thus, after a delay of 28d, 52.78% of all new pictures which were incorrectly endorsed as 'old' were semantically related, while only 23.14% and 24.08% were perceptually related or unrelated to the encoded pictures, respectively. This pattern of results suggests a semantic memory transformation over time. Our results did not suggest a statistically significant difference in FAs for perceptually related items compared to unrelated items at both 1d (paired t-test: $t(50) = -2.31$, $p = 0.073$, $d = -0.34$, 95% Confidence Interval = [−0.62, −0.05]) and 28d after encoding (paired t-test: $t(50) = -0.88$, $p = 0.767$, $d = -0.11$, 95% Confidence Interval = [−0.37, 0.14]).

Interestingly, this semantization over time was significantly more pronounced for emotionally negative compared to neutral pictures (delay × emotion × lure type: $F(1.96, 97.98) = 4.27$, $p = 0.017$, $\eta_p^2 = 0.08$, 95% Confidence Interval: [0.01, 0.21]), resulting in a significantly higher difference in FAs between emotionally negative and neutral semantically related lures at 28d (paired t-test: $t(50) = -2.72$, $p = 0.009$, $d = -0.58$, 95% Confidence Interval = [−1.00, −0.16]), compared to 1d (interaction contrast: $t(50) = 2.88$, $p = 0.006$, $d = 0.52$, 95% Confidence Interval = [0.17, 0.88]; paired t-test: $t(50) = 1.36$, $p = 0.181$, $d = 0.25$, 95% Confidence Interval = [−0.11, 0.6]). To follow up on this three-way interaction, we further analyzed the FAs by a separate ANOVA per lure type, each with the factors delay and emotion. These analyses confirmed a significant emotionality-dependent increase in the FA rate in the 28d-group compared to the 1d-group selectively for semantically related lures (delay × emotion: $F(1, 50) = 8.30$, $p = 0.006$, $\eta_p^2 = 0.14$, 95% Confidence Interval: [0.02, 0.34]) and did not indicate a statistically significant interaction effect for unrelated lures (delay × emotion:

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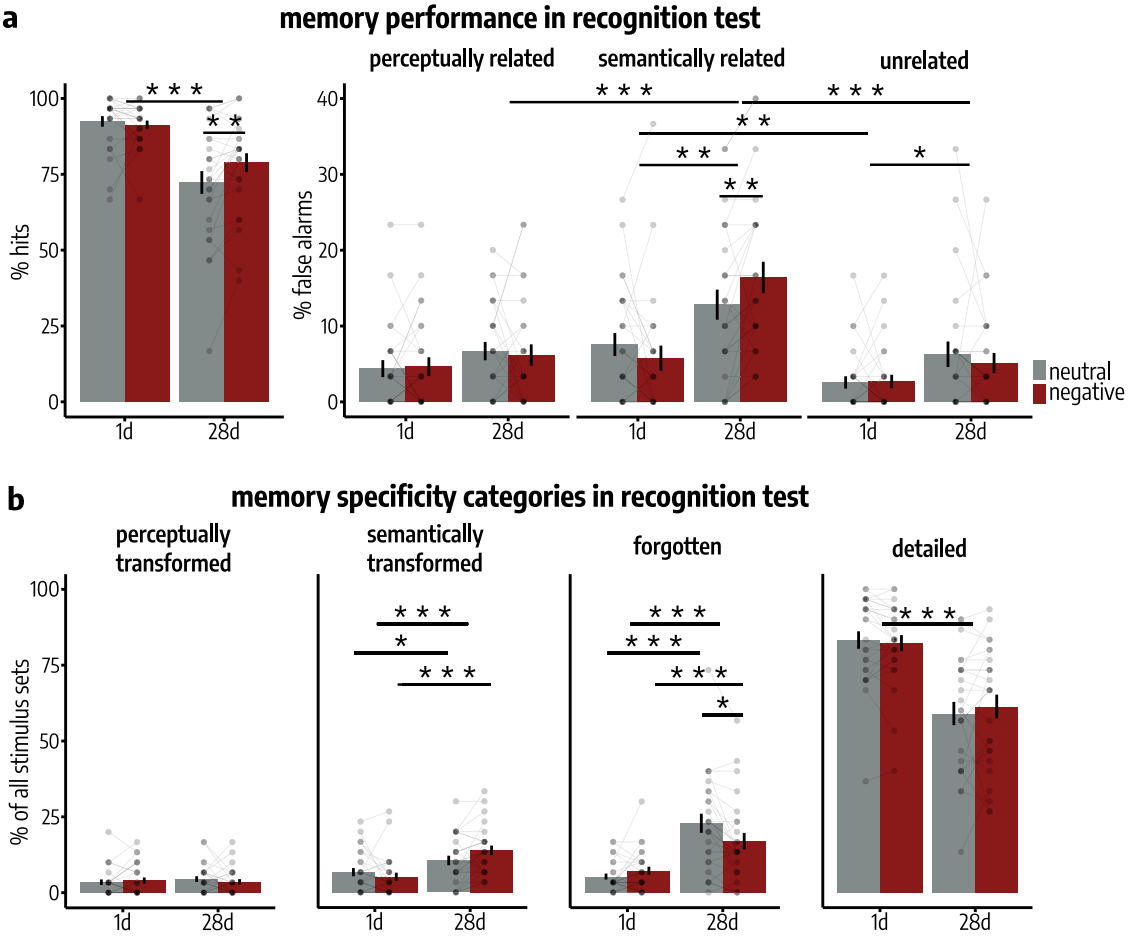

Fig. 2 | Memory performance during recognition testing based on stimulus categories. a Left: The decrease in hits from 1d to 28d after encoding (main effect delay: $p = 0.003$) was significantly higher for emotionally neutral than negative items (delay × emotion: $p = 0.004$; mixed ANOVA). Right: The increase in false alarms (FAs) from 1d to 28d after encoding (main effect delay: $p = 0.012$) was significantly higher for lures that were semantically related to the encoded pictures, compared to perceptually related (interaction contrast: $p = 2e{-}04$) or unrelated lures (interaction contrast: $p = 0.030$; delay × lure type: $p = 7e{-}04$). This semantization of memories over time was significantly higher for emotionally negative compared to neutral items (interaction contrast: $p = 0.006$; delay × lure type × emotion: $p = 0.017$; mixed ANOVA). All $n = 52$ participants. Bars represent mean ± SEM. Individual data points indicate the percentage of the 30 items per participant, emotion and item type which were correctly (left) or incorrectly (right) endorsed as 'old'. **b** Individual items were significantly more likely to be semantically transformed (main effect delay: $p = 0.030$), but not significantly more likely to be perceptually transformed in the 28d- compared to the 1d-group (all $p > 0.293$). Accordingly, detailed memory decreased with increasing delay after encoding (main effect delay: $p = 1e{-}07$). Moreover, emotionally negative memories were more robust against forgetting over time (delay × emotion: $p = 0.003$), but, again, more often semantically transformed than neutral ones (delay × emotion: $p = 0.014$; binomial generalized linear mixed models; all $n = 52$ participants). Bars represent mean ± SEM. Connected dots represent individual data points. All post-hoc tests were applied on estimated marginal means with Šidák correction for multiple comparisons. All reported p-values are two-tailed. Source data are provided as Source Data file. *$p < 0.050$; **$p < 0.010$; ***$p < 0.001$.

$F(1, 50) = 0.54$, $p = 0.467$, $\eta_p^2 = 0.01$, 95% Confidence Interval: [3e−05, 0.13]) or perceptually related lures (delay × emotion: $F(1, 50) = 0.23$, $p = 0.637$, $\eta_p^2 = 0.003$, 95% Confidence Interval: [2e−05, 0.11]).

Weighting the FAs by level of confidence (×1 = 'rather old', ×2 = 'definitely old') before analyzing them by means of a mixed ANOVA with the factors delay (1d vs. 28d), lure type (1d vs. 28d) and emotion (neutral vs. negative), did not change our pattern of results regarding delay-dependent effects on memory specificity (delay × lure type × emotion: $F(1.96, 98.12) = 5.57$, $p = 0.005$, $\eta_p^2 = 0.10$, 95% Confidence Interval: [0.02, 0.24]; delay × lure type: $F(1.50, 75.19) = 8.83$, $p = 0.001$, $\eta_p^2 = 0.15$, 95% Confidence Interval: [0.04, 0.32]; main effect lure type: $F(1.50, 75.19) = 37.45$, $p = 3e{-}10$, $\eta_p^2 = 0.43$, 95% Confidence Interval: [0.28, 0.58]; main effect delay: $F(1, 50) = 5.45$, $p = 0.024$, $\eta_p^2 = 0.10$, 95% Confidence Interval: [0.004, 0.29]; see Supplementary Fig. 3), indicating that our finding of an emotionally enhanced memory semantization in the course of time-dependent memory transformation was not significantly influenced by the confidence of FAs. Moreover, analyzing the confidence associated with FAs by means of binomial generalized linear mixed models (LMMs) did not reveal any significant main effect or interaction of the predictors delay and emotion, neither for semantically related (all $p > 0.455$), perceptually related (all $p > 0.131$) nor for unrelated lures (all $p > 0.448$; see Supplementary Table 2).

While the previous analyses showed a time-dependent increase in FAs depending on the lure type, the correspondence of each originally encoded picture to precisely one perceptually related and one semantically related lure during memory testing furthermore allowed us to analyze the response pattern at the level of each individual set of related stimuli to assess the extent of detailed, semantically transformed, perceptually transformed or entirely forgotten memories[19]. For this, we categorized the responses for each of the 60 related stimulus sets as either detailed, semantically transformed, perceptually transformed, or forgotten and analyzed the occurrence of each specificity category by means of binomial generalized LMMs with delay (1d vs. 28d), emotion (neutral vs. negative) and their interactions as fixed effects and the random intercept of participants and stimulus sets. Memories were classified as detailed when participants endorsed

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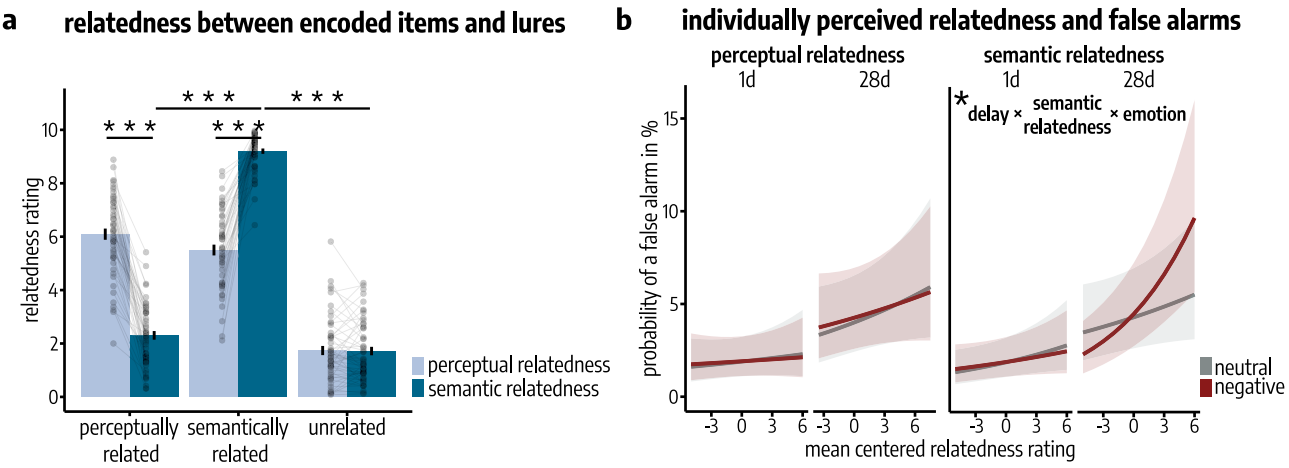

Fig. 3 | Individually perceived relatedness and memory specificity. **a** Participant's relatedness ratings confirmed that semantically related items were perceived as significantly more semantically related to the corresponding old picture than perceptually related (paired *t*-test: $p < 9e{-}99$) and unrelated lures (paired *t*-test: $p < 9e{-}99$; main effect lure type on semantic relatedness: $p = 1e{-}43$) and that perceptually related lures were perceived as significantly more perceptually related to their corresponding old picture than unrelated lures (paired *t*-test: $p < 9e{-}99$; main effect lure type on perceptual relatedness: $p = 6e{-}32$; mixed ANOVAs; all $n = 52$ participants). Bars represent mean ± SEM. Connected dots represent individual data points. **b** Taking these individual relatedness ratings into account when analyzing false alarms (FAs) by means of a binomial generalized linear mixed model (gLMM), confirmed that the delay-dependent increase in FAs (main effect delay: $p = 0.016$) was primarily driven by the semantic relatedness, specifically for emotionally negative stimuli (delay × semantic relatedness × emotion: $p = 0.018$). $N = 52$ participants. Lines represent predicted probabilities for FAs as estimated by the binomial gLMM, with error bands indicating the 95% Confidence Interval for these predicted probabilities. All post-hoc tests were applied on estimated marginal means with Šidák correction for multiple comparisons. All reported *p*-values are two-tailed. Source data are provided as Source Data file. $^{*}p < 0.050$; $^{***}p < 0.001$.

solely the originally encoded pictures as 'old' but not the semantically or perceptually related lures. If participants endorsed the semantically related lures but not the perceptually related lures, the respective memories were classified as being semantically transformed. Conversely, if participants endorsed the perceptually related lures but not the semantically related lures, the memories were classified as perceptually transformed. If participants endorsed neither the old nor the semantically or perceptually related items, the respective memories were classified as 'forgotten'. Thus, all 60 items per specificity category and participant are included in each analysis except of trials in which participants missed to indicate their memory for the previously presented item (missed responses), which on average led to only 0.95% (SEM = 0.44%) of missing data points per participant (no significant difference between delay groups; two-sample *t*-test: $t(31.20) = -1.07$, $p = 0.294$, $d = -0.30$, 95% Confidence Interval = [−0.86, 0.26]; see Supplementary Table 3 for an overview of the number of stimulus sets per category). Compared to the 1d-group, participants of the 28d-group had significantly fewer detailed (main effect delay: $z = -5.29$, $p = 1e{-}07$, $\beta = -1.51$, 95% Confidence Interval: [−2.07, −0.95]) and more forgotten memories (main effect delay: $z = 5.75$, $p = 9e{-}09$, $\beta = 1.79$, 95% Confidence Interval: [1.18, 2.41]; see Fig. 2b). Importantly, the 28d-group showed also significantly more semantically transformed memories than the 1d-group (main effect delay: $z = 2.17$, $p = 0.030$, $\beta = 0.64$, 95% Confidence Interval: [0.06, 1.22]) without a statistically significant increase in perceptually transformed memories (all $p > 0.293$; see Supplementary Table 4). Again, the nature of the time-dependent changes in memory was critically dependent on the emotionality of the items: Over time, significantly fewer emotionally negative pictures were forgotten than neutral ones (delay × emotion: $z = -3.00$, $p = 0.003$, $\beta = -0.75$, 95% Confidence Interval: [−1.25, −0.26]). Even more importantly, emotionally negative pictures were significantly more often semantically transformed over time (*z*-test: $z = -4.31$, $p = 2e{-}05$, $d = -1.31$, 95% Confidence Interval: [−1.90, −0.71]) than neutral ones (*z*-test: $z = -2.17$, $p = 0.030$, $d = -0.64$, 95% Confidence Interval: [−1.22, −0.06]; delay × emotion: $z = 2.46$, $p = 0.014$, $\beta = 0.66$, 95% Confidence Interval: [0.14, 1.19]), in line with findings suggesting that superior memory for emotional material, indicated here by a slower forgetting rate, may come at the cost of reduced memory specificity[19,23–25].

Participants' relatedness ratings on Day 3 confirmed the results of our behavioral pilot study (see methods section and Supplementary Fig. 1) that semantically related lures were perceived as being significantly more semantically related ($M = 9.20$, SEM = 0.10) to the corresponding old picture than perceptually related ($M = 2.30$, SEM = 0.16; paired *t*-test: $t(50) = -33.41$, $p < 9e{-}99$, $d = -4.59$, 95% Confidence Interval = [−4.86, −4.32]) and unrelated lures ($M = 1.72$, SEM = 0.16; paired *t*-test: $t(50) = -36.87$, $p < 9e{-}99$, $d = -5.02$, 95% Confidence Interval = [−5.28, −4.75]; main effect lure type on semantic relatedness: $F(1.22, 60.96) = 1157.08$, $p = 1e{-}43$, $\eta_p^2 = 0.96$, 95% Confidence Interval: [0.94, 0.97]; see Fig. 3a, Supplementary Fig. 4 and Supplementary Table 5). Perceptually related lures were perceived as being significantly more perceptually related (M = 6.09, SEM = 0.21) to their corresponding old picture than unrelated lures ($M = 1.74$, SEM = 0.17; paired *t*-test: $t(50) = -22.4$, $p < 9e{-}99$, $d = -3.05$, 95% Confidence Interval = [−3.32, −2.78]; main effect lure type on perceptual relatedness: $F(1.45, 72.71) = 201.81$, $p = 6e{-}32$, $\eta_p^2 = 0.80$, 95% Confidence Interval: [0.74, 0.85]). As expected, semantically related lures were also rated higher in perceptual relatedness to their corresponding old picture ($M = 5.50$, SEM = 0.20) compared to unrelated lures (paired *t*-test: $t(50) = -16.00$, $p < 9e{-}99$, $d = -2.18$, 95% Confidence Interval = [−2.44, −1.91]). Importantly, perceptually related lures were rated as significantly higher in perceptual than in semantic relatedness to their corresponding old image (paired *t*-test: $t(51) = 16.67$, $p = 3e{-}22$, $d = 3.25$, 95% Confidence Interval = [2.66, 3.83]) while semantically related items were rated as significantly more semantically than perceptually related to their corresponding old image (paired *t*-test: $t(51) = -16.38$, $p = 6e{-}22$, $d = -2.83$, 95% Confidence Interval = [−3.37, −2.28]).

The individual stimulus relatedness ratings on Day 3 further allowed us to analyze FAs by means of a binomial generalized LMM with the factors delay (1d vs. 28d), emotion (neutral vs. negative), semantic relatedness rating, perceptual relatedness rating and their interactions as fixed effects and the random intercept of participants and stimuli. This analysis showed, in line with the categorical analyses

above, a time-dependent increase in FAs that was primarily driven by the semantic relatedness, which affected the probability of a FA in particular for emotionally negative stimuli (delay × semantic relatedness × emotion: $z = 2.36$, $p = 0.018$, $\beta = 0.12$, 95% Confidence Interval = [0.02, 0.21]; main effect delay: $z = 2.40$, $p = 0.016$, $\beta = 0.85$, 95% Confidence Interval = [0.16, 1.55]; main effect semantic relatedness: $z = 2.04$, $p = 0.041$, $\beta = 0.07$, 95% Confidence Interval = [0.003, 0.13]; Fig. 3b). We obtained no statistically significant effect of the individual perceptual relatedness ratings on FAs and their increase over time (all $p > 0.127$; see Supplementary Table 6).

As semantically related items are usually also high in perceptual relatedness to original stimuli, we additionally analyzed whether the delay-dependent increase in FAs for semantically related items was equally evident in semantically related lures low (≤ 5) vs. high (> 5) in perceptual relatedness. A generalized LMM with the factors perceptual relatedness level (low vs. high), delay (1d vs. 28d) and emotion (neutral vs. negative) and the random intercept of participants and stimuli confirmed our previous finding of an emotionally enhanced increase in the probability for a FA for semantically related lures over time (delay × emotion: $\beta = 0.93$, $p = 0.029$, $z = 2.19$, 95% Confidence Interval = [0.09, 1.85]). This analysis did not indicate any influence of the level of perceptual relatedness of a semantically related stimulus to its corresponding original item on FAs (all $p > 0.215$; see Supplementary Table 7).

In sum, our behavioral data demonstrate that memories are semantically transformed over time while we found no statistically significant evidence for a perceptual memory transformation. This time-dependent semantization of memories was further consistently more pronounced for emotionally negative than for neutral stimuli.

Distinct pattern representations of encoded events in the anterior hippocampus decrease over time

In order to examine the neural mechanisms involved in the semantic transformation of memories over time, we leveraged model-based Representational Similarity Analyses (RSAs)[19,29,30] assessing how the similarity between activation patterns of encoded items and different lure types (semantically related vs. perceptually related vs. unrelated) at memory testing changes in the course of memory transformation. Here, neural representational similarity matrices (RSMs) were compared to three conceptual model RSMs (see Fig. 2a), each predicting different similarity patterns between old items and the different lure types at memory testing: (i) similar representations for old pictures that are distinct from patterns for all novel stimuli (model 1: 'old items are distinct from all lures'), (ii) similar representations between old items and semantically related lures which are distinct from perceptually related and unrelated lures (model 2: 'old and semantically related items are similar') and (iii) similar representations between old items and perceptually related lures, which are distinct from semantically related and unrelated lures (model 3: 'old and perceptually related items are similar'). Note that for all models we expected old items to be represented more similarly, as they should equally initiate recognition processes in neural areas relevant for memory representations that, in case of recent, specific memory, should be distinct from all lures (model 1), or, in case of transformed memory representations, similar to either semantically (model 2), or perceptually (model 3) related lures. Based on recent evidence[19], we hypothesized that the anterior hippocampus is particularly relevant for the specificity of recent memories while the posterior hippocampus represents remote, semantically transformed memories. Accordingly, the anterior hippocampus should reflect distinct representations (model 1) at a short delay, but this representation should decrease over time, while we expected the posterior hippocampus to represent semantically transformed memory that should increase over time (model 2). A mixed ANOVA with the factors delay (1d vs. 28d), emotion (neutral vs. negative), model (1: 'old items are distinct from all lures' vs. 2: 'old and semantically related items are similar' vs. 3: 'old and perceptually related items are similar') and hippocampal long axis (anterior vs. posterior) revealed a significant delay × model × long axis interaction ($F(1.55, 75.88) = 5.36$, $p_{corr} = 0.024$, $\eta_p^2 = 0.10$, 95% Confidence Interval: [0.02, 0.25]) and a delay × model × long axis × emotion interaction ($F(1.68, 82.19) = 4.64$, $p_{corr} = 0.034$, $\eta_p^2 = 0.09$, 95% Confidence Interval: [0.01, 0.23]; see Fig. 4b). Note that one extreme outlier (28d group) was excluded from this analysis. Post-hoc tests confirmed a significant decrease in recognition processes for the encoded material (model 1) over time in the anterior hippocampus (two-sample t-test: $t(49) = 2.42$, $p = 0.020$, $d = 0.36$, 95% Confidence Interval = [0.07, 0.64]), which was significant for emotionally negative items (two-sample t-test: $t(49) = 2.40$, $p = 0.021$, $d = 0.46$, 95% Confidence Interval = [0.08, 0.83]), while emotionally neutral items did not show a statistically significant decrease in model fit over time (two-sample t-test: $t(49) = 1.05$, $p = 0.297$, $d = 0.25$, 95% Confidence Interval = [−0.22, 0.73]). Interestingly, the anterior hippocampus also showed a delay-dependent decrease in perceptually similar memory representations for neutral items (model 3, two-sample t-test: $t(49) = 2.40$, $p = 0.003$, 0.94, 95% Confidence Interval = [0.34, 1.54]) indicating a time-dependent decrease in the representation of perceptual details in the anterior hippocampus for those items. Neither the anterior hippocampus (model 2: $t(49) = -0.01$, $p = 0.989$, $d = -3e{-}03$, 95% Confidence Interval = [−0.39, 0.38]) nor the posterior hippocampus ($t(49) = 1.11$, $p = 0.271$, $d = 0.23$, 95% Confidence Interval = [−0.17, 0.62]) showed a statistically significant delay-dependent change in the fit to the model reflecting semantically transformed pattern representations.

Together, these data indicate that the anterior hippocampus represents recently encoded events in a detailed manner, including perceptual features, and that these anterior hippocampal representations decrease over time, while our results did not yield reliable evidence for a more gist-like, transformed pattern representation in the anterior hippocampus, neither at the 1d- nor at the 28d-delay.

Semantically transformed representations of encoded events increase in prefrontal and parietal cortices over time

While the hippocampus has been implicated to be particularly important for recently encoded and specific memories in previous studies[16,18], neocortical regions are assumed to become more relevant for remote memory[9,16,18,31]. Specifically, the vmPFC[8–10], IFG[4,5], aCC[2,11–13], angular gyrus and the precuneus[14,15] have been associated with the formation of long-term memories. Thus, we analyzed time-dependent memory transformation processes in these neocortical long-term memory regions. We first performed a delay (1d vs. 28d) × model (1: 'old items are distinct from all lures' vs. 2: 'old and semantically related items are similar' vs. 3: 'old and perceptually related items are similar') × emotion (neutral vs. negative) ANOVA using a combined mask, including the vmPFC, IFG, aCC, angular gyrus and precuneus, as we expected a similar increase in transformed memory representations over time in all of those neocortical regions. This analysis showed a significant increase in representational similarity between old items and semantically related lures in the 28d- compared to the 1d-group in the neocortex (model 2; two-sample t-test: $t(50) = -2.04$, $p = 0.047$, $d = -0.62$, 95% Confidence Interval = [−1.21, −0.02]), and no statistically significant delay-dependent change in the fits to models reflecting distinct (model 1; two-sample t-test: $t(50) = -1.62$, $p = 0.111$, $d = -0.38$, 95% Confidence Interval = [−0.84, 0.08]) or perceptually similar memory representations (model 3; two-sample t-test: $t(50) = 0.83$, $p = 0.412$, $d = 0.13$, 95% Confidence Interval = [−0.18, 0.45]; delay × model: $F(1.48, 74.03) = 7.1$, $p = 0.004$, $\eta_p^2 = 0.12$, 95% Confidence Interval: [0.03, 0.29]; main effect model: $F(1.48,74.03) = 19.11$, $p = 3e{-}06$, $\eta_p^2 = 0.28$, 95% Confidence Interval: [0.13, 0.44]; see Fig. 5). Accordingly, neocortical activity patterns during memory testing showed a

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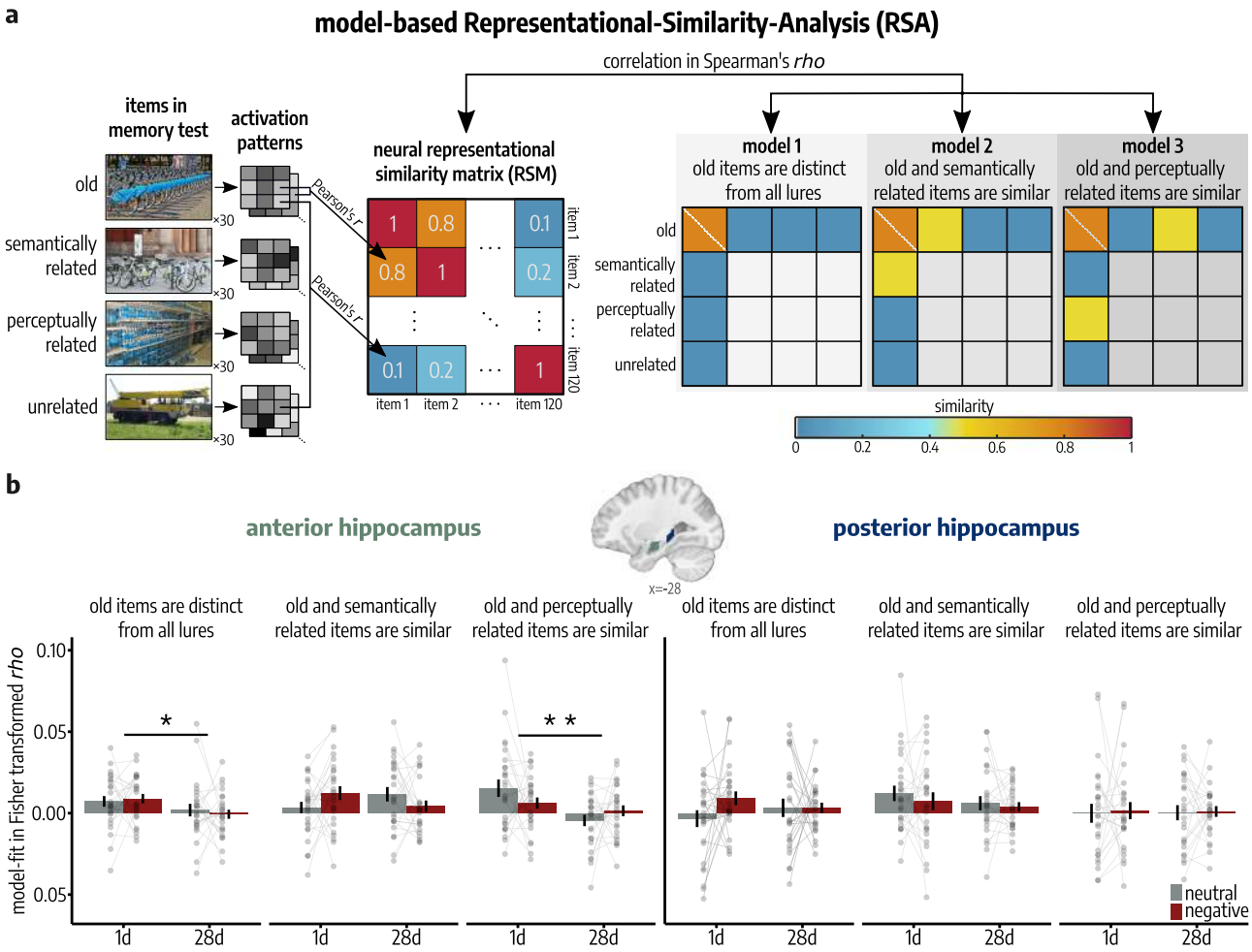

Fig. 4 | Computational approach for model-based RSA analyses and results along the hippocampal anterior-posterior axis. a Schematic overview over the creation of a neural RSM for emotionally neutral items with exemplary correlation values. Each neural RSM per region of interest (ROI), emotion category and subject was compared to three conceptual models. All depicted images are licensed under Creative Commons BY-SA License: image representing 'old' item is courtesy of W. Bulach (https://commons.wikimedia.org/wiki/File:00_2141_Bicycle-sharing_systems_-_Sweden.jpg; edited), image representing 'semantically related' item is courtesy of Matti Blume (https://commons.wikimedia.org/wiki/File:Bike_share_2019,_Berlin_(P1080139).jpg; edited), image representing 'perceptually related' item is courtesy of Ivy Main (https://fi.m.wikipedia.org/wiki/Tiedosto:Bottled_water_in_supermarket.JPG; edited), image representing 'unrelated' item is courtesy of Hannes Drexl (https://commons.wikimedia.org/wiki/File:Autokran_Seite.jpg?uselang=de; unchanged). **b** In the left anterior hippocampus, specifically for negative items (model 1; two-sample *t*-test: $p = 0.021$), distinct representations of encoded pictures (model 1; two-sample *t*-test: $p = 0.019$) and, specifically for emotionally neutral items (model 3; two-sample *t*-test: $p = 0.003$), perceptually similar representations (model 3; two-sample *t*-test: $p = 0.002$) decreased with increasing delay after encoding (delay × long axis × model: $p_{corr} = 0.024$; delay × emotion × long axis × model: $p_{corr} = 0.034$; mixed ANOVA; $n = 51$ participants). Bars represent mean ± SEM. If analyses were repeated for both hemispheres, Bonferroni-corrected *p*-values (p_{corr}) are reported. All reported *p*-values are two-tailed. All post-hoc tests were applied on estimated marginal means with Šidák correction for multiple comparisons. Regions of interest are visualized on a sagittal section of a T1-weighted template[82] in MNI-152 space. Source data are provided as Source Data file. *$p < 0.050$; **$p < 0.010$.

significantly higher fit to model 2 ('old and semantically related items are similar') than to both other models in the 28d-group (paired *t*-tests; model 1: $t(50) = -4.02$, $p = 6e{-}04$, $d = -0.61$, 95% Confidence Interval = [−0.91, −0.31]; model 3: $t(50) = 5.50$, $p = 4e{-}06$, $d = 0.93$, 95% Confidence Interval = [0.60, 1.26]) while there was no statistically significant difference in fit to either model in the 1d-group (paired *t*-tests; model 1: $t(50) = -2.15$, $p = 0.106$, $d = -0.27$, 95% Confidence Interval = [−0.52, −0.02]; model 3: $t(50) = 1.36$, $p = 0.446$, $d = 0.19$, 95% Confidence Interval = [−0.08, 0.46]). Thus, this analysis indicates the formation of semantically transformed representations of encoded events in the neocortex over time.

To investigate whether this time-dependent memory semantization was equally evident in all individual neocortical regions, we analyzed the fit of the RSM for each individual neocortical ROI to the model reflecting semantically transformed pattern representations (model 2) by means of mixed ANOVAs with the factors delay and emotion (see Fig. 5). This analysis confirmed a delay-dependent increase in representational similarity between old items and semantically related lures in the vmPFC (main effect delay: $F(1, 50) = 4.19$, $p = 0.046$, $\eta_p^2 = 0.08$, 95% Confidence Interval: [0.001, 0.26]) and right angular gyrus (main effect delay: $F(1, 50) = 8.34$, $p_{corr} = 0.011$, $\eta_p^2 = 0.14$, 95% Confidence Interval: [0.02, 0.34]). This analysis did not indicate a statistically significant delay-dependent change in similarity between model 2 and pattern representations in the precuneus (main effect delay: $F(1, 50) = 3.93$, $p = 0.053$, $\eta_p^2 = 0.07$, 95% Confidence Interval: [0.00, 0.25]; $F(1,50) = 0.01$, $p = 0.943$, $\eta_p^2 = 1e{-}04$, 95% Confidence Interval: [2e−05, 0.10]), IFG (main effect delay: $F(1,50) = 2.25$, $p = 0.140$, $\eta_p^2 = 0.04$, 95% Confidence Interval: [2e−04, 0.21]; delay × emotion: $F(1,50) = 1.8$, $p = 0.186$, $\eta_p^2 = 0.03$, 95% Confidence Interval: [1e−04, 0.19]), and aCC (main effect delay: $F(1, 50) = 1.15$, $p = 0.289$, $\eta_p^2 = 0.02$, 95% Confidence Interval: [6e−05, 0.16]; delay × emotion: $F(1,50) = 1.41$, $p = 0.240$, $\eta_p^2 = 0.03$, 95% Confidence Interval: [8e−05, 0.18]).

Furthermore, we repeated this model-based RSA in the bilateral occipital pole and Heschl's gyrus as neocortical control regions for

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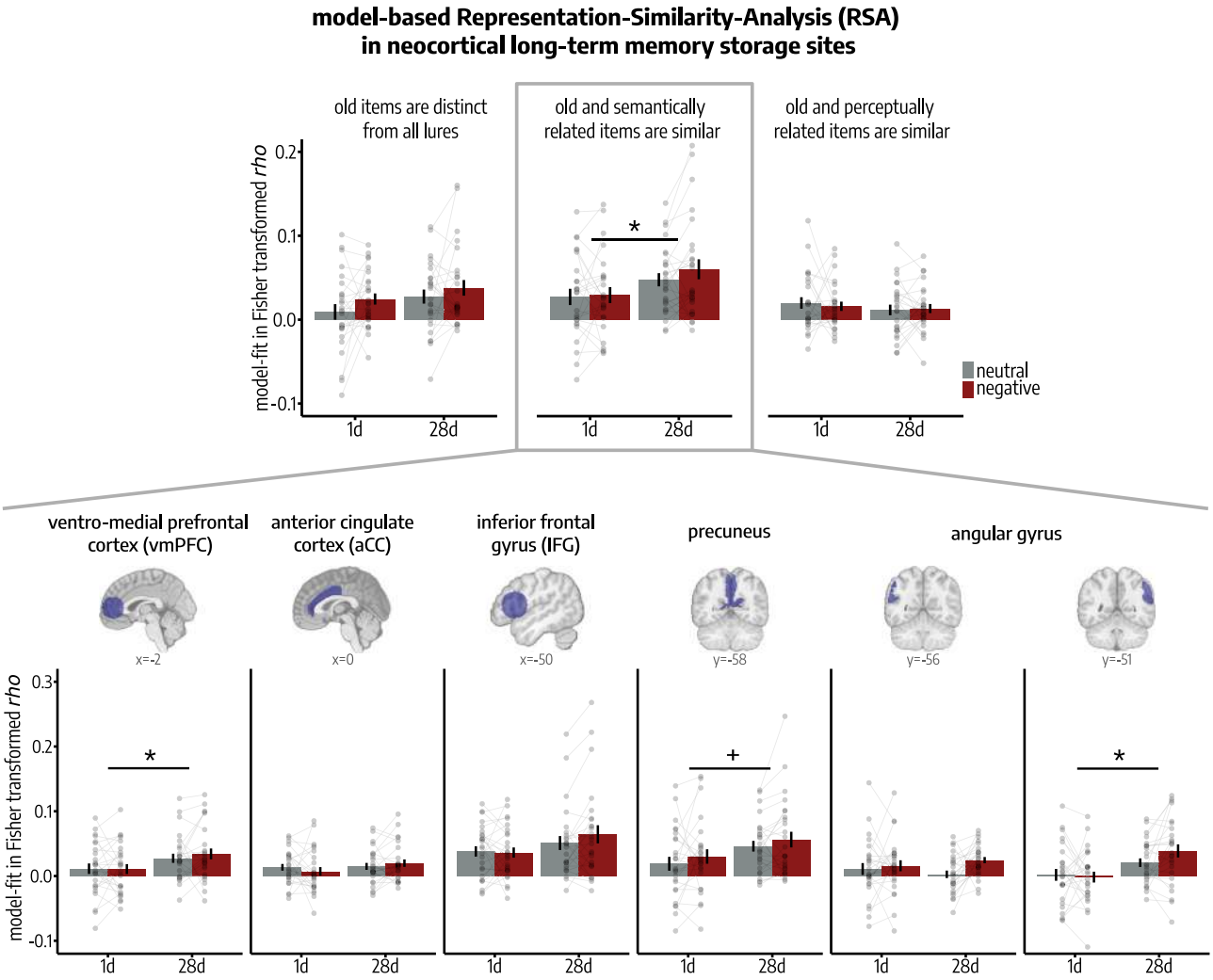

Fig. 5 | Model-based RSA results in neocortical long-term memory storage sites. *Upper panel:* Pattern representations in a combined ROI including long-term memory cortices (vmPFC, IFG, aCC, angular gyrus and precuneus) were semantically (model 2; two-sample *t*-test: $p = 0.047$) transformed over time, while there was no statistically significant effect for the model testing for perceptually transformed representation patterns (model 3; two-sample *t*-test: $p = 0.412$; delay × model: $p = 0.004$; mixed ANOVA). *Lower panel:* Post-hoc testing revealed that this time-dependent semantization of pattern representations (model 2) was specific to the vmPFC (main effect delay: $p = 0.046$) and right angular gyrus (main effect delay: $p_{corr} = 0.010$; mixed ANOVAs; $n = 52$ participants). Bars represent mean ± SEM. If analyses were repeated for both hemispheres, Bonferroni-corrected *p*-values (p_{corr}) are reported. All reported *p*-values are two-tailed. All post-hoc tests were applied on estimated marginal means with Šidák correction for multiple comparisons. Regions of interest (ROIs) are visualized on sagittal (prefrontal ROIs) and axial (parietal ROIs) sections of a T1-weighted template[82] in MNI-152 space. Source data are provided as Source Data file. $^{+}p < 0.060$; $^{*}p < 0.050$.

which we did not expect any statistically significant increase in transformed memory representations over time. Analyzing activation patterns in those regions by means of delay (1d vs. 28d) × model (1: 'old items are distinct from all lures' vs. 2: 'old and semantically related items are similar' vs. 3: 'old and perceptually related items are similar') × emotion (neutral vs. negative) ANOVAs did not indicate a statistically significant time-dependent change in fit of pattern representations, neither in the occipital pole (delay × model: $F(1.83, 91.39) = 0.87$, $p = 0.415$, $\eta_p^2 = 0.02$, 95% Confidence Interval: [0.001, 0.12]; delay × emotion × model: $F(2.00, 99.82) = 0.47$, $p = 0.624$, $\eta_p^2 = 9e{-}03$, 95% Confidence Interval: [0.001, 0.10]) nor in Heschl's gyrus (delay × model: $F(1.38, 68.96) = 0.32$, $p = 0.645$, $\eta_p^2 = 6e{-}03$, 95% Confidence Interval: [2e−04, 0.08]; delay × emotion × model: $F(1.69, 84.5) = 0.48$, $p = 0.587$, $\eta_p^2 = 1e{-}02$, 95% Confidence Interval: [5e−04, 0.10]). Interestingly, activation patterns in the occipital pole showed an overall higher fit to model 3 ('old and perceptually related items are similar') compared to model 1 (paired *t*-test: $t(50) = -4.87$, $p = 3e{-}05$, $d = -0.5$, 95% Confidence Interval = [−0.70, −0.30]) as well as model 2 (paired *t*-test: $t(50) = -3.85$, $p = 0.001$, $d = -0.49$, 95% Confidence Interval = [−0.73, −0.24]) without a statistically significant effect of temporal delay (main effect model: $F(1.83, 91.39) = 13.26$, $p = 2e{-}05$, $\eta_p^2 = 0.21$, 95% Confidence Interval: [0.09, 0.36]). This finding most likely reflects the processing of overlapping visual features in old and perceptually related images in this region.

Our model-based analyses thus indicate that semantically transformed representations of previously encoded events emerge in prefrontal and posterior parietal cortices in the course of memory transformation while we did not observe any credible evidence for a perceptual transformation in these regions.

Posterior hippocampal memory reinstatement increases over time

While our model-based approach assessed the time-dependent change in representational similarity between encoded and new item categories at memory testing, we further analyzed the reactivation of individual items during memory test, i.e., Encoding-Retrieval Similarity (ERS), as a measure of trial-specific memory reinstatement[20,32–37]. For this, we computed the similarity (Pearson's *r*) between activation

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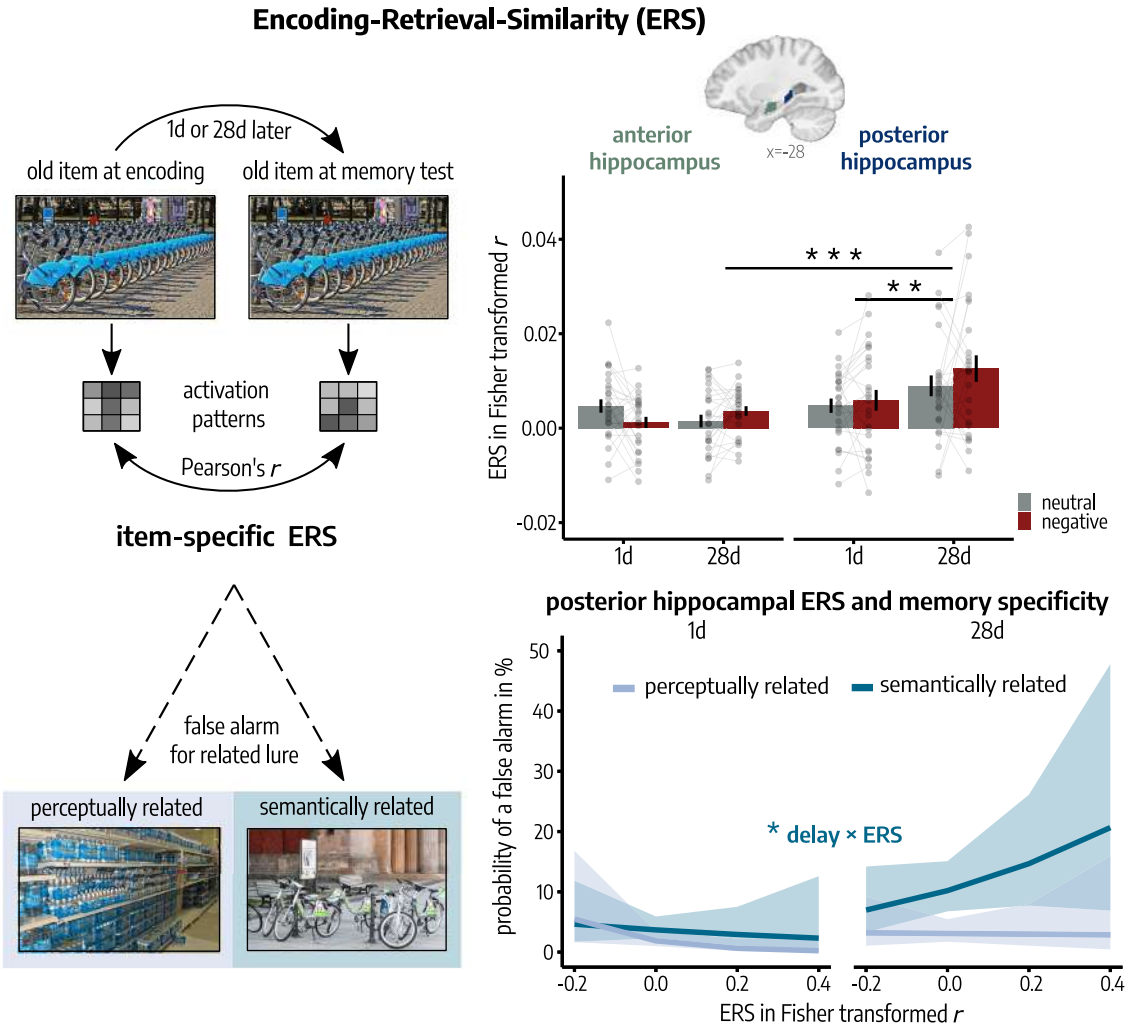

Fig. 6 | Time-dependent changes in memory reinstatement along the hippocampal anterior-posterior axis. *Upper Panel:* Posterior hippocampal memory reinstatement increased over time (paired *t*-test: $p = 0.004$; linear mixed model, LMM: delay × long axis: $p_{corr} = 0.038$). Bars represent mean ± SEM. Connected dots represent individual data points. *Lower Panel:* Posterior hippocampal ERS showed a significantly higher positive association with false alarms (FAs) for corresponding semantically related lures at a delay of 28d compared to 1d after encoding (delay × ERS: $p = 0.048$) but no statistically significant association with FAs for perceptually related lures (all $p > 0.184$, generalized LMMs). These results indicate that posterior hippocampal reinstatement of remote memories is associated with the semantic gist of the original memory. Lines represent predicted probabilities for FAs as estimated by the binomial generalized LMM, with error bands indicating the 95% Confidence Interval for these predicted probabilities. All $n = 52$ participants. If analyses were repeated for both hemispheres, Bonferroni-corrected *p*-values (p_{corr}) are reported. All reported *p*-values are two-tailed. All post-hoc tests were applied on estimated marginal means with Šidák correction for multiple comparisons. Regions of interest are visualized on a sagittal section of a T1-weighted template[82] in MNI-152 space. All depicted photographs are licensed under Creative Commons BY-SA License: image representing 'old' item is courtesy of W. Bulach (https://commons.wikimedia.org/wiki/File:00_2141_Bicycle-sharing_systems_-_Sweden.jpg; edited), image representing 'semantically related' item is courtesy of Matti Blume (https://commons.wikimedia.org/wiki/File:Bike_share_2019,_Berlin_(P1080139).jpg; edited), image representing 'perceptually related' item is courtesy of Ivy Main (https://fi.m.wikipedia.org/wiki/Tiedosto:Bottled_water_in_supermarket.JPG; edited). Source data are provided as Source Data file. $^{*}p < 0.050$; $^{**}p < 0.010$; $^{***}p < 0.001$.

patterns during encoding on Day 1 and activation patterns of the same item during memory testing either 1d or 28d after encoding (Day 2; see Fig. 6). Due to the crucial role of the hippocampus in the reinstatement of episodic details[38,39], we focused specifically on the hippocampus and the differentiation along its anterior-posterior axis in this ERS analysis. Based on recent data suggesting that recent, specific memories are represented by the anterior hippocampus while more gist-like memories are associated with the posterior hippocampus[19,20], we predicted that, after a longer delay after encoding, memory reinstatement should rely more on the posterior hippocampus, while the anterior hippocampus should reinstate recent, specific memories.

Time dependent changes in item-specific ERS were analyzed by means of trial-wise LMMs with the factors delay (1d vs. 28d), emotion (neutral vs. negative), long axis (anterior vs. posterior) and their interactions as fixed effects and the random intercept of participants and stimuli. This analysis showed that the ERS changed significantly along the left hippocampal long axis depending on the delay after encoding (delay × long axis: $t(6124) = 2.35$, $p_{corr} = 0.038$, $\beta = 0.01$, 95% Confidence Interval = [0.001, 0.01]) with a significantly greater ERS in the posterior compared to the anterior hippocampus in the 28d-group (paired *t*-test: $t(6124) = -5.25$, $p = 2e{-}07$, $d = -0.19$, 95% Confidence Interval = [−0.26, −0.11]), while there was no statistical difference in the 1d-group ($t(6124) = -1.53$, $p = 0.126$, $d = 0.06$, 95% Confidence Interval = [−0.13, 0.02]). No other effects approached statistical significance in this analysis (all $p_{corr} > 0.148$; see Supplementary Table 8). Note that repeating this analysis after excluding items that were not correctly recognized (misses) did not change the result of a significant increase in posterior hippocampal ERS from 1d to 28d (delay × long axis: $\beta = 0.01$, $t(5107.81) = 3.13$, $p_{corr} = 0.004$, 95% Confidence Interval = [0.001, 0.01]; see Supplementary Table 9).

Next, we investigated the relationship of left posterior hippocampal memory reinstatement and behavioral memory indicators. Analyzing the probability of a hit by means of a generalized LMM with ERS, emotion (neutral vs. negative), delay (1d vs. 28d) and their interaction as fixed effects and the random intercepts of participants and stimulus sets indicated that with increasing delay, posterior hippocampal memory reinstatement was significantly positively associated with the correct endorsement of an old item as 'old' (delay × ERS: $z = 2.17$, $p = 0.030$, $\beta = 7.31$, 95% Confidence Interval = [0.73, 13.89]; see Supplementary Table 10). However, correct memory could be supported by specific, detailed memory representations but also by more abstract, gist-like representations. We therefore further analyzed the specificity of the reinstated memories by taking into account the responses for corresponding related lures. Analyzing the probability of a detailed recognition (correct response for old items without FAs for related lures) by means of a binomial generalized LMM with the factors ERS, delay and emotion did not indicate a statistically significant association of ERS with detailed memory (all $p > 0.688$; see Supplementary Fig. 5 and Supplementary Table 11). However, analyzing the probability of a FA for the corresponding semantically or perceptually related lure of each old item, by means of binomial generalized LMMs with ERS, emotion, delay and their interaction as fixed effects and the random intercepts of participants and stimulus sets, indicated a significantly higher positive association of ERS with the probability of a FA for semantically related lures in the 28d- compared to the 1d-group (delay × ERS: $z = 1.98$, $p = 0.048$, $\beta = 7.16$, 95% Confidence Interval = [0.02, 14.29]; see Fig. 3). No effects including the factor ERS were statistically significant when analyzing FAs for perceptually related lures (all $p > 0.184$; see Supplementary Table 12). Furthermore, analyzing response times during memory testing, as an indicator of the attentiveness in the respective trial, by means of an LMM with delay, emotion, posterior hippocampal ERS and their interaction as fixed effects and the random intercept of participants and stimuli did not show any statistically significant main effect ($p > 0.421$) nor interaction (all $p > 0.186$) of the included factors (see Supplementary Table 13). Thus, we found no statistically reliable evidence that the delay-dependent increase in posterior hippocampal ERS might be related to attentional differences during memory testing between groups.

While ERS is computed by correlating pattern representations of individual items during encoding and memory test, i.e. old items, we furthermore explored the similarity elicited by perceptually or semantically related items at memory test and corresponding old items during encoding as a possible indicator for a reinstatement of the perceptual or semantic gist of the original memory. Analyzing the anterior-posterior hippocampal representational similarity between items at encoding and their corresponding semantically related lures by means of an LMM, the posterior hippocampus tended to show a higher reinstatement of the semantic gist of the original memory compared to the anterior hippocampus, which, however, failed to reach statistical significance (main effect long axis: $t(6124) = 1.94$, $p = 0.052$, $\beta = 0.004$, 95% Confidence Interval = [−4e−05, 0.01]; see Supplementary Fig. 6). No effect approached statistical significance when analyzing hippocampal reinstatement of the perceptual gist (all $p > 0.235$; see Supplementary Table 14). To assess whether the results of our memory reinstatement analyses were indeed specific to the hippocampus, we explored delay-dependent changes in memory reinstatement in neocortical areas that have been previously implicated in long-term memory (IFG, vmPFC, aCC, precuneus, angular gyrus) as well as sensory control ROIs (occipital pole, Heschl's gyrus) by means of LMMs with the factors delay, emotion and their interactions as fixed effects. These analyses did not indicate any statistically significant delay-dependent variations in pattern reinstatement, neither by old items (i.e. ERS; all $p > 0.164$; see Supplementary Table 15) nor by semantically (all $p > 0.243$; see Supplementary Table 16) or perceptually (all $p > 0.201$; see Supplementary Table 17) related lures.

Taken together, our memory reinstatement analyses indicated that the posterior hippocampus is associated with the reinstatement of remote memories that may be rather unspecific in nature representing the semantic gist of the original memory, while we found no statistically significant link between hippocampal ERS and a perceptual memory transformation.

Discussion

Memories are thought to undergo a transformation over time. Here, we aimed at elucidating the nature and neural signature of the proposed time-dependent memory transformation. Specifically, we determined whether memories are semantically or perceptually transformed, which neural mechanisms are involved in this process, and whether memories for emotionally neutral and negative material are transformed in a comparable manner over time. We show that episodic memories are semantically transformed over time, while we did not obtain any credible evidence for a perceptual transformation. Our results further show that this time-dependent memory semantization is more pronounced for emotionally negative compared to neutral information. At the neural level, the transformation of memories over time was linked to a time-dependent increase in semantically transformed memory representations in prefrontal and parietal cortices. Beyond these time-dependent changes in neocortical areas, we also report significant representational changes within the hippocampus, along its anterior-posterior axis. Activation patterns that were specific to previously encoded events were represented in the anterior hippocampus, while the posterior hippocampus was associated with the reinstatement of remote memories that were rather unspecific in nature and likely to be confused with the semantic gist of the original memory, without reliable evidence for links to the perceptual gist.

Although prominent theoretical accounts of the temporal dynamics of memory postulate a transformation of memory over time[16,17], the nature of this time-dependent memory transformation remained elusive. In particular, it has been unclear whether the generalization of memories over time is semantic in nature or due to a perceptual transformation, with the latter being more in line with the common view that memories fade over time[22]. Previous studies could not distinguish between these alternatives as test materials and contexts were typically both perceptually and semantically related to the original episode. Here, we aimed at overcoming this issue by using a recognition test that included lures carrying either the semantic or the perceptual gist of the original material. Participants showed a significant time-dependent increase in the endorsement of semantically related lures over time indicating that remote memories represented the semantic gist of the original memory. For the endorsement of perceptually related lures, however, we found no credible evidence for an increase over time. Even more strikingly, when we analyzed participants' individual perceptual and semantic relatedness ratings for each of the lures, we observed that participants' subjectively perceived semantic relatedness between lure and original stimulus predicted the time-dependent increase in FAs on a trial-by-trial basis, demonstrating that remote memories were semantically transformed, while there was no statistically significant effect of the perceptual relatedness. These findings are generally consistent with core tenets of the Multiple-Trace-Theory[18] and Trace-Transformation-Theory[16,17], which suggest a semantic transformation over time. Alternatively, however, it could also be argued that previously available perceptual detail, which prevented the FAs at 1d, has been lost over time, while coarse semantic information was still available at 28d. Instead of a semantic transformation, our findings would then rather suggest forgetting of identifiable detail. This detail could pertain to the perceptual domain or to the semantic domain. In other words, both semantic and perceptual information could be encoded during initial encoding but then being forgotten at different rates over time. Interestingly, however, our finding that semantically related items induce significantly higher FAs

compared to both unrelated lures and perceptually related lures indicates that memories are, regardless of temporal delay, mostly stored in a semantic rather than in a perceptual form.

The proposed memory transformation over time has been linked to a time-dependent neural reorganization of memories. According to the classic systems consolidation theory, the hippocampal involvement in memory should decrease as memories become more and more reliant on neocortical areas over time[12,40]. While the Trace-Transformation-Theory does also assume an increased involvement of neocortical areas, in particular for transformed memories, specific memories are thought to remain hippocampus dependent[16,17]. In line with both of these theories, we obtained pattern representations that were highly specific to encoded events in the (anterior) hippocampus when the retention interval was short (i.e. 1d) and that these specific representations decreased over time, as did participants' memory specificity. In parallel, neocortical patterns emerged as the time interval after encoding increased, in particular in the vmPFC, angular gyrus and precuneus, which have been previously associated with long-term memory storage[2,4,5,8,11–15]. Notably, while we show here a time-dependent increase in the involvement of these areas, there is also recent evidence that the recruitment of parietal storage sites may be accelerated as a function of the number of retrieval attempts[14,15]. Most importantly, however, our model-based RSA data revealed that the neocortical representations that emerged over time, coded the semantic gist of the originally encoded event, again, in line with the Trace-Transformation-Theory[16,17], while we found no credible evidence for a coding of the perceptual gist.

Whereas it is commonly assumed that the time-dependent neural reorganization of memory involves a reduced hippocampal and increased neocortical contribution[14,15], there is initial evidence that there may be also a time-dependent reorganization within the hippocampus, along its anterior-posterior axis[19,33,36,41,42]. In line with this view, we report here that while pattern representations that were specific to encoded events in the anterior hippocampus decreased over time, as indicated by a time-dependent decrease in the anterior hippocampal fit to the 'old items are distinct from all lures' model, posterior hippocampal memory reinstatement (i.e. ERS) increased with time. The exact functional differentiation of the anterior and posterior portions of the hippocampus is still a matter of debate. For example, a recent theoretical account suggests the exact opposite course of memory transformation along the hippocampal long axis[16,43–45]. This account was originally based on rodent data[46] showing that firing fields of place cells in the ventral hippocampus, corresponding to the human anterior hippocampus[47], are larger than those in the dorsal hippocampus, which might translate into more abstract, large-scale anterior hippocampal representations. It is further argued that through an increased connectivity of the anterior hippocampus to prefrontal areas and of the posterior hippocampus to the posterior neocortex, both hippocampal poles might be specifically prone to represent semantic or perceptually detailed memories, respectively. However, it has been shown that rodents' ventral hippocampal cell population allows decoding the precise location, despite each individual cell only representing a larger area of the environment[48], which points to a mnemonic specificity of anterior hippocampal representations. Moreover, recent research[14,15] has revealed that the role of posterior neocortical areas connected to the posterior hippocampus, such as the precuneus and angular gyrus[49], in memory goes far beyond the mere processing of perceptual information and, instead, represent long-term memory storage sites. This is also in line with the present model-based analyses indicating that these parietal areas might represent the semantic gist of a memory, while we obtained no credible evidence for the representation of perceptual details. Moreover, our results suggest that perceptual memory features are represented in the anterior hippocampus and that those representations decline over time. Our finding that the anterior hippocampus represents specific memories is further consistent with research implicating the anterior hippocampus with the recollection of contextual details[36], novelty detection[50], source memory specificity[42], constructing autobiographical memories[51] and detailed future event representations[52].

Although the increase in posterior hippocampal ERS over time and its direct association with our behavioral indicator of semantic transformation (i.e. FAs to semantically related lures) and the decrease in distinct representations of encoded stimuli in the anterior hippocampus over time supports the idea of a time-dependent transformation along the hippocampal anterior-posterior axis with detailed memory representations in the anterior hippocampus and remote, gist-like representations in the posterior hippocampus, it is important to note that we did not find reliable evidence for a decrease in the anterior hippocampal memory reinstatement over time. Moreover, our model-based RSA did not provide credible evidence that posterior hippocampal representations of encoded events increase in similarity to semantically related material. The absence of reliable evidence for an anterior hippocampal decrease over time or a time-dependent increase of a posterior hippocampal fit to the 'old and semantically related items are similar' model might be taken as support against the suggested differential memory transformation over time in anterior and posterior hippocampal areas. It is to be noted, however, that these seemingly discrepant findings may be owing to the different methodological approaches. Whereas the ERS measures a change in reinstatement of an individual memory at test, the model-based analysis is directed at representational changes for a specific item category at test, i.e. recognition processes that are either specific to old items (model 1), shared by semantically related (model 2) or perceptually related (model 3) lures. Thus, our pattern of results might point to distinct patterns of changes in anterior vs. posterior hippocampus. Elucidating the distinct contributions of anterior vs. posterior regions of the hippocampus to recent and remote memories remains a challenge for future research. Furthermore, it has to be noted that memory performance was overall high in the present study, in particular for the 1d-group, which did not allow an analysis of neural activity associated with FAs to specific types of lures. To enable an analysis focussed on incorrectly endorsed related material, future studies should thus consider increasing task difficulty, for instance by increasing the number of encoded items or extending the retention interval.

Notably, the time-dependent transformation of memories into semantically generalized representations was significantly impacted by the emotionality of the encoded material. Although emotionally negative items were more robust against forgetting over time compared to neutral memories—corroborating the well-known memory enhancement for emotionally arousing information[53,54]—there was also an increased FA rate to emotionally negative, semantically related lures, suggesting an increased semantic transformation over time for negative material (for perceptually related lures we did not find credible evidence for a similar effect). This pattern of results is generally well in line with previous research indicating that the memory-enhancing effect of emotional arousal is specific to central aspects of a memory and comes at the cost of its peripheral, emotionally less salient features[23,55]. In other words, emotional arousal may prioritize the storage of the most salient aspects of an experience, which are then particularly well retained in the long run. This process might reflect a 'better-safe-than-sorry' mechanism that is highly adaptive for emotionally arousing, potentially threatening experiences. At first glance, this increased memory semantization for emotional relative to neutral items might seem in conflict with recent rodent and human data showing that noradrenergic arousal after encoding may reverse the systems consolidation process and hence result in more specific memories in the long run[2,56]. These studies, however, increased noradrenergic arousal pharmacologically after encoding, whereas the arousal boosts in the present study were rather transient and occurred during the encoding of individual stimuli. Thus, in the present study,

arousal did not selectively affect memory consolidation but primarily encoding processes, including the attentional focus when processing stimuli. On the neural level, this increased semantization for emotional events over time were associated with a specific decrease in distinct representations of encoded events in the anterior hippocampus.

To conclude, our findings show that the transformation of memory over time is semantic in nature and that this time-dependent memory semantization is enhanced for emotionally negative events. For a potential perceptual transformation over time, we did not find any credible evidence. In the brain, this semantic transformation was not only linked to the emergence of semantically transformed representations in neocortical areas over time but also to time-dependent changes within the hippocampus, with highly specific pattern representations for encoded events in the anterior hippocampus that decreased over time while posterior hippocampal reinstatements were linked to the extent to which remote memories were semantically transformed. Those findings provide insights into a key aspect of memory, its evolution over time, and how episodic experiences may be abstracted into semantic knowledge structures.

Methods

Behavioral pilot study

To validate the semantic and perceptual relatedness of the stimulus set, we conducted a behavioral pilot study in a sample of 33 undergraduate students (24 females, 9 males; age: $M = 22.48$ years, SEM = 0.60 years). All participants gave informed consent and received course credit for participation. One participant did not finish the task due to discomfort during viewing the emotionally negative stimuli, resulting in a final sample of 32 participants (23 females, 9 males; age: $M = 22.53$ years, SEM = 0.62 years).

In this pilot study, participants were presented with 280 pictures of scenes, taken from the International Affective Picture System[57] and open internet platforms. Half of the pictures contained emotionally negative scenes or objects while the other half contained neutral contents. The pictures were divided into 70 sets of four stimuli each: (1) the original picture (i.e. the old item in the main study), (2) one picture containing the semantic gist of this original picture, (3) one picture containing a different gist, while being perceptually related to the original picture; and (4) one unrelated picture, i.e. neither perceptually nor semantically related to the original item. The four pictures belonging to a set were matched to a respective old item in terms of subjectively perceived visual complexity, the depiction of people or animals by the first author and another independent rater. All unrelated (and perceptually related) images carried a different semantic gist than all other images, i.e. if one original image carried the semantic gist 'rental bikes' no other lure (or old item) besides the corresponding semantically related lure depicted rental bikes.

During the pilot study, each original picture was presented once next to its corresponding semantically related, perceptually related or unrelated counterpart using PsychoPy2 (v1.90.1)[58]. Participants rated the semantic and perceptual similarity of each picture pair via mouse-click on a 10-point Likert-Scale from 0 ('not related') to 10 ('very related'). Participants either rated first the semantic and subsequently the perceptual relatedness of a picture pair or vice versa, with the order of rating scales being counterbalanced across participants. Which side of the screen the comparison picture was presented on as well as the presentation order of image pairs, was randomized. Prior to the task, participants conducted two practice trials: one with a semantically related picture pair and one with a perceptually related pair. Participants were instructed to focus exclusively on visual features, e.g. shapes and colors of the pictures, when rating the perceptual relatedness of a picture pair. Accordingly, they were asked to consider only content-related aspects when rating the semantic relatedness of a picture pair and were further informed that it might help to think of a short title representing the gist of each picture. Participants were instructed to look thoroughly at each picture before responding. The duration of each of the 210 trials was self-paced.

For the main study, we aimed at a final sample of 30 stimulus sets per emotionality category (neutral vs. negative). Based on the results of the pilot study, we therefore excluded 10 stimulus sets for which participants' ratings indicated that semantically and perceptually related pictures were not sufficiently distinct on the respective relatedness dimensions. In the resulting final stimulus sets, semantically related pictures were rated as being significantly more semantically related to the original picture (M = 9.38, SEM = 0.08) than both perceptually related (M = 2.38, SEM = 0.18; paired t-test $t(31) = 33.24$, $p = 8e{-}14$, $d = 5.64$, 95% Confidence Interval = [5.31, 5.97]) and unrelated pictures ($M = 1.97$, SEM = 0.22; paired t-test: $t(31) = -29.63$, $p = 8e{-}14$, $d = -4.84$, 95% Confidence Interval = [−5.16, −4.52]; main effect lure type for semantic relatedness: $F(1.59, 49.35) = 794.01$, $p = 3e{-}36$, $\eta_p^2 = 0.96$, 95% Confidence Interval: [0.95, 0.98]). Moreover, perceptually related items were rated as being significantly more perceptually related ($M = 7.22$, SEM = 0.14) to original pictures than both semantically related items (M = 5.66, SEM = 0.24; paired t-test: $t(31) = -6.32$, $p = 1e{-}06$, $d = -1.10$, 95% Confidence Interval = [−1.44, −0.76]) and unrelated items ($M = 2.05$, SEM = 0.20; paired t-test: $t(31) = -14.91$, $p = 3e{-}15$, $d = -2.57$, 95% Confidence Interval = [−2.91, −2.23]; main effect lure type for perceptual relatedness: $F(1.70, 52.68) = 284.85$, $p = 2e{-}27$, $\eta_p^2 = 0.90$, 95% Confidence Interval: [0.86, 0.94]). See Supplementary Fig. 1 for an overview of the relatedness ratings for the different stimulus categories in this pilot study.

Main study

Participants and design. Fifty-five healthy volunteers (28 males, 27 females, age: $M = 24.22$ years, SEM = 0.54 years) participated in this experiment. Exclusion criteria were checked in a standardized interview and comprised a history of any psychiatric or neurological diseases, medication intake or drug abuse, as well as any contraindications for MRI measurements. All participants provided informed consent before taking part in the experiment and received a monetary compensation for participation (70€ or 75€, depending on whether fMRI measurements were conducted within a 1d or a 28d time frame). This study is part of a larger project investigating modulators of time-dependent systems consolidation and memory-transformation processes. The study protocol was approved by the ethics committee of the Medical Chamber Hamburg (PV5480) and was in accordance with the declaration of Helsinki. Three participants had to be excluded from the analysis because of technical failure ($n = 1$ participant) or falling asleep during at least one of the MRI sessions ($n = 2$ participants), resulting in a final sample of 52 right-handed young adults (26 females, 26 males, age: $M = 24.29$ years, SEM = 0.55 years). Participants were pseudo-randomly assigned to the 1d or 28d group (13 females and 13 males per group). The investigators were not blinded to allocation during experiments and outcome assessment. The final sample size is in line with previous fMRI studies on time-dependent memory-transformation processes[4,19] and a sensitivity analysis using MorePower 6.0.4[59] confirmed that this sample size is sufficient to detect a medium-sized effect ($\eta_p^2 > 0.09$) for our primary behavioral effect of interest reflected in a 2 (delay) × 3 (lure type) × 2 (emotion) mixed ANOVA with a power of 0.80 ($\alpha = 0.05$).

Experimental procedure. Testing took place on three days: Day 1—encoding, Day 2—recognition testing, and Day 3—relatedness rating. We collected MRI data during experimental Day 1 and Day 2. Critically, in order to assess time-dependent changes in memory, the delay between encoding and memory testing was either 1d or 28d. All testing took place in the afternoon (between 1 and 6 pm).

Memory encoding (Day 1): After providing informed consent, participants completed the Trier Inventory for the Assessment of Chronic Stress (TICS)[60], the Beck Depression Inventory (BDI-II)[61] and

the State-Trait Anxiety Inventory (STAI)[62]. At the beginning of the second experimental day (either 1d or 28d after Day 1), participants also filled out the Pittsburgh Sleep Quality Index (PSQI)[63] extended by questions regarding the duration and quality of sleep in the last 24 h. We obtained no statistically significant difference between groups in any of these parameters (all $p > 0.180$; see Supplementary Table 18). Afterwards, participants performed three encoding runs in the MRI scanner. In each run, participants encoded the same 60 pictures (30 emotionally neutral, 30 negative) presented in random order using MATLAB (The Mathworks, Inc, Natick, US) Version 2016b with the Psychophysics Toolbox 3 extensions[64], i.e. each picture was presented once in each of the three encoding sessions. On each trial, a picture was presented for 3 s followed by a jittered fixation period of 4 ± 1 s. Participants were instructed to memorize the presented pictures and informed that there will be a subsequent memory test immediately afterwards. To make sure that participants remained fully attentive throughout the encoding task, they were instructed to press a button as soon as the fixation-cross appeared on the screen. Immediately after the encoding task, participants completed a free recall task outside the MRI scanner. Here, participants had 15 min to recall as many stimuli in as much detail as possible, while an experimenter ticked off the correct stimuli from a list.

Memory testing (Day 2): Depending on the experimental condition, participants returned to the lab either 1d or 28d after Day 1. On this second experimental day, participants performed a recognition task in the MRI scanner, which was separated into three consecutive runs. During the recognition test, participants saw the 60 pictures that were presented on Day 1 ('old') and 60 pictures that were new but semantically related to the old pictures, 60 pictures that were perceptually related to the old pictures and 60 pictures that were neither perceptually nor semantically related to the old pictures. Immediately after a picture was presented for 3 s, participants were requested to indicate via button press whether the shown picture had been presented on Day 1 or not, using a four-point scale ('definitely new', 'rather new', 'rather old', 'definitely old'). Between trials, a jittered fixation cross was presented for 4 s ± 1 s. Finally, the participants rated all pictures with respect to picture-valence and -arousal on a scale from 0 ('very negative'/'not arousing') to 10 ('very positive'/'very arousing'). In retrospect, these data confirmed that negative pictures ($M = 2.56$, SEM = 0.09) were perceived as significantly more negative than neutral ones ($M = 5.65$, SEM = 0.14; paired t-test: $t(51) = 14.94$, $p = 3e{-}20$, $d = -3.65$, 95% Confidence Interval = [−4.28, −3.02]). Furthermore, negative pictures ($M = 5.37$, SEM = 0.17) were associated with significantly higher subjective arousal than neutral ones ($M = 2.59$, SEM = 0.21; paired t-test: $t(51) = -15.55$, $p = 5e{-}21$, $d = 2.03$, 95% Confidence Interval = [1.55, 2.50]).

Relatedness Rating (Day 3): Participants returned to the lab for a last, behavioral task after at least three and a maximum of eight days after experimental Day 2 ($M = 4.17$d, SEM = 0.18d; without a statistically significant difference between groups regarding the delay between experimental Day 2 and Day 3; two-sample t-test: $t(43.13) = 0.99$, $p = 0.329$, $d = -0.28$, 95% Confidence Interval = [−0.82, 0.27]). In this final task, participants rated the semantic and perceptual relatedness of the 60 encoded pictures to each of its perceptually related, semantically related or unrelated lure on a scale reaching from 0 ('not related) to 10 ('very related'). This task was identical to the behavioral validation task (see the pilot study above), comprising the 240 pictures of the recognition task presented using MATLAB (The Mathworks, Inc, Natick, US) Version 2016b with the Psychophysics Toolbox 3 extensions[64].

Behavioral data analysis. To control for attentiveness during encoding on Day 1, the number of missed responses to the fixation cross was analyzed by means of a mixed ANOVA with the between-subjects factor delay (1d vs. 28d) and the within-subject factor run (run 1 vs. run 2 vs. run 3). To control for potential group differences in immediate memory, free recall performance right after encoding was analyzed by means of a mixed ANOVA with the between-subjects factor delay (1d vs. 28d) and the within-subject factor emotion (neutral vs. negative).

To assess the overall performance in the recognition test, we subjected the percentage of hits to a mixed ANOVA with delay (1d vs. 28d) as between-subjects factor and the within-subject factor emotion (neutral vs. negative). In order to assess the specificity of memory, the key question of this study, we further analyzed the percentages of FAs for each lure type by means of a mixed ANOVA with the between-subjects factor delay (1d vs. 28d) and the within-subject factors lure type (semantically related vs. perceptually related vs. unrelated) and emotion (neutral vs. negative). To further test for potential differences in the confidence in those FAs, we multiplied each FA by its level of confidence (1 = 'rather old', 2 = 'definitely old') before subjecting the FA rate to another mixed ANOVA with the factors delay, lure type and emotion. Moreover, we analyzed the confidence in FAs for each lure type by means of binomial generalized LMMs with delay (1d vs. 28d), emotion (neutral vs. negative) and their interaction as fixed effects and the random intercept of participants and stimuli.

We further assessed changes in memory quality for each encoded item by considering the response pattern over each related stimulus set, i.e. containing the original stimulus and its corresponding perceptually related and semantically related lure[19]. To this end, we assigned memories to one of four categories: (1) detailed memories, for which participants rated old pictures as 'old' and all other pictures of a set as 'new', (2) semantically transformed memories, for which participants endorsed the semantically related picture, but not the perceptually related picture, as 'old' (irrespective of the response to the old picture), (3) perceptually transformed memories, for which participants endorsed the perceptually related lure as 'old' while classifying the semantically related lure as 'new', and (4) forgotten sets, for which participants missed the old picture and correctly rejected both semantically and perceptually related pictures. The occurrence of each specificity category was analyzed by means of binomial generalized LMMs with a logit function, i.e. logistic mixed models, with delay (1d vs. 28d), emotion (neutral vs. negative) and their interaction as fixed effects and the random intercept of participants and stimulus sets.

The individual stimulus relatedness ratings on Day 3 further allowed us to analyze FAs by means of a binomial generalized LMM with a logit function and the factor delay (1d vs. 28d), emotion (neutral vs. negative), semantic relatedness, perceptual relatedness and their interactions as fixed effects and the random intercept of participants and stimuli. As our main effect of interest contained a cross-level interaction requiring unbiased estimates of the Level-1 association[65], our continuous level-1 predictors (semantic and perceptual relatedness ratings) were group mean-centered prior to fitting the generalized LMM. Note that results did not change when these predictors were grand mean-centered.

All statistical analyses were performed with R Version 4.0.2 (https://www.r-project.org/). All reported p-values are two-tailed. In case of violated sphericity, as indicated by Mauchly's test, results of ANOVA-models are reported with Greenhouse-Geisser corrected degrees of freedom and p-values. Results of all main analyses were tested on distortions due to extreme outliers, defined as data points with a standard deviation ± 3 SD of the mean of the interesting condition. Note that if not stated otherwise, results did not change after excluding outliers. Post-hoc tests were conducted using t-tests, z-tests and interaction contrasts, i.e. contrasts between contrasts, by comparing estimated marginal means of each ANOVA-model or (generalized) LMM, with Šidák correction for multiple comparisons, using the R-package emmeans Version 1.7.2[66]. For ANOVAs and LMMs, Satterthwaite's approximation method was applied to calculate degrees of freedom for post-hoc t-tests. For all generalized LMMs and

corresponding post-hoc *z*-tests, *p*-values were computed using Wald *z*-distribution approximation, which does not rely on the specification of degrees of freedom. LMMs were fitted with Restricted Maximum Likelihood and the 'nloptwarp' optimizer. Generalized LMMs were fitted with Maximum Likelihood and the 'BOBYQA' optimizer. All (generalized) LMMs were estimated using the package lme4[67] Version 1.1. Results were visualized by utilizing bar plots and individual data points with the package ggplot2[68] Version 3.4.2 and plotting marginal effects of generalized LMMs with the package sjPlot[69] Version 2.8.12.

MRI acquisition. MRI data were acquired using a 3 T Prisma Scanner (Siemens, Germany) with a 64-channel head coil. Each MRI session consisted of three functional runs and a magnetic (B0) field map to unwarp the functional images (TR = 634 ms, TE_1 = 4.92 ms, TE_2 = 7.38 ms, 40 slices, voxel size = 2.9 × 2.9 × 3.0mm^3, FOV = 224 mm). For the functional scans, T2*-weighted echo planar imaging sequences were used to obtain 2 mm thick transversal slices (TR = 2000ms, TE = 30 ms, flip angle = 60°, FOV = 224). Additionally, a high-resolution T1 weighted anatomical image (TR = 2500 ms, TE = 2.12 ms, 256 slices, voxel size = 0.8 × 0.8 × 0.9 mm^3) was collected at the end of the MRI session of Day 2.

Preprocessing. All scans underwent the same preprocessing steps using SPM12 (Wellcome Trust Centre for Neuroimaging, London, UK). To allow for magnetic field (T1) equilibration, the first three functional scans were discarded. The images were first realigned and unwarped using the field maps, then coregistered to the structural image followed by a normalization to Montreal Neurological Institute (MNI) space, as implemented in SPM12 (IXI549Space). No smoothing was performed on the echoplanar imaging data that entered the GLM.

ROI definition. Anatomical masks for the aCC, precuneus, angular gyrus (left and right), the occipital pole and Heschl's gyrus (left and right) were derived from the Harvard-Oxford atlas using a probability threshold of 50%. For the IFG and vmPFC, a sphere with 20 mm radius was used that was centered on the peak voxel (x = −50, y = 16, z = 12) derived from 386 imaging studies reporting 'IFG' and on the peak voxel (x = −2, y = 46, z = −8) derived from 199 imaging studies reporting 'vmPFC', respectively, as determined by meta-analyses conducted on the neurosynth.org platform (status 02/06/2022). As we expected a time-dependent representational change along the hippocampal long axis, we used anatomical masks of the anterior and posterior hippocampus (left and right), which were derived using the WFU pick-atlas[70,71].

Quantification and statistical analysis. For our MRI data analysis, each trial of the encoding and recognition task was modeled as an individual regressor convolved with a hemodynamic response function along with six session-constants in one GLM per subject using SPM12. To increase the reliability by normalizing for noise[72], the resulting beta-values were transformed into *t*-statistics. Data were further subjected to RSAs[29] using custom scripts in MATLAB Version 2020b (The Mathworks, Inc, Natick, USA). Note that for our neural analyses, activation patterns of all trials of relevant item types were included. We opted for an analysis at the category level instead of relying on participants' correct or incorrect responses because (i) we were interested in how the encoding-retrieval delay and lure type affected the similarity between representational patterns as an indicator of the specificity of the neural representational patterns rather than the underlying neural patterns of a specific behavioral response; (ii) (multivariate) neural data are much more sensitive to fine-grained changes in memory representations compared to behavioral data that is merely based on dichotomous 'yes' vs. 'no' (i.e. 'old' vs. 'new') responses; (iii) reducing analyses on incorrectly endorsed lures (FAs) would have resulted in an insufficient number of trials for the fMRI analyses while (iv) focusing solely on correctly endorsed items (hits) would exclude items that are particularly low in memory specificity, which are of particular interest when investigating the neural underpinnings in memory transformation over time.

Model-based retrieval-similarity analysis. We analyzed time-dependent changes of representational similarities between the different stimulus-types at recognition testing by applying a model-comparison RSA[29,30,73]. This approach, i.e. comparing multivariate representational patterns of all experimental trials (irrespective of the correctness of the response) to conceptual models, allows inferences about the structure of neural representations[29,30,73] and has been successfully employed in previous studies to characterize memory representations, even at longer delays after encoding[19,74–77] and is thus highly suitable for investigating changes in memory quality over time.

Here, separately for both emotionality categories, each trial's activation pattern across voxels was correlated (Pearson's *r*) with the activation patterns of each other trial during memory testing. Next, we computed the mean pattern similarity for comparisons within each of the three runs and for each between-run combination (run 1 and run 2, run 2 and run 3 or run 3 and run 1). Those run-related pattern similarities where then subtracted from each correlation estimate of the corresponding run-combination to account for inflated correlations as a function of temporal proximity between scans[78,79]. In the resulting 120 × 120 RSMs, each combination of trials was placed in the respective cells, ordered by stimulus type (Fig. 4a, left panel). The resulting neural RSMs were compared to three theoretical model RSMs (Fig. 4a, right panel), each predicting different similarity patterns between the four stimulus categories at recognition testing: similar representations for old pictures that are distinct from patterns for all novel stimuli (model 1: 'old items are distinct from all lures'), similar representations between old items and semantically related lures which are distinct from perceptually related and unrelated lures (model 2: 'old and semantically related items are similar') and a model that expects similar representations between old items and perceptually related lures which are distinct from semantically related and unrelated lures (model 3: 'old and perceptually related items are similar'). Note that for all models we expected old items to be represented more similarly, as they should equally initiate recognition processes in neural areas relevant for specific (model 1) or transformed (model 2 and model 3) memory representations. We computed Spearman's rank correlation coefficient for each single-subject RSM and the conceptual models as we did not assume a direct linear match between the compared RSMs[29]. The resulting *rho*-values were further Fisher *z*-transformed and subjected to mixed ANOVAs with the factors delay (1d vs. 28d), emotion (neutral vs. negative) and a-priori model (1: 'old items are distinct from all lures' vs. 2: 'old and semantically related items are similar' and' vs. 3: 'old and perceptually related items are similar') in R. As we expected a time-dependent differentiation along the anterior-posterior hippocampal long axis, we additionally included the factor long axis (anterior vs. posterior) in the analysis regarding the hippocampus. For the neocortex, we predicted a comparable increase in semantically transformed memory representations (model 2) with increasing delay in each of our prefrontal (aCC, IFG, vmPFC) and parietal (precuneus, angular gyrus) long-term memory ROIs. We therefore first performed a mixed ANOVA with the between-subjects factor delay (1d vs. 28d) and the within-subject factors emotion (neutral vs. negative) and model RSM (model 1 vs. model 2 vs. model 3) using a combined mask that included all of these prefrontal and parietal ROIs. To confirm whether the resulting effect in model 2 was equally evident in the individual neocortical storage sites, we repeated this delay × emotion ANOVA with the neural RSM of each neocortical ROI. In case analyses were repeated for both hemispheres, resulting *p*-values were Bonferroni corrected (p_{corr}) to account for multiple comparisons.

Memory reinstatement analysis. Additionally, we assessed ERS as a measure of trial-specific memory reinstatement[20,32–37]. Due to the important role of the hippocampus in the reinstatement of episodic memories[38,39], we focused specifically on the hippocampus and the differentiation along its anterior-posterior axis in the analyses of ERS. We computed the similarity (Pearson's *r*) between activation patterns across all encoding runs as a reliable indicator of encoding-related activation patterns on experimental Day 1 and activation patterns of the same item during memory testing at Day 2 (see also[20]). Note that contrasting this ERS measure with ERS measures based on each individual encoding run, i.e. run 1, run 2, run 3, on a trial-by-trial level yielded a very similar pattern of results and no differences in anterior (all $p > 0.333$) nor posterior hippocampal ERS (all $p > 0.165$) between different ERS measures. Resulting correlation estimates were Fisher *z*-transformed before statistical analyses in R were conducted. First, time-dependent changes in item-specific hippocampal ERS were analyzed by means of trial-wise LMMs with the factors delay (1d vs. 28d), emotion (neutral vs. negative), long axis (anterior vs. posterior) and their interactions as fixed effects and the random intercept of participants and stimuli. As this analysis was repeated for both hemispheres, resulting *p*-values were Bonferroni corrected (p_{corr}) to account for multiple comparisons. Further, we followed up whether the observed delay-dependent increase in left posterior hippocampal ERS was associated with a decrease in specificity of the reinstated memories. To this end, we analyzed the occurrence of a FA for a semantically related or perceptually related lure by means of binomial generalized LMMs with emotion (neutral vs. negative), delay (1d vs. 28d), ERS and their interaction as fixed effects and the random intercept of participants and stimuli.

While ERS is computed by correlating pattern representations of individual items during encoding and memory test, i.e. 'old' items, we furthermore assessed the similarity elicited by perceptually or semantically related items at memory test and corresponding old items during encoding as a possible indicator for a reinstatement of the perceptual or semantic gist of the original memory. The resulting Fisher transformed *r*-values were again subjected to LMMs with delay (1d vs. 2d), emotion (neutral vs. negative), long axis (anterior vs. posterior) and their interaction as fixed effects and the random effects of subjects and stimuli. Furthermore, we explored delay-dependent changes in memory reinstatement, i.e. ERS, and reinstatement by related material in our neocortical long-term memory as well as sensory control ROIs by means of LMMs with the fixed effects of delay (1d vs 28d), emotion (neutral vs. negative) and their interactions.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

The behavioral and fMRI data generated in this study have been deposited in the Open Science Framework (OSF) (https://doi.org/10.17605/OSF.IO/W5MXR[80]). Raw and processed fMRI data are available at OSF. Raw behavioral data is available at OSF. The data that can be used to reproduce the figures and tables are provided in the Source Data file and at OSF. ROI masks used for fMRI analyses were derived from the Harvard-Oxford atlas as included in the FMRIB Software Library, (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSL) from the WFU pick-atlas[70,71] and from the neurosynth.org database. All ROIs adapted for this study are available at OSF. Source data are provided with this paper.

Code availability

Custom code used to model and analyze the data is available at Zenodo: https://doi.org/10.5281/zenodo.8363230[81] and integrated in the study's repository at OSF[80].

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Author contributions

L.S. and B.R. designed research; V.K. performed research; V.K., A.A. and T.S. analyzed data; V.K. and L.S. drafted and revised the manuscript; B.R., TS. and A.A. revised the manuscript.

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Supplementary Information

Time-dependent memory transformation in hippocampus and neocortex is semantic in nature

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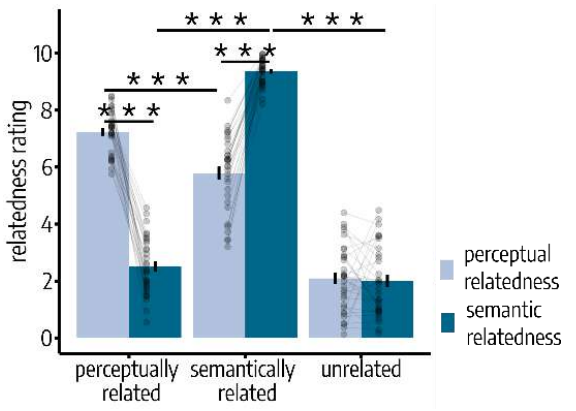
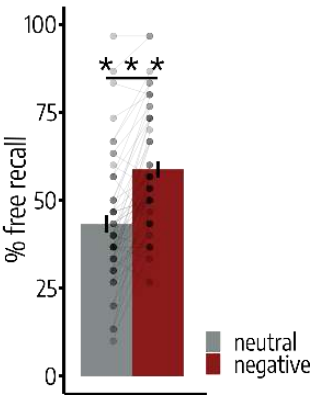
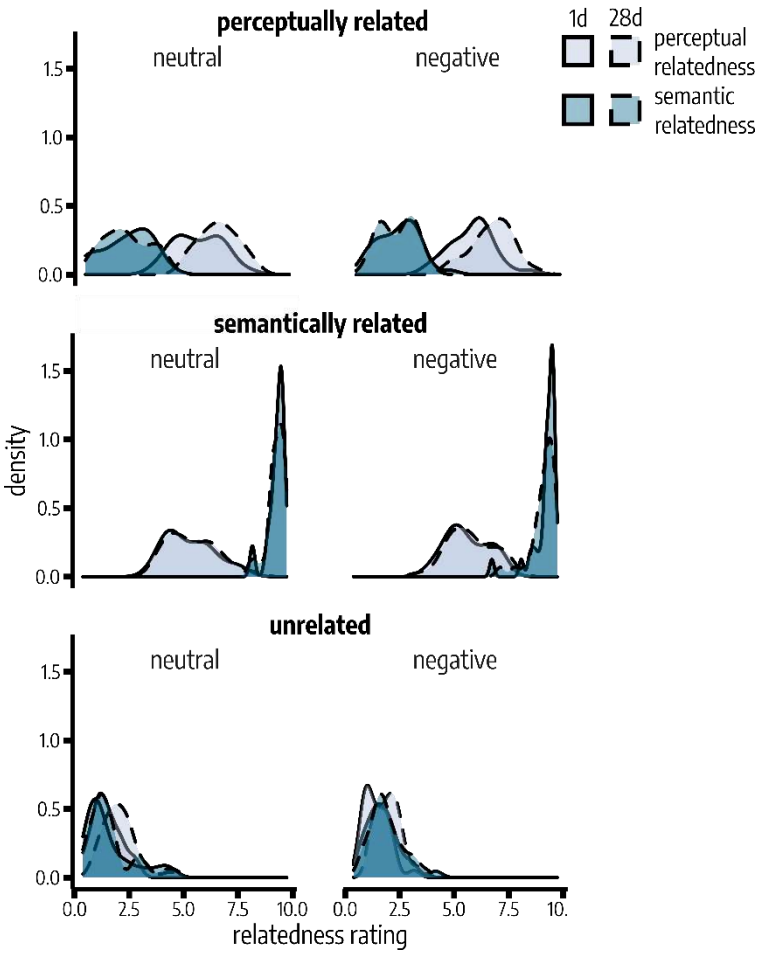
Supplementary Figures



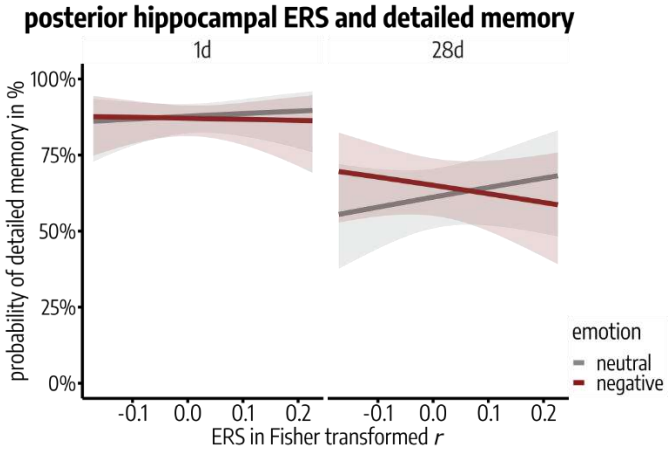
Supplementary Figure 1. **Results of the behavioral pilot.** Semantically related pictures were rated as being significantly more semantically related to the original picture (M = 9.38, SEM = 0.08) than both perceptually related (M = 2.38, SEM = 0.18; paired *t*-test $t(31) = 33.24$, $p = 8e\text{-}14$, $d = 5.64$, 95% Confidence Interval = [5.31, 5.97]) and unrelated pictures (M = 1.97, SEM = 0.22; paired *t*-test: $t(31) = -29.63$, $p = 8e\text{-}14$, $d = -4.84$, 95% Confidence Interval = [-5.16, -4.52]; main effect lure type for semantic relatedness: $F(1.59, 49.35) = 794.01$, $p = 3e\text{-}36$, $\eta_p^2 = 0.96$, 95% Confidence Interval: [0.95, 0.98]). Moreover, perceptually related items were rated as being significantly more perceptually related (M = 7.22, SEM = 0.14) to original pictures than both semantically related items (M = 5.66, SEM = 0.24; paired *t*-test: $t(31) = -6.32$, $p = 1e\text{-}06$, $d = -1.1$, 95% Confidence Interval = [-1.44, -0.76]) and unrelated items (M = 2.05, SEM = 0.20; paired *t*-test: $t(31) = -14.91$, $p = 3e\text{-}15$, $d = -2.57$, 95% Confidence Interval = [-2.91, -2.23]; main effect lure type for perceptual relatedness: $F(1.70, 52.68) = 284.85$, $p = 3e\text{-}36$, $\eta_p^2 = 0.90$, 95% Confidence Interval: [0.86, 0.94]). Bars represent mean ± SEM. Connected dots represent individual data points. All $n = 52$ participants. All post-hoc tests were applied on estimated marginal means with Šidák correction for multiple comparisons. All reported *p*-values are two-tailed. Source data are provided as Source Data file. ***$p<0.001$.



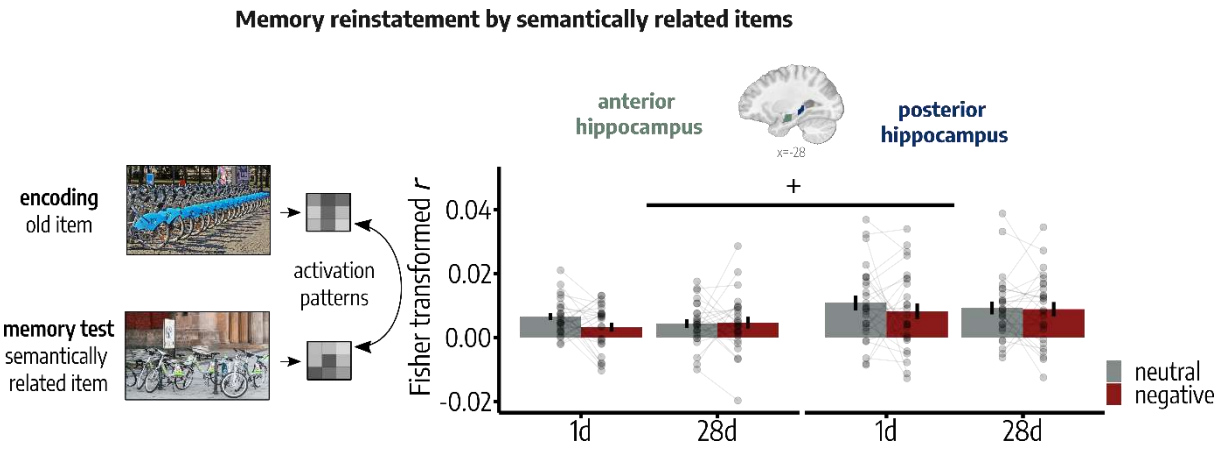
Supplementary Figure 2. **Emotional enhancement of immediate free recall.** Immediately after encoding, participants recalled significantly more often emotionally negative than neutral items (main effect emotion: $F(1, 50) = 69.33$, $p = 5e\text{-}11$, $\eta_p^2 = 0.58$, 95% Confidence Interval: [0.42, 0.72]). This analysis did not indicate a statistically significant difference between delay groups in immediate memory performance (main effect delay: $F(1, 50) = 0.17$, $p = 0.678$, $\eta_p^2 = 0.004$, 95% Confidence Interval: [2e-05, 0.11]; delay × emotion: $F(1, 50) = 1.13$, $p = 0.293$, $\eta_p^2 = 0.02$, 95% Confidence Interval: [6e-05, 0.16]; mixed ANOVA). Bars represent mean ± SEM. Connected dots represent individual data points. $N = 52$ participants. All reported p-values are two-tailed. Source data are provided as Source Data file. ***$p < 0.001$.



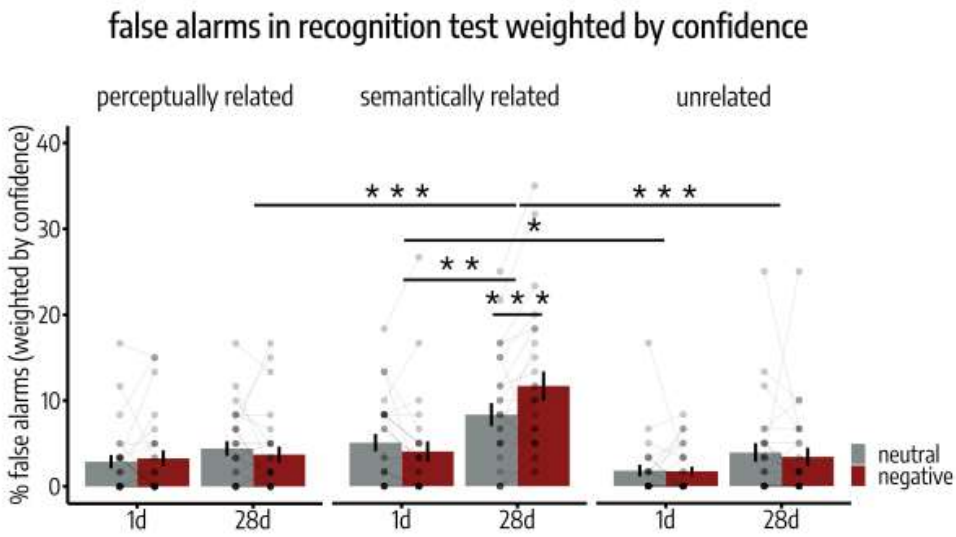
Supplementary Figure 3. **Distribution of semantic and perceptual relatedness ratings on Day 3, separately for each emotion, lure type and delay group.** Perceptually related lures were rated as significantly higher in perceptual than in semantic relatedness to their corresponding old image (paired *t*-test: *t*(51) 16.67, *p* = 3*e*-22, *d* = 3.25, 95% Confidence Interval = [2.66, 3.83]), while semantically related items were rated as significantly more semantically than perceptually related to their corresponding old image (paired *t*-test: *t*(51) = -16.38, *p* = 6*e*-22, *d* = -2.83, 95% Confidence Interval = [-3.37, -2.28]). Unrelated images were rated low in perceptual (M = 1.74, SEM = 0.17) as well as semantic relatedness (M = 1.72, SEM = 0.16) without a significant difference between rating scales *t*(51) = -0.16, p = 0.872, *d* = -0.02, 95% Confidence Interval = [-0.4, 0.37]. *N* = 52 participants. All reported *p*-values are two-tailed. Source data are provided as Source Data file.



Supplementary Figure 4. **Posterior hippocampal Encoding-Retrieval-Similarity (ERS) was not associated with detailed memory representations.** Analyzing the probability of a detailed recognition (correct response for old items without false alarms for related items) by means of a binomial generalized linear mixed model with the factors left posterior hippocampal ERS, delay and emotion did not show a significant association of ERS with detailed memory (all $p > 0.688$; $n = 52$). Lines represent the predicted probability for a detailed memory with 95% Confidence Interval. All reported *p*-values are two-tailed. Source data are provided as Source Data file.



Supplementary Figure 5. **Hippocampal pattern similarities between original items at encoding and corresponding semantically related lures at memory test.** The posterior hippocampus tended to show a higher reinstatement of the semantic gist of the original memory compared to the anterior hippocampus (main effect long axis: $t(6124)= 1.94$, $p = 0.052$, $\beta = 0.004$, 95% Confidence Interval = [-4e-05, 0.01]; linear mixed model, LMM). No effect approached significance when analyzing hippocampal reinstatement of the perceptual gist (all $p > 0.235$; LMM). Bars represent mean ± SEM. Connected dots represent individual data points. $N = 52$ participants. All reported p-values are two-tailed. All depicted images are licensed under Creative Commons BY-SA License: image representing 'old' item is courtesy of W. Bulach (https://commons.wikimedia.org/wiki/File:00_2141_Bicycle-sharing_systems_-_Sweden.jpg; edited), image representing 'semantically related' item is courtesy of Matti Blume (https://commons.wikimedia.org/wiki/File:Bike_share_2019,_Berlin_(P1080139).jpg; edited). Regions of interest are visualized on a sagittal section of a T1-weighted template[1] in MNI-152 space. Source data are provided as Source Data file. $^{+}p < 0.060$.



Supplementary Figure 6. **Time dependent changes in false alarms weighted by confidence.** The increase in false alarms (FAs) from 1d to 28d after encoding was significantly higher for lures that were semantically related to the encoded pictures, compared to perceptually related (interaction contrast: $t(50) = -3.89$, $p = 0.001$, $d = -0.6$, 95% Confidence Interval = [-0.9, -0.3]) or unrelated lures (interaction $t(50) = -2.61$, $p = 0.035$, $d = -0.48$, 95% Confidence Interval = [-0.83, -0.12]; delay × lure type: $F(1.50, 75.19) = 8.83$, $p = 0.001$, $\eta_p^2 = 0.15$, 95% Confidence Interval: [0.04, 0.32]; main effect lure type: $F(1.50, 75.19) = 37.45$, $p = 3e\text{-}10$, $\eta_p^2 = 0.43$, 95% Confidence Interval: [0.28, 0.58]). This semantization of memories over time was significantly higher for emotionally negative compared to neutral items (delay × lure type × emotion: $F(1.96, 98.12) = 5.57$, $p = 0.005$, $\eta_p^2 = 0.10$, 95% Confidence Interval: [0.02, 0.24]; mixed ANOVA). Bars represent mean ± SEM. Connected dots represent individual data points. $N = 52$ participants. All reported p-values are two-tailed. Source data are provided as Source Data file. ***$p < 0.001$; **$p < 0.010$; *$p < 0.050$.

Supplementary Tables

Supplementary Table 1. **Responses on Day 2 for each of the 30 stimuli per emotion and item category.**

	1d		28d	
response category	**neutral**	**negative**	**neutral**	**negative**
old				
hit	27.73 (0.52)	27.38 (0.43)	21.69 (1.13)	23.65 (0.93)
miss	2.12 (0.50)	2.24 (0.41)	8.19 (1.11)	6.12 (0.89)
no response	0.15 (0.07)	0.19 (0.08)	0.12 (0.12)	0.23 (0.16)
perceptually related				
correct rejection	28.69 (0.34)	28.54 (0.37)	27.88 (0.39)	27.85 (0.50)
false alarm	1.31 (0.34)	1.38 (0.37)	2.00 (0.36)	1.85 (0.42)
no response	-	0.08 (0.08)	0.12 (0.12)	0.31 (0.17)
semantically related				
correct rejection	27.69 (0.46)	28.27 (0.49)	26.00 (0.62)	24.96 (0.62)
false alarm	2.27 (0.45)	1.73 (0.49)	3.85 (0.59)	4.92 (0.62)
no response	0.04 (0.04)	-	0.15 (0.09)	0.12 (0.08)
unrelated				
correct rejection	29.15 (0.26)	29.15 (0.26)	27.92 (1.88)	28.35 (0.43)
false alarm	0.77 (0.24)	0.81 (0.27)	1.88 (9.50)	1.54 (0.40)
no response	0.08 (0.05)	0.04 (0.04)	0.19 (0.10)	0.12 (0.06)

Data represents mean (SEM). Source data are provided as Source Data file.

Supplementary Table 2. **Analyses of confidence in false alarms for each lure type.**

parameters for generalized linear mixed models				
semantically related lures				
fixed effects	*z*	*p*	*β*	95% CI
intercept	-2.21	0.027	-0.76	-1.43, -0.09
delay	-0.66	0.506	-0.28	-1.12, 0.55
emotion	0.35	0.725	0.16	-0.75, 1.07
delay × emotion	0.75	0.455	0.41	-0.66, 1.47
random effects	variance	SD	*n*	
participant (intercept)	0.31	0.55	46	
stimulus (intercept)	0.15	0.39	58	
marginal R^2 / conditional R^2: 0.01 / 0.13				
perceptually related lures				
fixed effects	*z*	*p*	*β*	95% CI
intercept	-1.77	0.077	-0.93	-1.95, 0.1
delay	-0.22	0.828	-0.14	-1.41, 1.13
emotion	0.68	0.497	0.42	-0.79, 1.62
delay × emotion	-1.51	0.131	-1.21	-2.79, 0.36
random effects	variance	SD	*n*	
participant (intercept)	0.9	0.95	39	
stimulus (intercept)	0.25	0.50	50	
marginal R^2 / conditional R^2: 0.05 / 0.3				
unrelated lures				
fixed effects	*z*	*p*	*β*	95% CI
intercept	-1.08	0.28	-0.85	-2.4, 0.69
delay	-0.76	0.449	-0.73	-2.63, 1.16
emotion	-0.16	0.873	-0.15	-1.96, 1.67
delay × emotion	0.26	0.792	0.29	-1.87, 2.46
random effects	variance	SD	*n*	
participant (intercept)	2.31	1.52	31	
marginal R^2 / conditional R^2: 0.01 / 0.42				

Note that all models were fitted on the whole data set (52 participants and 60 lures). Any discrepancies in *n* are due to an insufficient number of cases (false alarms) in a specific condition. Source data are provided as Source Data file.

Supplementary Table 3. **Average number of stimulus sets that were perceptually transformed, semantically transformed, detailed or entirely forgotten on Day 2, separately for each emotionality and delay group.**

	1d		28d	
specificity category	**neutral**	**negative**	**neutral**	**negative**
perceptually transformed	1.04 (0.27)	1.19 (0.31)	1.35 (0.28)	1.08 (0.27)
semantically transformed	2.00 (0.40)	1.54 (0.41)	3.15 (0.47)	4.15 (0.47)
forgotten	1.58 (0.29)	2.15 (0.40)	6.85 (0.95)	5.08 (0.81)
detailed	24.96 (0.87)	24.65 (0.80)	17.69 (0.95)	18.38 (1.18)

Data represents mean (SEM) number of stimulus sets per category. Source data are provided as Source Data file.

Supplementary Table 4. **Analyses of the probability for a detailed, forgotten, semantically or perceptually transformed stimulus on Day 2.**

parameters for generalized linear mixed models				
detailed				
fixed effects	*z*	*p*	*β*	95% CI
intercept	8.69	4*e*-18	1.97	1.53, 2.42
delay	-5.29	1*e*-07	-1.51	-2.07, -0.95
emotion	-0.35	0.723	-0.07	-0.44, 0.31
delay × emotion	1.13	0.258	0.21	-0.15, 0.57
random effects	variance	SD	*n*	
participant (intercept)	0.81	0.9	52	
stimulus set (intercept)	0.23	0.48	60	
marginal R^2 / conditional R^2: 0.10 / 0.32				
forgotten				
fixed effects	*z*	*p*	*β*	95% CI
intercept	-12.31	8*e*-35	-3.26	-3.78, -2.74
delay	5.75	9*e*-09	1.79	1.18, 2.41
emotion	1.22	0.223	0.31	-0.19, 0.82
delay × emotion	-3.00	0.003	-0.75	-1.25, -0.26
random effects	variance	SD	*n*	
participant (intercept)	0.78	0.88	52	
stimulus set (intercept)	0.31	0.56	60	
marginal R^2 / conditional R^2: 0.11 / 0.33				
semantically transformed				
fixed effects	*z*	*p*	*β*	95% CI
intercept	-11.78	5*e*-32	-3.12	-3.64, -2.6
delay	2.17	0.03	0.64	0.06, 1.22
emotion	-1.2	0.23	-0.35	-0.92, 0.22
delay × emotion	2.46	0.014	0.66	0.14, 1.19
random effects	variance	SD	*n*	
participant (intercept)	0.63	0.79	52	
stimulus set (intercept)	0.52	0.72	60	
marginal R^2 / conditional R^2: 0.06 / 0.3				
perceptually transformed				
fixed effects	*z*	*p*	*β*	95% CI
intercept	-11.18	5*e*-29	-4.19	-4.93, -3.46
delay	1.02	0.308	0.42	-0.38, 1.22
emotion	0.61	0.542	0.23	-0.51, 0.97
delay × emotion	-1.05	0.294	-0.41	-1.18, 0.36
random effects	variance	SD	*n*	
participant (intercept)	1.00	1.00	52	
stimulus set (intercept)	0.79	0.89	60	
marginal R^2 / conditional R^2: 0.004 / 0.35				

Source data are provided as Source Data file.

Supplementary Table 5. **Relatedness ratings on Day 3.**

lure type	1d		28d	
	perceptual relatedness	**semantic relatedness**	**perceptual relatedness**	**semantic relatedness**
perceptually related				
neutral	5.56 (0.32)	2.32 (0.22)	6.48 (0.25)	2.27 (0.25)
negative	5.71 (0.34)	2.34 (0.22)	6.63 (0.23)	2.28 (0.26)
semantically related				
neutral	5.27 (0.33)	9.27 (0.12)	5.37 (0.27)	9.25 (0.17)
negative	5.60 (0.31)	9.19 (0.11)	5.76 (0.25)	9.11 (0.17)
unrelated				
neutral	1.47 (0.22)	1.57 (0.20)	2.05 (0.27)	1.65 (0.22)
negative	1.43 (0.23)	1.77 (0.26)	1.99 (0.25)	1.88 (0.26)

Data represents mean (SEM). Source data are provided as Source Data file.

Supplementary Table 6. **Analysis of false alarms depending on individual rating of semantic and perceptual relatedness between encoded items and lures.**

parameters for generalized linear mixed				
fixed effects	*z*	*p*	*β*	95% CI
intercept	-14.13	3*e*-45	-3.95	-4.50, -3.40
delay	2.40	0.016	0.85	0.16, 1.55
semantic rel.	2.04	0.041	0.07	0.003, 0.13
perceptual rel.	0.78	0.435	0.03	-0.05, 0.11
emotion	0.05	0.964	0.009	-0.39, 0.41
delay × semantic rel.	-0.69	0.490	-0.02	-0.09, 0.04
delay × perceptual rel.	0.45	0.651	0.02	-0.07, 0.12
semantic rel. × perceptual rel.	0.61	0.539	0.006	-0.01, 0.02
delay × emotion	0.16	0.870	0.03	-0.36, 0.42
semantic rel. × emotion	-0.48	0.629	-0.02	-0.11, 0.07
perceptual rel. × emotion	-0.25	0.799	-0.01	-0.13, 0.10
delay × semantic rel. × perceptual rel.	1.52	0.128	0.02	-0.005, 0.04
delay × semantic rel. × emotion	2.36	0.018	0.12	0.02, 0.21
delay × perceptual rel. × emotion	-0.01	0.991	-7*e*-04	-0.13, 0.13
semantic rel. × perceptual rel. × emotion	-0.92	0.360	-0.01	-0.04, 0.01
delay × semantic rel. × perceptual rel. × emotion	0.07	0.940	0.001	-0.03, 0.03
random effects	variance	SD	*n*	
participant (intercept)	1.28	1.13	52	
stimulus (intercept)	0.64	0.80	180	
marginal R^2 / conditional R^2: 0.07 / 0.41				

Source data are provided as Source Data file. Semantic rel. = group mean centered semantic relatedness rating between a lure and its corresponding original stimulus; perceptual rel. = group mean centered perceptual relatedness rating between a lure and its corresponding original stimulus.

Supplementary Table 7. **Analysis of false alarms for semantically related lures depending on the level of perceptual relatedness to their corresponding original item.**

parameters for generalized linear mixed model				
fixed effects	*z*	*p*	*β*	95% CI
intercept	-9.81	1*e*-22	-3.16	-3.8, -2.53
perceptual rel. level	0.71	0.476	0.21	-0.37, 0.8
delay	1.23	0.218	0.49	-0.29, 1.26
emotion	-1.05	0.291	-0.41	-1.17, 0.35
perceptual rel. level × delay	1.24	0.215	0.47	-0.28, 1.22
perceptual rel. level × emotion	0.13	0.898	0.06	-0.81, 0.92
delay × emotion	2.19	0.029	0.93	0.1, 1.76
perceptual rel. level × delay × emotion	-0.86	0.392	-0.46	-1.51, 0.59
random effects	variance	SD	*n*	
participant (intercept)	0.87	0.93	52	
stimulus (intercept)	0.45	0.67	60	
marginal R^2 / conditional R^2: 0.07 / 0.34				

Perceptual relatedness (perceptual rel. level) level represents low (≤ 5) vs. high (> 5) rating in perceptual relatedness of a semantically related stimulus to its corresponding lure. Source data are provided as Source Data file.

Supplementary Table 8. **Analysis of delay-dependent changes in the anterior-posterior axis in Encoding-Retrieval-Similarity.**

parameters for linear mixed model				
fixed effects	*t* (df)	p_{corr}	*β*	95% CI
intercept	2.68 (279.33)	0.016	0.005	0.001, 0.01
delay	-1.31 (352.02)	0.381	-0.003	-0.01, 0.002
emotion	-1.53 (687.11)	0.253	-0.003	-0.01, 0.001
long axis	0.04 (6124)	1.931	1*e*-04	-0.004, 0.004
delay × emotion	1.78 (6124)	0.149	0.01	-0.001, 0.01
delay × long axis	2.35 (6124)	0.038	0.01	0.001, 0.01
emotion × long axis	1.47 (6124)	0.283	0.005	-0.002, 0.01
delay × emotion × long axis	-0.7 (6124)	0.974	-0.005	-0.01, 0.01
random effects	variance	SD	*n*	
participant (intercept)	1*e*-05	0.003	52	
stimulus set (intercept)	3*e*-06	0.002	60	
marginal R^2 / conditional R^2: 0.07 / 0.34				

Source data are provided as Source Data file. p_{corr} = Bonferroni corrected *p*-values.

Supplementary Table 9. **Analysis of delay-dependent changes in the anterior-posterior axis in Encoding-Retrieval-Similarity including only trials with correct recognition (hits).**

parameters for linear mixed model				
fixed effects	*t* (df)	p_{corr}	*β*	95% CI
intercept	2.66 (225.68)	0.017	0.005	0.001, 0.01
delay	-1.79 (332.73)	0.148	-0.005	-0.01, 4*e*-04
emotion	-1.63 (455.09)	0.209	-0.004	-0.01, 0.001
long axis	-0.41 (5107.81)	1.358	-0.001	-0.01, 0.004
delay × emotion	1.91 (5134.11)	0.112	0.01	-2*e*-04, 0.01
delay × long axis	3.13 (5107.81)	0.004	0.01	0.004, 0.02
emotion × long axis	1.62 (5107.81)	0.209	0.01	-0.001, 0.01
delay × emotion × long axis	-1.32 (5107.81)	0.372	-0.01	-0.02, 0.003
random effects	variance	SD	*n*	
participant (intercept)	2*e*-05	0.004	52	
stimulus set (intercept)	9*e*-06	0.003	60	
marginal R^2 / conditional R^2: 0.07 / 0.34				

Source data are provided as Source Data file. p_{corr} = Bonferroni corrected *p*-values.

Supplementary Table 10. **Analysis of association between left posterior hippocampal Encoding-Retrieval-Similarity (ERS) and correct recognition, i.e. hits.**

parameters for generalized linear mixed model				
fixed effects	*z*	*p*	*β*	95% CI
intercept	11.28	2*e*-29	3.03	2.51, 3.56
ERS	-1.61	0.108	-4.51	-10.02, 1.00
emotion	-0.44	0.662	-0.11	-0.61, 0.39
delay	-5.72	1*e*-08	-1.83	-2.46, -1.21
ERS × emotion	0.09	0.925	0.37	-7.34, 8.07
ERS × delay	2.18	0.030	7.31	0.73, 13.89
emotion × delay	2.71	0.007	0.65	0.18, 1.13
ERS × emotion × delay	-1.23	0.218	-5.81	-15.06, 3.43
random effects	variance	SD	*n*	
participant (intercept)	0.91	0.95	52	
stimulus set (intercept)	0.35	0.59	60	
marginal R^2 / conditional R^2: 0.12 / 0.36				

Source data are provided as Source Data file.

Supplementary Table 11. **Analysis of association between left posterior hippocampal Encoding-Retrieval-Similarity (ERS) and detailed memory performance.**

parameters for generalized linear mixed model				
fixed effects	*z*	*p*	*β*	95% CI
intercept	8.66	5*e*-18	1.97	1.52, 2.42
ERS	0.4	0.689	0.84	-3.26, 4.94
emotion	-0.32	0.747	-0.06	-0.44, 0.31
delay	-5.3	1*e*-07	-1.52	-2.08, -0.96
ERS × emotion	-0.38	0.705	-1.13	-7.01, 4.74
ERS × delay	0.2	0.845	0.53	-4.75, 5.8
emotion × delay	1.23	0.219	0.23	-0.14, 0.6
ERS × emotion × delay	-0.38	0.705	-1.44	-8.86, 5.99
random effects	variance	SD	*n*	
participant (intercept)	0.81	0.9	52	
stimulus set (intercept)	0.23	0.48	60	
marginal R^2 / conditional R^2: 0.1 / 0.32				

Source data are provided as Source Data file.

Supplementary Table 12. **Analyses of association between left posterior hippocampal Encoding-Retrieval-Similarity (ERS) and memory specificity, i.e. false alarms for semantically related and perceptually related lures.**

parameters for generalized linear mixed model				
semantically related lures				
fixed effects	*z*	*p*	*β*	95% CI
intercept	-10.88	1*e*-27	-3.08	-3.63, -2.52
ERS	-1.22	0.223	-3.41	-8.9, 2.08
emotion	-1.31	0.19	-0.37	-0.92, 0.18
delay	2.22	0.026	0.73	0.09, 1.38
ERS × emotion	1.01	0.312	4.44	-4.17, 13.04
ERS × delay	1.97	0.049	7.16	0.02, 14.29
emotion × delay	2.71	0.007	0.71	0.19, 1.22
ERS × emotion × delay	-1.45	0.146	-7.78	-18.26, 2.71
random effects	variance	SD	*n*	
participant (intercept)	0.91	0.95	52	
stimulus set (intercept)	0.5	0.71	60	
marginal R^2 / conditional R^2: 0.07 / 0.35				
perceptually related lures				
fixed effects	*z*	*p*	*β*	95% CI
intercept	-10.75	6*e*-27	-4.07	-4.81, -3.32
ERS	-1.33	0.184	-5.26	-13.02, 2.5
emotion	0.52	0.606	0.19	-0.53, 0.91
delay	1.51	0.132	0.63	-0.19, 1.44
ERS × emotion	-0.12	0.905	-0.66	-11.61, 10.29
ERS × delay	0.50	0.619	2.60	-7.64, 12.83
emotion × delay	-0.57	0.569	-0.20	-0.88, 0.48
ERS × emotion × delay	0.78	0.434	5.63	-8.46, 19.71
random effects	variance	SD	*n*	
participant (intercept)	1.26	1.12	52	
stimulus set (intercept)	0.84	0.92	60	
marginal R^2 / conditional R^2: 0.02 / 0.40				

Source data are provided as Source Data file.

Supplementary Table 13. **Analysis of association between left posterior hippocampal Encoding-Retrieval-Similarity (ERS) and response time during recognition testing.**

parameters for linear mixed model				
fixed effects	*t* (df)	*p*	*β*	95% CI
intercept	18.07 (61.17)	3*e*-26	525.53	468.51, 582.54
ERS	0.15 (3060.25)	0.883	33.81	-417.43, 485.05
delay	0.81 (58.82)	0.422	32.88	-46.75, 112.52
emotion	0.59 (176.09)	0.556	10.13	-23.52, 43.79
ERS × delay	-0.52 (3071.11)	0.603	-171.25	-816.75, 474.25
ERS × emotion	0.46 (3065.52)	0.644	151.79	-492.65, 796.23
delay × emotion	-1.32 (3007.11)	0.187	-29.77	-74.00, 14.46
ERS × delay × emotion	0.19 (3069.05)	0.851	86.27	-815.23, 987.78
random effects	variance	SD	*n*	
participant (intercept)	18177.38	134.82	52	
stimulus set (intercept)	670.65	25.9	60	
marginal R^2 / conditional R^2: 0.1 / 0.32				

Source data are provided as Source Data file.

Supplementary Table 14. **Analyses of delay-dependent changes in anterior-posterior hippocampal representational similarity between original items at encoding and corresponding related lures during recognition testing.**

parameters for linear mixed model				
semantically related lures				
fixed effects	*t* (df)	*p*	*β*	95% CI
intercept	3.61 (263)	0.0004	0.01	0.003, 0.01
delay	-0.85 (319.68)	0.396	-0.002	-0.01, 0.003
emotion	-1.44 (660.89)	0.151	-0.003	-0.01, 0.001
long axis	1.94 (6124)	0.052	0.004	-4*e*-05, 0.01
delay × emotion	1.13 (6124)	0.26	0.004	-0.003, 0.01
delay × long axis	0.16 (6124)	0.869	0.001	-0.01, 0.01
emotion × long axis	0.19 (6124)	0.848	0.001	-0.01, 0.01
delay × emotion × long axis	-0.28 (6124)	0.778	-0.001	-0.01, 0.01
random effects	variance	SD	*n*	
participant (intercept)	2*e*-05	0.004	52	
stimulus set (intercept)	4*e*-06	0.002	60	
marginal R^2 / conditional R^2: 0.1 / 0.32				
Perceptually related lures				
fixed effects	*t* (df)	*p*	*β*	95% CI
intercept	2.77 (401.67)	0.006	0.005	0.001, 0.01
delay	0.03 (401.67)	0.977	7*e*-05	-0.005, 0.005
emotion	0.08 (6182)	0.938	2*e*-04	-0.004, 0.005
long axis	1.14 (6182)	0.256	0.003	-0.002, 0.01
delay × emotion	-1.19 (6182)	0.236	-0.004	-0.01, 0.002
delay × long axis	0.53 (6182)	0.599	0.002	-0.005, 0.01
emotion × long axis	0.14 (6182)	0.89	4*e*-04	-0.01, 0.01
delay × emotion × long axis	0.73 (6182)	0.467	0.003	-0.01, 0.01
random effects	variance	SD	*n*	
participant (intercept)	1*e*-05	0.003	52	
marginal R^2 / conditional R^2: 0.1 / 0.32				

Source data are provided as Source Data file.

Supplementary Table 15. **Analyses of delay-dependent changes in Encoding-Retrieval-Similarity in long-term memory cortices (anterior cingulate cortex, ventro-medial prefrontal cortex, inferior frontal gyrus, angular gyrus, precuneus) and sensory control regions.**

parameters for linear mixed models				
long-term memory storage sites				
fixed effects	*t* (df)	*p*	*β*	95% CI
intercept	8.73 (77.59)	4*e*-13	0.02	0.01, 0.02
delay	0.52 (67.12)	0.604	0.001	-0.004, 0.01
emotion	2.25 (138.12)	0.026	0.004	5*e*-04, 0.01
delay × emotion	-0.42 (3008)	0.675	-0.001	-0.005, 0.003
random effects	variance	SD	*n*	
participant (intercept)	6*e*-05	0.01	52	
stimulus set (intercept)	1*e*-05	0.003	60	
marginal R^2 / conditional R^2: 0.1 / 0.32				
occipital pole				
fixed effects	*t* (df)	*p*	*β*	95% CI
intercept	13.84 (70.02)	1*e*-21	0.32	0.27, 0.36
delay	0.28 (51.5)	0.784	0.01	-0.05, 0.07
emotion	0.66 (66.75)	0.513	0.01	-0.02, 0.04
delay × emotion	-1.29 (3008)	0.196	-0.01	-0.02, 0.005
random effects	variance	SD	*n*	
participant (intercept)	0.01	0.11	52	
stimulus set (intercept)	0.003	0.05	60	
marginal R^2 / conditional R^2: 0.1 / 0.32				
Heschl's gyrus				
fixed effects	*t* (df)	*p*	*β*	95% CI
intercept	4.20 (85.69)	0.0001	0.02	0.01, 0.020
delay	-1.40 (91.49)	0.165	-0.01	-0.02, 0.003
emotion	-0.97 (205.93)	0.333	-0.004	-0.01, 0.004
delay × emotion	1.20 (3008)	0.232	0.01	-0.004, 0.02
random effects	variance	SD	*n*	
participant (intercept)	2*e*-04	0.01	52	
stimulus set (intercept)	1*e*-05	0.004	60	
marginal R^2 / conditional R^2: 0.1 / 0.32				

Source data are provided as Source Data file.

Supplementary Table 16. **Analyses of delay-dependent changes in similarity between encoded images and corresponding semantically related lures in long-term memory cortices (anterior cingulate cortex, ventro-medial prefrontal cortex, inferior frontal gyrus, angular gyrus, precuneus) and sensory control regions.**

parameters for linear mixed model				
long-term memory storage sites				
fixed effects	*t* (df)	*p*	*β*	95% CI
intercept	9.11 (89.82)	2*e*-14	0.02	0.01, 0.02
delay	0.18 (70.43)	0.856	4*e*-04	-0.004, 0.01
emotion	0.95 (115.16)	0.345	0.002	-0.002, 0.01
delay × emotion	0.7 (3008)	0.486	0.001	-0.002, 0.01
random effects	variance	SD	*n*	
participant (intercept)	5*e*-05	0.01	52	
stimulus set (intercept)	2*e*-05	0.004	60	
marginal R^2 / conditional R^2: 0.1 / 0.32				
occipital pole				
fixed effects	*t* (df)	*p*	*β*	95% CI
intercept	9.11 (89.82)	2*e*-14	0.02	0.01, 0.02
delay	0.18 (70.43)	0.856	4*e*-04	-0.004, 0.01
emotion	0.95 (115.16)	0.345	0.002	-0.002, 0.01
delay × emotion	0.7 (3008)	0.486	0.001	-0.002, 0.01
random effects	variance	SD	*n*	
participant (intercept)	5*e*-05	0.01	52	
stimulus set (intercept)	2*e*-05	0.004	60	
marginal R^2 / conditional R^2: 0.1 / 0.32				
Heschl's gyrus				
fixed effects	*t* (df)	*p*	*β*	95% CI
intercept	3.32 (87.27)	0.001	0.01	0.01, 0.02
delay	-0.23 (93.61)	0.821	-0.001	-0.01, 0.01
emotion	0.92 (203.67)	0.357	0.004	-0.004, 0.01
delay × emotion	-1.17 (3008)	0.243	-0.01	-0.02, 0.004
random effects	variance	SD	*n*	
participant (intercept)	2*e*-04	0.01	52	
stimulus set (intercept)	1*e*-05	0.004	60	
marginal R^2 / conditional R^2: 0.1 / 0.32				

Source data are provided as Source Data file.

Supplementary Table 17. **Analyses of delay-dependent changes in similarity between encoded images and corresponding perceptually related lures in long-term memory cortices (anterior cingulate cortex, ventro-medial prefrontal cortex, inferior frontal gyrus, angular gyrus, precuneus) and sensory control regions.**

parameters for linear mixed models				
long-term memory storage sites				
fixed effects	*t* (df)	*p*	*β*	95% CI
intercept	8.7 (79.59)	4*e*-13	0.02	0.01, 0.02
delay	0.07 (67)	0.943	2*e*-04	-0.01, 0.01
emotion	1.43 (130.24)	0.155	0.003	-0.001, 0.01
delay × emotion	-0.33 (3008)	0.744	-0.001	-0.005, 0.003
random effects	variance	SD	*n*	
participant (intercept)	7*e*-05	0.01	52	
stimulus set (intercept)	2*e*-05	0.004	60	
marginal R^2 / conditional R^2: 0.1 / 0.32				
occipital pole				
fixed effects	*t* (df)	*p*	*β*	95% CI
intercept	13.75 (69.55)	2*e*-21	0.32	0.27, 0.36
delay	-0.06 (51.58)	0.951	-0.002	-0.06, 0.06
emotion	0.8 (67.47)	0.429	0.01	-0.02, 0.04
delay × emotion	-0.47 (3008)	0.635	-0.004	-0.02, 0.01
random effects	variance	SD	*n*	
participant (intercept)	0.01	0.11	52	
stimulus set (intercept)	0.002	0.05	60	
marginal R^2 / conditional R^2: 0.1 / 0.32				
Heschl's gyrus				
fixed effects	*t* (df)	*p*	*β*	95% CI
intercept	3.08 (96)	0.003	0.01	0.004, 0.02
delay	-0.22 (96)	0.828	-0.001	-0.01, 0.01
emotion	0.67 (3066)	0.503	0.003	-0.01, 0.01
delay × emotion	0.11 (3066)	0.916	0.001	-0.01, 0.01
random effects	variance	SD	*n*	
participant (intercept)	2*e*-04	0.01	52	
marginal R^2 / conditional R^2: 0.1 / 0.32				

Source data are provided as Source Data file.

Supplementary Table 18. **Control variables.**

	M (SEM)		two-sample *t*-test			
control variable	**1d**	**28d**	***t* (df)**	***p***	***d***	**95% CI**
state anxiety (STAI-S)	32.92 (0.67)	34.77 (1.43)	-1.17 (35.56)	0.250	0.33	-0.22, 0.88
trait anxiety (STAI-T)	33.19 (1.16)	32.77 (1.44)	0.23 (47.79)	0.820	-0.06	-0.61, 0.48
sleep quality (PSQI)						
global score (last 28d)	4.23 (0.39)	4.92 (0.53)	1.05 (45.59)	0.297	0.30	-0.25, 0.84
sleep quality in the last 24h	1.69 (0.12)	1.92 (0.12)	0.67 (48.15)	0.505	-0.19	-0.73, 0.36
sleep latency in the last 24h	7.44 (0.22)	7.21 (0.26)	-1.34 (49.99)	0.188	0.38	-0.17, 0.92
depressive mood (BDI II)	4.23 (0.72)	3.77 (0.74)	0.45 (49.97)	0.657	0.45	-0.67, 0.42
subjective chronic stress (TICS)	10.88 (1.06)	12.73 (1.21)	-1.15 (49.09)	0.257	0.32	-0.22, 0.87

Source data are provided as Source Data file.

Supplementary References

1. Ciric, R. *et al.* TemplateFlow: FAIR-sharing of multi-scale, multi-species brain models. *Nat. Methods* **19**, 1568-1571 (2021).

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Erklärung gemäß *(bitte Zutreffendes ankreuzen)*

☐ **§ 4 (1c) der Promotionsordnung des Instituts für Bewegungswissenschaft der Universität Hamburg vom 18.08.2010**

☐ **§ 5 (4d) der Promotionsordnung des Instituts für Psychologie der Universität Hamburg vom 20.08.2003**

Hiermit erkläre ich,

_____ (Vorname, Nachname),

dass ich mich an einer anderen Universität oder Fakultät noch keiner Doktorprüfung unterzogen oder mich um Zulassung zu einer Doktorprüfung bemüht habe.

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BEWEGUNGSWISSENSCHAFT

Institut für Bewegungswissenschaft
Institut für Psychologie

Eidesstattliche Erklärung nach *(bitte Zutreffendes ankreuzen)*

☐ **§ 7 (4) der Promotionsordnung des Instituts für Bewegungswissenschaft der Universität Hamburg vom 18.08.2010**

☐ **§ 9 (1c und 1d) der Promotionsordnung des Instituts für Psychologie der Universität Hamburg vom 20.08.2003**

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