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Multiple routes to enhanced memory for emotionally relevant events

Nina Rouhani[1], Yael Niv[2], Michael J. Frank[3], and Lars Schwabe[4]

[1] Division of Biology and Biological Engineering and Division of Humanities and Social Sciences, California Institute of Technology, Pasadena, USA
[2] Department of Psychology and Princeton Neuroscience Institute, Princeton University, USA
[3] Department of Cognitive, Linguistic & Psychological Sciences and Carney Institute for Brain Science, Brown University, USA
[4] Department of Cognitive Psychology, Institute of Psychology, Universität Hamburg, Germany

Events associated with aversive or rewarding outcomes are prioritized in memory. This memory boost is commonly attributed to the elicited affective response, closely linked to noradrenergic and dopaminergic modulation of hippocampal plasticity. Here, we review and compare this 'affect' mechanism to an additional, recently discovered, 'prediction' mechanism whereby memories are strengthened by the extent to which outcomes deviate from expectations, that is, by prediction errors. The mnemonic impact of prediction errors is separate from the affective outcome itself and has a distinct neural signature. While both routes enhance memory, these mechanisms are linked to different, and sometimes opposing, predictions for memory integration. We discuss new findings that highlight mechanisms by which emotional events strengthen, integrate, and segment memory.

Highlights

Memory is enhanced for threatening and rewarding events, which has important implications for psychiatric disorders.

Arousal and motivation ('affect route') are driving forces in the encoding and consolidation of emotional memory, shaping the course of systems consolidation.

In addition to this affect route, a 'prediction route', governed by reinforcement-learning prediction errors, boosts memory for emotionally relevant events.

Putative dopaminergic (DA) and noradrenergic (NE) mechanisms both enhance memory; however, they are associated with distinct mnemonic signatures: DA helps integrate while NE segments memory, giving rise to distinct representations of experience.

Keywords: Memory, Emotion, Prediction Error, Arousal, Reward Learning, Aversive Learning

Revisiting emotional memory: remembering the unexpected

While we forget mundane events rapidly, we remember events associated with strong emotions, such as a lottery win or a bear attack, for much longer. Indeed, events linked to rewarding or aversive outcomes are preferentially stored in memory [1–4], adaptively enabling prediction and selection of appropriate actions for similar events in the future. Selective memory enhancement has important consequences for a broad range of contexts including education, eyewitness testimony, and psychiatry, where disorders such as post-traumatic stress disorder (PTSD) and depression can be marked by crippling reminders of the past.

Better memory for emotionally-relevant events is linked to an affective response that increases noradrenergic or dopaminergic modulation of hippocampal neuroplasticity [5–8]. While knowledge about this well-established affect route continues to develop, there is accumulating evidence for an additional, 'prediction' route, where the prediction error ('PE') elicited by rewarding or threatening events improves memory. PE is defined as the difference between prediction and actual outcome, whose magnitude ('unsigned PE') represents the surprise elicited by that outcome. In reinforcement learning, reward and punishment-related PEs, that is, ('signed') PEs defined by affective outcomes, are the canonical signals driving value updating and action selection (Box 1). The predictive and affective components of an event are often tied, but we can test their distinct contributions. For example, if you were expecting a tax refund of $1000 but instead owed $1000 in taxes, the affective outcome of -$1000 is separate from the outcome's unexpectedness, i.e., the unsigned PE: |outcome – prediction| = $2000. To note, the signed PE: outcome – prediction = -$2000, includes both affective and predictive components.

While PEs can elicit affective responses, recent work shows their mnemonic influence to be separate from affect alone. Further, their role in optimizing fundamental computational trade-offs is distinct from the discussed affect route. Namely, the magnitude of PE is thought to determine whether a new experience initiates a distinct memory trace (related to hippocampal 'pattern separation' and memory segmentation, given a sufficiently large PE) or if not, whether the experience is integrated into previous memory (or 'schema', related to hippocampal 'pattern completion' and memory generalization) [9,10]. Moreover, this affect-prediction division may help distinguish treatment options for memory-related disorders. While the affect route suggests arousal-reduction interventions, the prediction route targets expectation change instead.

Overall, the impact of emotional events on memory is complex, dynamic and depends, for instance, on its influence at initial encoding, consolidation, or later retrieval [8,11]. Here, we aim to provide an overview of the multiple mechanisms by which aversive or rewarding events shape memory for inherently neutral stimuli that precede or occur at the time of the emotional event. We will focus on memory encoding and consolidation, but note that emotion also modulates recall dynamics [12].

We acknowledge that while aversive and appetitive events are associated with 'opposite' affect, they may deploy similar mechanisms. For example, while appetitive events are linked to dopaminergic modulation of hippocampal plasticity [4], aversive events also activate midbrain dopamine to support hippocampal memory [13]. Moreover, historically, paradigms testing aversive events have elicited higher arousal while those testing appetitive events have elicited higher motivation, leading to different kinds of behavior and memory for those events [14]. Regardless, we consider each described mechanism to contribute to improved emotional memory no matter the valence.

We also distinguish between noradrenergic and dopaminergic memory mechanisms, but memory is contingent on both [15]. To further obfuscate this division, the locus coeruleus co-

releases dopamine along with norepinephrine to influence hippocampal memory [16–18]. We nevertheless discuss each system separately to highlight their potentially predominant roles in shaping memory, but note that the described mechanisms are unlikely to be selective to dopaminergic or noradrenergic systems.

In this review, we first focus on recent insights into how affective state shapes memory. We next discuss new evidence demonstrating that large PEs enhance memory for rewarding and aversive experiences, separate from the effect of the affective outcome itself. We then integrate findings and suggest that PE-driven memory boosts can signal an update of the existing model of the environment, resulting in the re-organization and segmentation of events in memory. Finally, we discuss the application of these findings to psychiatric disorders.

The "affect" route to enhancing memory

We begin by examining new research that validates and extends arousal-based models of memory whereby norepinephrine ('NE') prioritizes emotionally-relevant events. We then discuss how reward-based motivation, engaging a dopaminergic ('DA') circuit, also enhances memory. We nevertheless elaborate upon the mnemonic distinctions between reward-based DA and arousal-based NE, namely in generating more integrated versus disjointed memories, respectively.

Arousal-based noradrenergic mechanism

Decades of research establish that better memory for emotional events can be explained by arousal-driven noradrenergic activation of the amygdala. Specifically, the release of NE from the adrenal medulla activates – via the vagal nerve – noradrenergic brainstem nuclei projecting to the amygdala, which then modulates memory consolidation in other brain areas (Box 2)[3,19]. These NE effects can be amplified by glucocorticoids released from the adrenal cortex, which further activate glucose known to enhance memory [20]. Core assumptions of this model receive continuous support. For example, post-encoding functional connectivity between the amygdala and neocortical representation areas predict subsequent recognition memory for emotional events [21]. Moreover, a recent study using vagal-nerve stimulation in humans provides causal evidence for the role of vagal activity in memory formation [22]. Similarly, direct electrical stimulation of the human amygdala causes better recognition memory for ongoing neutral events, and does so through the amygdala's interactions with the hippocampus and perirhinal cortex, consistent with the idea that the amygdala modulates memory in other brain areas [23]. Recent work further highlights that later reinstatement of amygdalar-hippocampal patterns [24,25] boosts encoding of ongoing neutral events [26]. Such carry-over effects provide another opportunity to tag events in memory [27,28], creating an extended context for the emotionally-arousing event.

New findings further underline the key role of the locus coeruleus ('LC'), the primary source of NE in the brain, projecting to virtually all other brain areas (Figure 1) [29], in emotional memory. A recent ultra-high-resolution human fMRI study showed that at encoding, LC activity correlates with the amygdala and arousal to predict emotional memory [30]. This study further revealed that LC connectivity with areas of the medial temporal lobe changes dynamically across encoding and consolidation, suggesting distinct roles of the LC during memory encoding and maintenance. Moreover, there is evidence that LC strengthens goal-relevant memory representations in particular, indicating an LC-arousal prioritization mechanism [31]. Intriguingly, we can read from a participant's eyes which stimuli elicit arousal and are thus selected for long-term storage. Pupil dilation is a biomarker of both arousal and LC activity, and

several reports show that it reliably predicts trial-by-trial variability in successful memory encoding [31,32] and retention [33].

Emerging work in this area increasingly focuses on the mechanisms supporting the long-term fate of arousing memories. In addition to synaptic consolidation requiring several hours to complete, a proposed systems-consolidation process can take weeks to months to complete. During systems consolidation, memories become less dependent on the hippocampus and more reliant on neocortical areas [34,35]. This neural reorganization is thought to change memory from a detailed representation to a more gist-like representation [36,37]. Nevertheless, recent evidence demonstrates that noradrenergic arousal can overturn the dynamics of systems consolidation: rats that received NE injection after encoding were able to discriminate a previous threat context from very similar contexts even 28 days after training, indicating that post-encoding NE kept memories specific (i.e., episodic) over time. This specificity was accompanied by increased hippocampal involvement in memory over time [38]. In striking parallel, in human fMRI study, pharmacological increase of noradrenergic arousal after encoding similarly led to more hippocampal involvement after 28 days [39]. These data suggest that post-encoding noradrenergic arousal may not only decelerate but even reverse the dynamics of systems consolidation, potentially providing a mechanism that keeps memories vivid long-term.

Motivation-based dopaminergic mechanism

While arousal certainly plays a part in motivation, the memory boost linked to periods of behavioral invigoration, such as when seeking hedonic rewards, engages a largely separate neural mechanism centered on DA (Figure 1). Like arousal, high motivation can enhance memory at all stages of mnemonic processing; however, with different consequences. For example, both arousal and motivation enhance attention; however, aversive arousal can narrow attention to the most salient feature (e.g., a gun; [40]) whereas reward motivation can broaden attention (e.g., taking in the landscape), which allows for better binding of surrounding features in memory [14].

The ventral tegmental area (VTA), a primary source of DA in the midbrain, is structurally and functionally linked to the hippocampus where long-term potentiation and maintenance is modulated by DA [4,6]. DA further strengthens neutral or weak memories that were temporally close to an emotional event, as in the ‘Synaptic Tag and Capture’ model of synaptic consolidation [41,42]. This plasticity is thought to occur only after a period of consolidation, and indeed, several fMRI studies observe that reward motivation amplifies activity and connectivity between the midbrain and hippocampus, predicting better post-consolidation memory for reward-motivated events [43–47]. Rewarding memories, are additionally bolstered by offline ‘replay’ in the VTA and hippocampus [48], where the relevant neuronal sequences that were active during encoding are repeated and relayed between regions, putatively supporting systems-level consolidation.

Theoretical and empirical work have furthermore distinguished between dopaminergic and noradrenergic memory signatures [14]. DA is thought to integrate experiences across features and events, producing the rich, relational representations characteristic of hippocampal memory [49]. Accordingly, increased post-encoding interactions between the VTA and higher-order sensory cortex support better associative memory for reward-motivated events [50]. In contrast, negative events, which engage the amygdalar arousal-based mechanism described above, impair integrative and associative memory [51]. Previous work already highlighted this key difference: while the hippocampus promotes relational encoding, the amygdala disrupts it

[49]. Consistent with this, negatively-arousing images can engage the amygdala during encoding to strengthen item memory, but reduce hippocampal activity, thereby weakening associative memory [52–54] (although an amygdala-hippocampal phase code is observed to support memory for negative images in intracranial recordings [55]). Highly-arousing negative events, such as acute stress, can similarly diminish hippocampal memory [56–59] and impair hippocampus-dependent (contextual) conditioning [60]. On the other hand, positive emotion and reward motivation, putatively relying on DA-hippocampal modulation, increase item and associative memory as well as the clustering of rewarding events during free recall [54,61,62]. These potentially distinct roles of DA and NE in integrating versus segmenting memories is not limited to 'affect' but extends to neural computations at large (discussed more below).

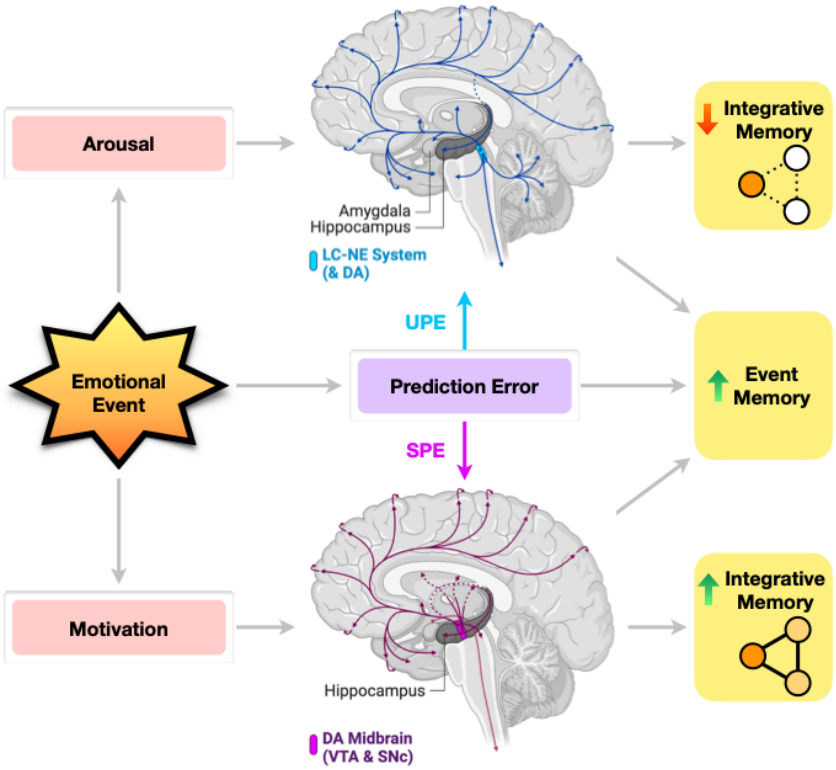

Figure 1. Emotion improves memory through multiple 'affect' and 'prediction' routes. The affect route is comprised of arousal and motivation. Arousal engages locus-coeruleus norepinephrine ('LC-NE', that also co-releases dopamine, 'DA') as well as peripheral (nor)epinephrine from the adrenal medulla (Box 2) to modulate amygdala and hippocampal memory. Motivation activates midbrain dopamine (ventral tegmental area: 'VTA', and substantia nigra pars compacta: 'SNc') to boost memory in the hippocampus. Recent work has identified a prediction-error route in emotional-memory enhancement, where, in parallel, unsigned prediction errors ('UPE's) act on the LC-NE system and signed prediction errors ('SPE's) act on DA midbrain neurons to influence hippocampal memory (Box 1). While these routes each give rise to better event memory, they are associated with opposite effects on mnemonic integration. Specifically, DA-memory is thought to promote integration of the emotional memory with associated features and events whereas NE-memory is thought to disrupt such integration. For a related theoretical framework see Figure 3 in [14]. (neural pathways constructed with BioRender.com.)

The "prediction" route to improving memory

We next present recent evidence of a prediction mechanism which, separate from the effects of affect alone, boosts and organizes memory across aversive and appetitive domains. Aside from triggering an affect response, emotional events can engage fundamental learning

mechanisms whereby predictions of the outside world are formed and updated by experience. Given that emotional events can elicit strong expectations and are often unpredictable in nature (with each contributing to arousal [63]), a rapidly developing literature quantifies the effect of emotional expectation, subsequent outcome, and the difference between these (PE), on memory [64–70]. Although mechanisms supporting memory for large PE events likely overlap with those engaged by novel, salient or oddball events, we focus on PEs for rewarding or aversive (i.e., 'emotional') outcomes during incremental learning. These PEs dynamically change with new or more learning (i.e., changes in expectations) and their outcomes are emotionally stimulating.

While appetitive and aversive learning can engage distinct neural systems [71], below we describe shared effects. We moreover characterize how signed PEs ('SPE') and unsigned PEs ('UPE') differentially influence memory for the outcome-predicting cue versus the outcome event itself. After discussing findings in threat and reward learning separately, we summarize results across paradigms (for a list of highlighted findings, see Figure 3).

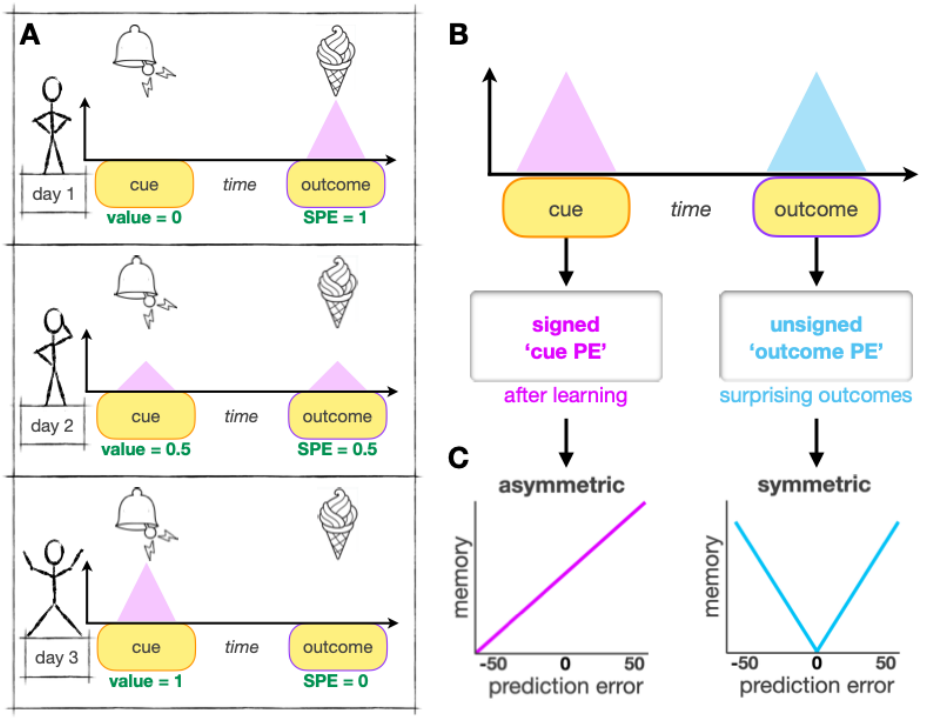

Figure 2. Memory predictions for signed prediction error ('SPE') and unsigned prediction error ('UPE') signals. (A) The reward SPE travels from outcome to the cue predicting reward over the course of learning. Initially (day 1), the cue (sound of the bell) has no value. When it is paired with reward (ice-cream), the unexpected outcome elicits a strong positive prediction error. By day 2, the bell starts to become associated with ice-cream (increased value), activating a small positive PE at the time of the cue and a smaller positive PE at outcome (as the ice cream is partly predicted and less surprising by now). After the bell has become associated with ice-cream (day 3), a strong positive PE, reflecting high value and expectation of reward, only occurs at cue – the ice cream event, while (hedonically) appreciated, is no longer unexpected. After learning, the SPE at cue (B) putatively gives rise to an asymmetric effect on memory (C) where increased dopamine enhances memory for cues that predict higher reward (Box 1). On the other hand, a UPE signal is thought to activate LC-NE during surprising outcomes throughout learning, symmetrically boosting memory for both positive and negative outcomes that substantially deviate from prior expectation. In line with these predictions, both SPE at cue and UPE at outcome improve memory during reward learning [65].

Threat learning

Recent experiments examine how PEs influence memory for predictive cues during threat conditioning. In an initial study, participants completed an incidental-encoding Pavlovian-threat-conditioning paradigm where they predicted whether unique exemplars from two different stimulus categories would lead to electric shock [66]. Large UPEs (surprising shock or no-shock), and not the expectation of shock nor the outcome itself, boosted recognition memory for the exemplars; this effect was replicated in a second experiment. PEs' mnemonic influence was moreover spotlighted in another study demonstrating that when the PE associated with a stressful event is reduced by prior information, the well-known memory enhancement of stressful episodes [72,73] can be largely abolished [74].

A subsequent experiment further explored the role of SPEs, and found that large positive PEs (i.e., unexpected shock omission, 'negative aversive PEs' in empirical paper) particularly improved memory [75]. This result is consistent with emerging findings in rodent work demonstrating that unexpected-shock omission activates midbrain dopamine at outcome, suggesting a PE mechanism similar to early reward learning (Box 1, Figure 2; [76–78]), and one that could support positive-PE (dopamine-dependent) avoidance of threatening outcomes [79,80]. Together, these results suggest that unexpected outcomes, not specifically aversive outcomes, improve memory, and may be responsible for the memory enhancement of stressful episodes.

Given that unpredictability and uncertainty elicit arousal [63,81], these studies have further probed the relationship between PE, arousal, and memory. In line with classic arousal-based models (Box 2), outcome-related arousal indeed improves recognition memory [66,81]. Critically, however, large PEs predict memory independently from arousal, with both predictors explaining recognition memory better than either alone [66,75]. In fact, diminishing the PE associated with a stressful event reduces recognition memory but does not modulate the physiological stress response [74], highlighting the separate effects of arousal and PE on memory.

New fMRI data further show that memory enhancement for large shock-omission PEs is orchestrated by a neural mechanism distinct from arousal [75], and one consistent with pattern separation (giving rise to new, distinct memory traces) versus pattern completion (the integration of experience with prior representations or schemas). Indeed, while recognition memory for expectancy-congruent (low-PE) events is linked to para/hippocampal activity at encoding, memory enhancement for high (shock-omission) PEs, is associated with *reduced* activity and connectivity both within medial temporal lobe and 'schema' networks [82,83]. Instead, shock-omission PEs increased activity in a 'salience network' including the insula and dorsal anterior cingulate cortex, as well as its connectivity with the medial-temporal-lobe network, which predicted better recognition memory for cue events. These neural changes could not be explained by increases in arousal. Together, these data show that large shock-omission PEs elicit a salience signal that shifts memory mechanisms to encode or 'pattern separate' an event rather than integrate it with previous memory. In line with this, recent findings show that PEs not only disrupt sustained memory representations in the hippocampus [84], but bias it to encode new information [85]. PE's strengthening and segmenting of memory is further discussed below in 'Prediction errors organize memories'.

Reward learning

Several recent studies have characterized PE's influence on memory for rewarding events, and like those on threat learning, found that UPE memory modulation is independent of classic 'affect' effects, in this case, reward receipt. First, a series of experiments using an incidental-encoding Pavlovian-reward-conditioning paradigm investigated which features of reward learning impact recognition memory. Consistently and across variations of the paradigm, at reward outcome, UPE and not SPE nor the reward outcome itself, predict recognition memory for the outcome event [64,86].

This finding is consistent with the classic Pearce-Hall model of associative learning that posits enhanced attention and learning for surprising outcomes (i.e., the learning of values; Box 1, Figure 1)[87]. These large UPEs furthermore elicit a phasic response from the LC-NE system [29,88]. Intriguingly, while large UPEs increased both trial-by-trial learning rate and event memory, learning rate and memory were consistently uncorrelated, suggesting dissociable effects [64]. In fact, in one paradigm, where reward variance (i.e., 'risk') was either high or low (generating frequent large or small PEs, respectively), learning rate inversely related to variance (i.e., learning rate was higher overall in the low-variance context, in line with previous work [89,90]) whereas recognition memory showed the flipped result (i.e., memory was higher overall in the high-variance context). Such findings are reminiscent of the trade-off between rapid adjustment during learning (higher learning rates) and long-term, PE-driven, retention of values [91]. Given the rich body of work examining dopaminergic scaling in PEs [92] as well as cholinergic and noradrenergic modulation of expected and unexpected uncertainty, respectively [93], future neuroscientific work is ripe to examine the potentially independent and interacting effects of UPEs on value versus memory updating [94].

Along with the memory-enhancing effects of UPEs during outcomes, new work highlights the additional role of SPEs within [65,95,96] and outside of reinforcement learning [70,97]. Importantly, in contrast to UPEs, SPEs do not seem to influence memory when they occur at the time of the outcome, but only improve memory when they occur at reward cue (results test SPEs and UPEs in the same model, controlling for all potential effects [65,95], Figure 3). This mnemonic boost is reminiscent of the dopaminergic PE signal that transfers from reward outcome to cue over the course of learning (Box 1, Figure 2), and suggests that, after initial learning, dopamine release at cue could strengthen hippocampal memory [4,98]. The SPE putatively supports another classic associative model, the Mackintosh model [99], where attention and learning increase for cues that reliably predict reward. Interestingly, this model is paradoxical to the aforementioned Pearce-Hall model where unreliable (high-PE) events are predicted to enhance attention and learning.

In fact, a recent experiment indicates that both signals bolster memory, but do so during different phases of learning [65]. In this paradigm, participants learned the values of two stimulus categories and were later tested for recognition memory of trial-unique images occurring at reward cue or outcome. Here, the 'cue-PE' (Figure 2) was calculated as the difference between the expected value of the current reward category versus the alternative one. Reinforcement learning models including both cue-SPE and outcome-UPE signals to modulate learning rate fit behavior better than models with either component alone. Moreover, the mnemonic boost of the UPE at outcome was again replicated, and in tandem, the SPE at cue was found to improve memory for cue images. In other words, the more participants learned that one category was more rewarding than the other, the more likely they were to remember the cue belonging to the more-rewarding category, whereas any surprising outcome, positive or negative,

enhanced memory for the outcome images. This SPE mechanism at cue could potentially initiate and support memory enhancement during high-reward anticipation [43,44,47,100].

Memory Event	Study	Delay	Stimuli	Response	Outcome	# Cats.	PE Event	PE Type	Result
cue	R ('21)	sd	s rel.	**prediction** 0-100	reward 0-100	2	cue	SPE	+
cue	JN ('19)	sd/nd	a/i rel.	**choice** play/pass	reward/loss -10/1-100	2	cue	SPE	+
outcome	R ('18/'21)	sd	s/o rel.	**prediction** 0-100	reward 0-100	2	outcome	SPE	
outcome	R ('20)	sd	s rel.	**no response**	reward 0-100	1	outcome	SPE	
outcome	D ('16)	sd	o irrel.	**choice** 2 bandits	correct/ incorrect	2	outcome	SPE	
outcome	R ('18/'21)	sd	s/o rel.	**prediction** 0-100	reward 0-100	2	outcome	UPE	+
outcome	R ('20)	sd	s rel.	**no response**	reward 0-100	1	outcome	UPE	+
cue	JN ('19)	sd/nd	a/i rel.	**choice** play/pass	reward/loss -10/1-100	2	outcome	SPE	
cue	R ('21)	sd	s rel.	**prediction** 0-100	reward 0-100	2	outcome	SPE	
cue	K ('21)	nd	o rel.	**prediction** shock slider	shock/ no-shock	3	outcome	SPE	+
cue*	W ('14)	nd	o irrel.	**choice** 2 bandits	reward 0/0.25	2	outcome	SPE	—
cue	K ('20)	nd	a/i rel.	**prediction** shock	shock/ no-shock	2	outcome	UPE	+
cue	R ('21)	sd	o rel.	**prediction** 0-100	reward 0-100	1	outcome	UPE	+
cue	R ('21)	sd	s rel.	**prediction** 0-100	reward 0-100	2	outcome	UPE	
cue	JN ('19)	sd/nd	a/i rel.	**choice** play/pass	reward/loss -10/1-100	2	outcome	UPE	
next-trial cue	K ('20)	nd	a/i rel.	**prediction** shock	shock/ no-shock	2	outcome	UPE	
next-trial cue	R ('18)	sd	s/o rel.	**prediction** 0-100	reward 0-100	2	outcome	UPE	

Figure 3. Prediction-error (PE) effects on recognition memory in selected incremental-learning paradigms. 'Memory Event' indicates when during learning the memoranda (trial-unique stimulus) occurred; 'cue': stimulus representing the outcome-predictive cue (*indicates two cue stimuli presented, otherwise single cue presented); 'outcome': stimulus occurring during the outcome; 'next-trial cue': cue occurring immediately after the tested PE ('proactive' memory). 'Study' abbreviations, D('16): Davidow et al., 2016[96], reporting adult results; JN('19): Jang, Nassar et al., 2019[95]; K('20): Kalbe & Schwabe, 2020[66]; K('21): Kalbe & Schwabe, 2021[75]; R('18): Rouhani et al., 2018[64]; R('20): Rouhani et al., 2020[86]; R('21): Rouhani & Niv, 2021[65]; W('14): Wimmer et al., 2014[101]. 'Delay': time between encoding (learning task) and recognition (memory task); 'sd' = same day and 'nd' = next day. 'Stimuli': type of stimuli used and whether they were task relevant; 's' = scenes, 'a/i' = animate/inanimate items, 'o' = objects; 'rel.' = relevant, 'irrel.' = irrelevant. 'Response': participant action prior to receiving the outcome; 'prediction' or 'no response' refer to Pavlovian-conditioning paradigms and 'choice' to instrumental/operant-conditioning paradigms. 'Outcome': type of feedback received. '# Cats.': number of categories (or 'bandits') learned about concurrently. 'PE Event' indicates when (cue or outcome) the tested PE occurred. 'PE Type' indicates whether the tested PE was signed (SPE) or unsigned (UPE). Finally, 'Result' indicates whether the tested PE led to memory enhancement ('+' green), decrement ('-' red), or a null result (grey block).

Summary across paradigms

Taken together, PEs improve memory independent of the effects of shock or reward alone. To further compare PE effects on memory, we organized relevant findings from incremental-learning paradigms (Figure 3). As previously discussed, SPEs at cue consistently enhance memory for a reward-predictive cue, similar to a value signal, and UPEs (but not SPEs) at outcome enhance memory for the outcome event [64,65,86,95,96]. Of note, memory consolidation does not appear to exert a strong influence across paradigms, as PEs influence memory when tested immediately after encoding and 24-hours later [95]. Similarly, whether the learning task is operant ('choice') or Pavlovian ('prediction/no response') does not seem to exert an obvious effect across these memory results.

Aside from PE effects on concurrently-occurring events, prioritizing cues predictive of important outcomes has great adaptive utility. Studies have thus assessed the retroactive influence of outcome-PEs on predictive cues, although with mixed results. During shock learning, outcome-PEs enhance memory for their cues [66,75], especially when shock is expected but omitted (a relief, i.e., positive outcome-SPE). On the other hand, during reward learning, outcome-SPEs do not enhance cue or outcome-event memory [65,95] but do predict later choice [65]. Here, positive outcome-SPEs increase preference for the outcome (over the cue) event of that trial, whereas negative outcome-SPEs increase preference for the cue event, pointing to outcome-SPE effects on non-declarative memory. These different results could be due to task engagement: learning about shocks may be more engaging, potentially bolstering subsequent reactivation of the predictive cue, while outcome-SPEs during (online) reward learning may not be salient enough to influence, at least, declarative memory.

Competition between learning and memory signals could also account for inconsistent results across paradigms. For example, during reward learning, outcome-UPEs increased cue memory only when there was a single category to learn about; this effect was eliminated when learning about two categories which elicit additional, potentially competing, PEs at cue [65]. Moreover, in a paradigm that presented two choices at once and where the two trial-unique stimuli were task irrelevant, the outcome-SPE competed with and decreased memory for those events [101]. Future work could test how task manipulations, specifically those modulating engagement, competition, and relevance, govern whether PEs enhance or diminish memory for predictive cues.

Finally, given that memory-boosting signals can "spillover" to adjacent events [102], threat and reward-learning paradigms have assessed "proactive" memory for the cue following the PE-eliciting outcome, but have not found an effect [64,66]. To note, although we previously discussed retroactive memory for preceding predictive cues, these results may not generalize to preceding non-predictive events and should be separately evaluated.

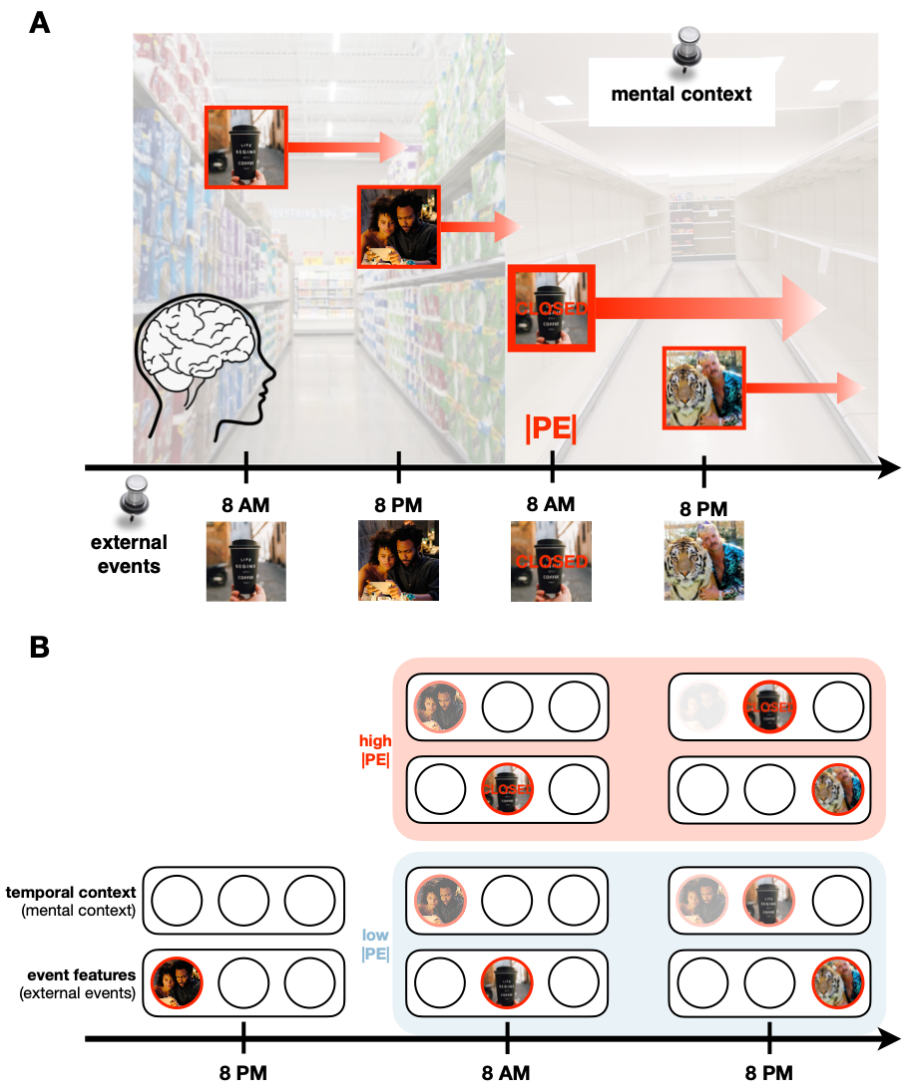

Figure 4. Prediction-error ('PE') segmentation of events in memory [86,103]. (A) External events activate and linger in the brain ('mental or temporal context') to create associations with new events experienced in temporal proximity (overlap between red arrows indicates associative binding between events). The pictured individual has a routine of coffee at 8 AM and television at 8 PM. If each event elicits the same amount of activation, events are uniformly associated with previous ones in memory. However, a high-magnitude PE can disrupt integration, splitting events that came before it from those that came after. Here, the individual learns of COVID-19 when noticing their coffee-shop is closed. This surprising event enters temporal context with higher drift rate, meaning it is stamped strongly in memory and clears out previously active events, leading to the formation of two distinct contexts, one pre-pandemic (stocked aisles) and one post-pandemic (empty aisles). (B) Similarly, within the computational model [86], external events ('event features') enter into (the next event's) temporal context with a stable drift rate. PEs increase this drift rate, consequently enhancing event activation at the expense of other active events in temporal context. The temporal context of the next event, in turn, is strongly associated with the high-PE event, but not with events that came before it (compare 'high |PE|' versus 'low |PE|' above). The high-PE event itself is still associated with the previous and subsequent context, but impairs integration across it, as supported by empirical evidence [86]. (Image source: Atlanta (FX), 2018; Tiger King (Netflix), 2020).

Prediction errors organize memories

In previous sections, we discussed that while 'affect' and 'prediction' mechanisms both contribute to emotional-memory enhancement, they may differentially organize memories. For example, mnemonic structure formed through the affect route may rely more on consolidation mechanisms [104], whereas it emerges without delay through the prediction route, suggesting stronger reliance on encoding processes [86]. Moreover, different putative neuromodulators, namely midbrain DA and LC NE (and DA), are linked to integrating across versus segmenting memories, respectively [14,105]. Segmentation, linked to hippocampal pattern separation, can occur after detecting an external (or potentially internal) change. This change can lead to an 'event boundary' in memory, which divides events that came before the change from those that followed, giving rise to distinct representations or 'chunks' of past experience (Figure 4) [9,106–109]. Although memory for the event boundary itself is boosted, temporal-order memory for events spanning it is worse, demonstrating a mnemonic trade-off between the distinct event and the temporal integration of adjacent events [110].

Large reward PEs have recently been shown to act like event boundaries in memory, improving recognition memory for the event itself but diminishing temporal memory for events across them [86]. Relatedly, in the threat-learning study described above [75], high-magnitude PEs upregulated a neural 'salience' network and downregulated a 'schema' network, which was associated with better cue memory. These neural dynamics further suggest that large PEs disrupt integration of continuous events in memory.

Nevertheless, whether high-magnitude PEs strengthen and/or segment memory depends on whether they (are inferred to) represent an event boundary or not. For example, an environment marked by frequent surprising changes ('high-outcome variance'), such as gambling in Las Vegas, may be segmented differently in memory than a single surprising event ushering in a lasting change ('change-point'), such as the COVID-19 pandemic (e.g., Figure 4; for a longitudinal, ecological examination of memory across the pandemic, see [111]). In fact, two separate experiments investigated the mnemonic effects of large PEs generated by either high-outcome variance [64] or by a change-point in the mean of the underlying reward distribution [86]. High-magnitude PEs boosted recognition memory in both tasks. When these PEs were generated by high-outcome variance (e.g., gambling events), they additionally improved overall temporal memory for items in the high-(versus low)-variance context [64]. However, when large PEs signaled a change-point (e.g., events before and after the pandemic), they disrupted temporal memory for items across the boundary [86]. These two seemingly contradictory results indicate that high-magnitude PEs alone do not create event boundaries in memory, they need to further reflect a (meaningful) change in the latent state [112].

New work demonstrates that increased pupil dilation, a marker of LC-NE release and arousal, predicts segmentation between events spanning boundaries [113]. How the LC-NE system helps strengthen and/or segment events in memory is still unclear, but research suggests that each process could occur at different time-points. For example, a surprising event leads to an early *increase* in pupil dilation whereas a change-point leads to a late *decrease* in pupil dilation [114]. Potentially, a surprising change-point event could first increase noradrenergic firing thereby strengthening that event in memory, and then decrease it to engage memory segmentation. Consistent with this hypothesis/idea, the observed segmentation for large change-point PEs [86] did not occur between the high-PE event and its predecessor, but rather sometime during the high-PE event, sparing the connection of that event to its predecessor, but segmenting events that crossed it. Accordingly, in the computational model developed to reproduce these

results (a variant of the Context, Maintenance and Retrieval model; [103]), segmentation in the mental (or 'temporal') context occurred after the high-PE event. The high-PE event itself was strongly stamped in temporal context, demonstrating intact associations with both preceding and subsequent contexts, thereby representing a junction between them.

Memory strengthening and segmenting could additionally, or alternatively, be orchestrated by distinct mechanisms. Event segmentation across change-points indeed predicts shifting state representations or pattern separation in the orbitofrontal cortex [115] and the hippocampus [116,117]. Large PEs experienced within a latent state (e.g., a high-variance context) are not expected to induce representational changes. In fact, a recent theoretical model proposes that similar sequences of PEs may be later clustered (or 'de-segmented') in memory to form an abstract representation of that state. This (non-episodic) abstraction can then be applied to new, relevant situations, enabling useful generalization [118]. Future work could characterize how PEs (within and across latent states) may differentially deploy mnemonic integration and segmentation to support adaptive behavior.

In short, a consistently growing literature shows that PEs are a fundamental modulator of memory by enhancing memory for emotional events and by further structuring those memories into distinct representations. The extent to which PEs may act independently or interactively with more 'affective' mechanisms is a promising direction for future work. For example, SPEs, associated with DA release, and UPEs, associated with activation of the LC-NE system, are strong candidates for modulating the integration versus separation of emotional events in memory. While large SPEs may help integrate rewarding cues with their outcomes, potentially giving rise to reward schemas, large UPEs may help divide those schemas (e.g., rewarding versus punishing) in memory.

Applications of prediction-error memory enhancement

Research on emotional-memory mechanisms aims to develop novel approaches to modifying unwanted and debilitating memory. While the affect route suggests pharmacological or psychological (emotion-focused) treatment targeting arousal processes, the prediction route emphasizes interventions that update patients' prior expectation and beliefs (e.g., cognitive-behavioral therapy). Within the affect route, the classic arousal-based mechanism inspired several pharmacological interventions that targeted norepinephrine or glucocorticoid signaling to disrupt overly strong emotional memory in anxiety disorders and PTSD [119,120]. However, although such pharmacological treatments may be effective, they risk side effects. PE-based modification offers a less invasive approach to modifying unwanted memories. One potential application relates to the finding that stress-induced memory boost is diminished when people receive prior information about the stressful event [66]. Of course, many emotional events occur without warning. However, some can be predictable to an extent, for example, in emergency units, fire services or combat situations, detailed information of what could occur might help attenuate the strength of potentially traumatic memory.

PE-based memory mechanisms might also be biased in psychiatric disorders. For instance, individuals with depressive symptoms are more likely to remember events associated with high-magnitude negatively-valenced PEs whereas those without depressive symptoms preferentially remember events associated with large positively-valenced PEs [121]. These findings may contribute to the reported memory bias for negative versus positive events in depression and vice-versa in healthy individuals (memory bias is demonstrated for low or matched-arousal events: [122–124]). Attentional interventions may help re-orient depressed

patients towards surprising positive outcomes during encoding. Moreover, along with weakening of unwanted memories, therapeutic interventions can leverage PE-based mechanisms to strengthen positively surprising outcomes that challenge patient expectations and prior beliefs. Indeed, learning from expectancy violations is a key mechanism predicting success in exposure-based therapy for anxiety disorders [125].

Concluding remarks

Accumulating evidence shows that high-magnitude PEs associated with aversive or rewarding events boost memory for neutral events that predict or co-occur with the emotional outcome. This PE-driven mechanism can further update and structure our mnemonic representation of the world, enabling better prediction of future rewards and threats. Crucially, PE-based memory enhancement is separate from the well-described 'affect' mechanism governed by arousal and motivational state. We therefore suggest that two routes—affect and prediction—enhance memory and encourage different strategies in tackling aberrant emotional memory.

While the described PE-based mechanism broadens our perspective on the components driving memory enhancement, several key questions remain (see Outstanding questions). Addressing these and related questions may not only further our understanding of how emotional events shape memory but may ultimately offer more effective interventions to diminish disruptive memory in psychiatric disorders.

Box 1: Prediction-error modulation of memory during reinforcement learning

The signed reward prediction error (SPE) is a canonical signal in reinforcement learning that updates the stored values of experiences. SPEs modulate dopaminergic firing from the midbrain, increasing dopamine when outcomes are better than expected, and decreasing its release to below baseline when outcomes are worse than expected [126,127]. These signals are used to update expectations so that they better align with reality. As learning progresses, the dopaminergic SPE transfers from the outcome event to the predictive cue, a marker of reward anticipation [128]. This SPE may also give rise to stronger memory traces, given that dopamine modulates neural plasticity in the hippocampus - the key structure for episodic memory [4,98]. If memory formation is modulated by the SPE, then we would expect an asymmetric effect on memory, such that a positive PE would improve memory whereas a negative PE would worsen it [95,96]. Indeed, SPEs at the time of predictive cues enhance memory for the cue event, boosting memory for more valued cues [65,95].

Another possibility is that the absolute magnitude of the PE influences memory, enhancing memory for surprising events regardless of whether they were much better or much worse than expected. The locus-coeruleus-norepinephrine (LC-NE) system is thought to mediate the effects of such unsigned prediction errors (UPEs), demonstrating a transient response for unexpected outcomes in both reward and fear learning [87,88]. The LC-NE system provides an alternative source of dopamine to the hippocampus by co-releasing dopamine with norepinephrine, potentially contributing to dopamine-dependent plasticity in the hippocampus [16–18]. Consistent with this mechanism, UPEs in both reward and threat learning reliably boost memory for associated events in a variety of paradigms [64,66].

To note, new work has expanded upon and complicated the role of dopamine from a single, scalar ‘model-free’ value signal to a multiplexed ‘model-based’ prediction signal [129,130], recently suggested to reflect mnemonic, causal inference [131]. Unsigned (nonrewarding) dopaminergic PEs enable broader associative learning of an environment, creating links between two cues, rather than just cue-outcome associations [132]. Unlike striatal-dopamine mechanisms tuned for outcome valence [133], dopaminergic state PEs may indeed have a more direct impact on hippocampal processes.

Box 2: How noradrenergic arousal helps make emotional memory last

Emotionally-arousing events activate a number of physiological systems that help the organism cope with the situation at hand. This orchestrated physiological response includes the release of hormones and neurotransmitters, such as catecholamines. These substances, in particular norepinephrine, act on the medial temporal lobe and prefrontal areas critically involved in memory formation [3,134,135]. In fact, during emotional arousal, norepinephrine is both rapidly released from brainstem nuclei such as the locus coeruleus, and (nor)epinephrine is secreted from the adrenal medulla. This peripheral (nor)epinephrine cannot pass the blood-brain barrier but activates β-adrenergic receptors on vagal afferents projecting to the brainstem nucleus tractus solitarius. Noradrenergic projections from this region project to the amygdala, a key region for emotional memory formation. In particular, lesions of the basolateral part of the amygdala or pharmacological blockade of β-adrenergic activation in this area, abolish emotional-memory enhancement [136,137]. Beta-adrenergic mechanisms of amygdala activation can be further amplified by concurrent activity of glucocorticoids, released during highly stressful events. Simultaneous noradrenergic and glucocorticoid activation of the basolateral amygdala indeed results in especially strong memory for ongoing events [3,138]. Importantly, the amygdala is not the storage site for memories but regulates consolidation in other areas, such as the hippocampus, prefrontal cortex and dorsal striatum. Moreover, amygdalar modulation is not limited to the emotionally-arousing event itself but extends to events preceding the event as well [138–140].

In sum, decades of research have established that noradrenergic arousal in the basolateral amygdala modulates memory consolidation in other areas, including the hippocampus, to enhance emotional memory. However, recent years have seen exciting new discoveries including, for example, the specific involvement of the locus coeruleus, and the long-term vividness of arousal-modulated memory.

Glossary

Event segmentation: a process by which a continuous stream of information is split into separate 'chunks' or representations in memory. 'Event boundaries' represent the event eliciting segmentation.

Latent state: a hidden generative model that causes events in the environment; a shift in the latent state ('change point' event) indicates a change in the statistics governing observed outcomes.

Learning rate: regulates the extent to which new outcomes are integrated into the stored value of an associated event (or action). A high learning rate indicates that a new outcome updates value to a greater extent, diminishing the influence of previous outcomes on that value.

Locus coeruleus (LC): a brainstem nucleus representing the main source of norepinephrine in the brain.

Medial temporal lobe: an anatomically-linked system of structures in the brain critical for memory, including the hippocampus and surrounding entorhinal, perirhinal, and parahippocampal cortices.

Prediction error (PE): the difference between expected and actual outcome; signed PEs ('SPE') represent the signed difference (outcome – expectation), whereas unsigned PEs ('UPE') represent the absolute deviation between expectation and outcome.

Reinforcement learning: an associative learning process whereby expectation and behavior are strengthened or weakened by motivationally relevant outcomes (e.g., reward or punishment).

Reinstatement (also "replay"): a process where the pattern of neural activity present at encoding is repeated after the event.

Salience network: a large-scale neural network that prioritizes the processing of emotionally salient information, including areas such as the insula, the amygdala or the dorsal cingulate cortex.

Schema network: a large-scale neural network implicated in the encoding of information congruent with prior knowledge, including the medial prefrontal cortex, precuneus, and angular gyrus.

Ventral tegmental area (VTA): a midbrain area that is a primary source of dopamine to the brain and the origin of the mesocorticolimbic system, widely implicated in reward processing.

Outstanding questions

If both affect-driven and PE-driven memory mechanisms are linked to noradrenergic and dopaminergic action, how do these mechanisms differ? What neural processes make PE effects on memory distinct from affect (and vice versa)?

How do dopaminergic and noradrenergic systems interact to balance the strengthening, integration and segmentation of memory (e.g., between PEs that reflect a change in the latent state versus not)?

While unsigned PEs increase both learning rate and memory, these effects are uncorrelated; which mechanisms differentiate value (outcome) and memory (outcome-event) updating as well as long-term retention of values?

How do value and surprise signals interact to modulate memory in the brain?

Do positively-valenced PEs across threat and reward learning (e.g., a reward PE and a shock-omission PE) act similarly or differently on neural memory mechanisms?

Is PE-memory enhancement selective for predictive information or is there a similar enhancement for non-predictive stimuli present in temporal proximity to the PE?

Is PE-memory enhancement dependent on the temporal distance of a stimulus to the outcome PE?

Do affect and prediction routes produce different mnemonic signatures and dynamics at retrieval?

Does the deployment of affect versus prediction mechanisms vary depending on age? For instance, is emotional-memory enhancement in young children primarily driven by arousal mechanisms, while PE- mechanisms become more relevant when the hippocampus and the prefrontal cortex are fully developed?

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