

Acetylcholine: a candidate substrate for hippocampal predictive learning?

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Abstract

Acetylcholine release in the hippocampus has been associated with diverse neural functions in learning and memory, including novelty, uncertainty detection, error correction, arousal and hidden state inference, while also modulating theta oscillations. Confronted with this plurality of roles, a unifying framework for interpreting cholinergic function is lacking. Recently, predictive models have emerged as a normative lens for understanding neural function, viewing the brain as learning to predict environmental dynamics. Within this framework, we propose that hippocampal acetylcholine serves as a fundamental learning signal, encoding state transition prediction errors – the magnitude of mismatches between predicted and actual transitions in environmental states. We suggest that, analogously to how dopamine signals reward prediction errors to guide value learning, acetylcholine guides structural learning, signalling state transition prediction errors. By condensing behaviour onto timescales amenable to spike-timing-dependent plasticity, theta sequences provide a potential substrate for calculating state transition prediction errors and driving the synaptic updates that revise the internal world model. Within the septo-hippocampal circuit, we propose that theta sequences relay predictions to the septum for comparison against observed state transitions, with the resulting cholinergic feedback gating plasticity in proportion to the mismatch. Plausibly, this mechanistic account unifies the diverse roles of acetylcholine, from novelty detection to hidden state inference, as aspects of a single computational principle – learning predictive internal world models from precisely-timed neural sequences.

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Introduction

Cholinergic innervation of the hippocampus is essential for the formation of spatial and episodic memory^{1,2}, with anticholinergic drugs producing profound anterograde amnesia^{3–5}. Acetylcholine, a neuro-modulator released in the hippocampus principally by projections from the medial septum, shapes numerous hippocampal functions: enhancing responses to novel stimuli^{6–8}, signalling environmental uncertainty^{9–11}, biasing neural dynamics towards encoding over retrieval states^{12–14}, and regulating the power and phase of theta oscillations^{15,16}. This functional diversity has led to multiple theoretical accounts of hippocampal cholinergic function^{1,9,17}, each capturing important aspects of the empirical data, but none providing an overarching computational framework¹. The absence of such a framework has hindered progress in understanding how cholinergic dysfunction contributes to cognitive decline in neurodegenerative diseases, particularly Alzheimer's disease, in which basal forebrain cholinergic degeneration is an early and prominent feature^{18–20}.

Over the past decade, computational neuroscience has increasingly cast the hippocampus as learning to anticipate upcoming states rather than representing only the present. These predictive models of hippocampal function^{21–25} offer new perspectives on the problem of unifying the diverse functions of acetylcholine^{26–35}. In such frameworks, the hippocampus maintains internal world models of transitions between environmental states – spatial locations, sensory contexts or task-relevant variables – with discrepancies between predicted and observed transitions driving updates that refine the models by adjusting the strength of synaptic connections^{25,29}. Building on this foundation, we propose that hippocampal acetylcholine serves as a state transition prediction error signal – encoding mismatches between predicted and observed sequences of environmental states. This hypothesis positions acetylcholine as the structural learning counterpart to the established dopaminergic role in signalling reward prediction errors in value learning^{36,37}. Whereas dopaminergic prediction errors update value estimates to guide reward-seeking behaviour, cholinergic state transition prediction errors update internal world models of environmental dynamics to guide flexible navigation and memory formation.

In this Perspective, we develop this state transition prediction error framework, examine its empirical support and explore its implications for cholinergic contributions to memory and its disorders, providing a parsimonious account of the diverse functions of acetylcholine through a simple principle: larger prediction errors drive greater septal cholinergic output to the hippocampus. Although we focus on spatial navigation and hippocampal function, we propose that this may represent a general computational principle of cholinergic signalling throughout the brain^{6,7,9,38–44}. We first set out how predictive learning models of hippocampal function are acquired through structural learning, arguing that revising these internal world models requires a teaching signal reporting state transition prediction errors. We then develop our central hypothesis that septal acetylcholine is this signal, with the septo-hippocampal circuit positioned to compute the prediction error and feed it back to gate hippocampal plasticity. Next, we show how a single principle accounts for functions previously treated separately: robust hippocampal cholinergic release during novelty^{6,7,45,46}, tonically elevated hippocampal acetylcholine via septal activation during environmental uncertainty^{9,11,47}, and the cholinergic enhancement of encoding over retrieval^{1,12–14}. We then describe how cholinergic modulation of theta sequences could both compute state transition prediction errors and drive the resulting

internal world model updates. Finally, we set out the experimental predictions that distinguish this account from existing theories, and consider its implications for cholinergic dysfunction in Alzheimer's disease.

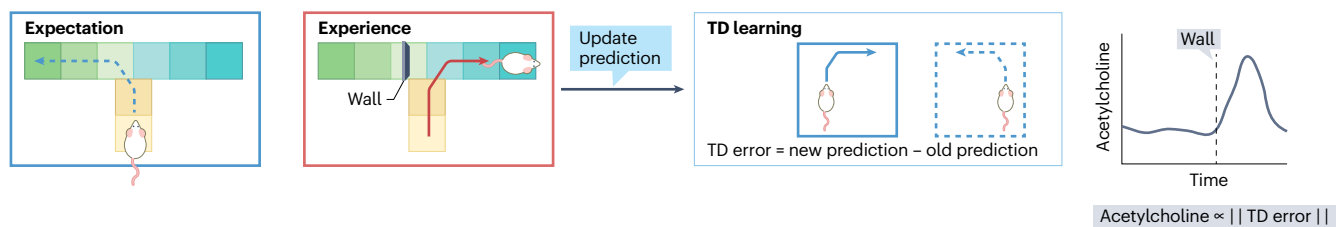
Predictive learning as a normative framework

The conception of hippocampal function has expanded markedly, with foundational discoveries of spatial mapping^{48,49} laying the groundwork for contemporary accounts that cast the hippocampus as maintaining predictive models^{22,33,50}. Whereas early studies characterized place cells as encoding current location, subsequent discoveries demonstrated that these neurons encode far more than static position. Place cells show prospective firing biases^{51,52}, anticipatory activity before reaching locations^{53–55} and experience-dependent remapping that reflects learned statistics of the environment^{22,56}. Moreover, hippocampal cells encode sequential structure beyond physical space, representing auditory sequences⁵⁷, temporal intervals^{58,59} and abstract task states^{60,61}. This evolution in understanding – from place cells as spatial sensors to generalized predictive units – mirrors a broader reconceptualization of the hippocampus as encoding not only just where an animal is, but also what it is going to experience next^{62,63}. Thus, modern frameworks cast hippocampal representations as encoding state transition probabilities, maintaining dynamic internal world models of how environmental states unfold over time^{22,26}.

Temporal difference learning provides a computational framework for acquiring and updating these predictive models of the environment^{64,65}. The successor representation exemplifies this approach, encoding each state not by its immediate features but by expected future state occupancy^{21,22,28,32,66}. Under the successor framework, the activity of a place cell reflects the probability of visiting future locations given current position and behavioural policy. Learning these representations – whether through successor representations^{22,25}, predictive maps^{26–29} or other temporal difference models^{23,24,67} – requires computing prediction errors between expected and observed state transitions. When an animal's trajectory deviates from predictions – taking an unexpected turn or encountering a blocked path – the mismatch generates state transition prediction errors signalling the internal world model of environmental dynamics must be updated (Fig. 1a). Such updating is an instance of structural learning, realized through changes in synaptic connectivity, so that the internal world model comes to reflect the newly observed structure of the environment. This framework can naturally account for types of place field remapping during environmental changes^{22,25,56,68} and the need for enhanced plasticity during novel experiences²⁹.

Critically, this structural learning differs fundamentally from value learning mediated by dopamine³⁶ (Fig. 1b). The brain faces two distinct learning challenges: understanding how the world is structured – the sequences in which states follow one another – and evaluating which states are rewarding. Dopamine signals reward prediction errors to update value estimates, for example, learning that a particular location contains food or shelter³⁶; but before an animal can learn the value of locations, it must learn the structure of how these locations connect⁶⁹. This structural learning requires different prediction errors: not 'was this more or less rewarding than expected?' but rather 'did the path end up where it was expected to?'. Although some hippocampal neurons encode the location of rewards⁷⁰, the state transition prediction error itself should be computed independently of reward, allowing an accurate internal world model of environmental structure to be learned regardless of where reward is encountered^{28,71}.

a State transition prediction error



b Reward prediction error

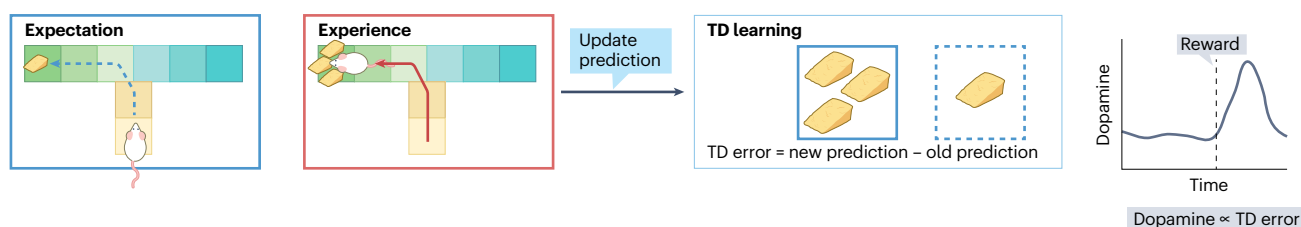


Fig. 1 | The state transition prediction error framework in a spatial setting. **a**, State transition prediction errors arise when an animal's trajectory deviates from expectation, such as taking an unexpected turn at a T-maze choice point. Acetylcholine release is proposed to scale with error magnitude. **b**, By contrast,

reward prediction errors carried by dopamine encode signed differences between expected and received rewards. Both systems use temporal difference (TD) learning to update predictions but serve distinct functions: dopamine updates value estimates, acetylcholine updates internal world models.

This computational division suggests distinct neuromodulatory systems for value versus structural learning. Just as midbrain dopamine neurons signal reward prediction errors to guide value learning, structural learning requires a dedicated signal tracking errors in predicted state transitions. Such a signal should remain lower when state transitions unfold as expected (during routine navigation of well-learned environments) but increase when environmental dynamics violate predictions (during novelty or environmental change), thereby gating structural plasticity to revise the internal world model when needed. These requirements align precisely with known properties of hippocampal acetylcholine: elevated during novel experiences and environmental uncertainty⁷⁹, suppressed during familiar navigation, and necessary for encoding but not retrieval¹. We propose that acetylcholine serves as this structural learning signal, conveying state transition prediction errors to guide construction and revision of the hippocampal internal world model – a role as fundamental to structural learning as dopamine is to value learning.

We next define this error precisely – the state transition prediction error – and set out how it is computed.

The state transition prediction error hypothesis

We define state transition prediction errors as mismatches between expected and actual sequences of environmental states. Although such states are features of the environment, they are encoded in hippocampal activity, from which both predictions and observations are readout: the error is therefore computed over neural representations even as it quantifies a transition in the world. The states themselves need not be spatial, but we focus on spatial navigation to illustrate the structural learning framework. When navigating a familiar route, the brain continuously predicts upcoming locations based on current position and intended direction. A state transition prediction error occurs when reality violates these predictions: taking an unexpected turn, encountering a blocked path or finding that a familiar corridor now

connects to a different room. Crucially, large state transition prediction errors can occur even with entirely familiar states: entering your office through what should be a cupboard door generates a substantial prediction error despite both being well known.

These errors differ fundamentally from reward prediction errors, which signal unexpected rewards or their absence. Instead, state transition prediction errors signal unexpected changes in environmental structure – not just whether a location now contains food, but whether the route to reach it has changed. Such errors would be largest when experiencing entirely novel state sequences and smallest during routine navigation of well-learned environments. This distinction is crucial – state transition prediction errors provide a teaching signal to refine the internal world model: a representation of how environments are structured, that is, of how states connect to one another. A central claim of our account concerns dimensionality. Whereas state transition prediction errors for structural learning are inherently high-dimensional – reflecting the complexity of the neural state space – we propose that cholinergic release in the hippocampus reflects only their scalar magnitude (Fig. 1a), functioning as a signal that modulates the extent of the required plasticity without determining its locus. Synaptic specificity may instead arise from local coincidence detection: synapses are modified where presynaptic and postsynaptic activity coincides in time, within the windows for spike-timing-dependent plasticity (STDP)^{72,73}, with cholinergic tone scaling the magnitude of these updates^{74–76}.

The septo-hippocampal circuit is well positioned to compute state transition prediction errors. Anatomically, the medial septum receives extensive direct and indirect projections from the hippocampus^{77–79}, with both cholinergic and GABAergic neurons in the medial septum projecting back to the hippocampus^{80–82}, establishing a closed feedback loop. Hippocampal neurons generate predictions about upcoming states through prospective coding^{22,51,83} and theta sequences⁸⁴, which progressively sweep from current to future locations during each ~100-ms cycle of the hippocampal theta oscillation^{55,62,85,86}.

However, the direct projection from hippocampus to medial septum originates predominantly from GABAergic interneurons rather than the place cells, CA3/CA1 pyramidal cells, that generate theta sequences^{87,88}. Although these projections provide one means through which the hippocampus shapes medial septal output, and thus cholinergic feedback⁸⁹, it raises the question of how sequential content reaches septal circuits. An alternative indirect route runs through the lateral septum: hippocampal pyramidal neurons project onto GABAergic neurons in the lateral septum^{90,91}, which in turn project to the medial septum⁷⁹. Disinhibition through the lateral septum – whereby exciting these inhibitory relay neurons suppresses medial septal activity, and withdrawing that drive releases it – has been described in other functional domains⁹¹, although whether lateral septal terminals act directly on cholinergic neurons or via intervening medial septal interneurons remains unresolved.

We propose that this architecture could support prediction error computation through such a disinhibitory mechanism. Lateral septal neurons driven by predicted state transitions would maintain tonic GABAergic inhibition of medial septal cholinergic neurons; an unexpected state transition, by violating that prediction, would transiently reduce lateral septal drive, withdrawing the medial septal inhibition and releasing cholinergic output to the hippocampus. Consistent with this proposal, optogenetic suppression of lateral septal somatostatin neurons disinhibits the cholinergic septo-hippocampal pathway⁹². Nevertheless, the precise circuit by which sequential activity of hippocampal pyramidal cells is translated into modulated cholinergic output remains to be determined. Importantly, the lateral septum is well suited to convey state transition prediction-relevant content to the medial septum: lateral septal neurons inherit theta-organized spatial representations from place cells in the hippocampus, including a rate-independent phase code for position that reflects the convergent superposition of hippocampal place fields^{93,94}, theta phase precession^{93,94} and theta cycle skipping⁹⁴. The faithful representation of hippocampal theta sequences in the lateral septum means that the sequential structure required to evaluate state transition predictions is available at the input to the medial septum, providing a sufficient basis for the comparison between predicted and observed state transitions, as described next.

Within this circuit, we propose hippocampal theta sequences provide a plausible temporal substrate for computing state transition prediction errors. Each theta cycle generates a single compressed trajectory from current to predicted states^{55,62,84,85}, and as the animal moves forward, previously predicted states become sensory constrained in subsequent cycles, providing the septum with a continuously updated stream of sequential activity containing both predictive and observational components. The comparison between predicted and observed state transitions could be implemented in two complementary ways. First, it may unfold over successive theta cycles: as states that were predicted in one theta cycle become sensory defined in the next, septal circuits can compare these successive representations. Second, sensory-constrained and internal world model-dependent representations coexist within individual theta cycles as sequences sweep from past through present to future locations⁶², encoding internally generated predictions^{54,58,85,95} – enabling a within-cycle comparator between observed and predicted states. This within-cycle account is also consistent with the rapid timescale of individual cholinergic neuron responses: whereas fibre photometry measures extracellular acetylcholine dynamics on the order of hundreds of milliseconds^{96,97}, single-neuron recordings from medial septum cholinergic neurons

reveal phasic responses – brief, event-locked increases on the order of tens of milliseconds⁹⁸ – fast enough to operate within individual theta cycles. In either implementation, integrating hippocampal input probably depends on local processing within the septum, where dense, locally interconnected networks of cholinergic, glutamatergic and GABAergic neurons^{99–102} are well positioned to compute these comparisons between predicted and observed state transitions. Tonic cholinergic signals, associated with sustained uncertainty^{9,47}, would then reflect the accumulation of frequent phasic cholinergic prediction error signals arising per transition over behavioural timescales. Together, this establishes a closed-loop system: the hippocampus generates sequential predictions, the septum detects violations of those predictions and cholinergic feedback modulates hippocampal plasticity to improve future predictions.

Empirical measurements of cholinergic release dynamics align with theoretical predictions for state transition prediction errors: hippocampal acetylcholine levels increase sharply when animals encounter novel environments (Fig. 2a), situations that would generate large state transition prediction errors^{6,7,45}. Conversely, the novelty-driven component of cholinergic release diminishes as environments become familiar, consistent with increasingly predictable state transitions^{6,103,104}. Crucially, cholinergic release patterns dissociate from reward signalling: acetylcholine responses scale with the unexpectedness of reinforcement regardless of valence¹⁰⁵, consistent with an unsigned prediction error signal^{98,106} – one that reports the magnitude of a mismatch but not its direction. This contrasts with the dopaminergic reward prediction error, which is signed, increasing for better-than-expected outcomes and decreasing for worse-than-expected ones³⁶. This dissociation distinguishes the functional role of acetylcholine from that of dopamine and supports its proposed role in structural learning – although notably reward states can constitute critical structural features in the hippocampal representation of tasks⁷⁰. The state transition prediction error hypothesis predicts not only tonic changes in acetylcholine, but also phasic, event-locked cholinergic transients at individual state transitions (Fig. 2a). Thus, cholinergic transients occur within hundreds of milliseconds of state transitions within tasks^{96,97,107}, a timescale well suited for real-time state transition prediction error signalling. Evidence from other basal forebrain regions reinforces this picture: cholinergic neurons rapidly acquire phasic responses to behaviourally relevant stimuli during associative learning across multiple target regions (including auditory cortex^{108,109} and basolateral amygdala¹¹⁰) and during innate and learned behaviours more broadly¹¹¹. However, much of this evidence derives from basal forebrain cholinergic populations outside the medial septum^{105,107}, which forms a molecularly and functionally distinct subnetwork¹¹² specialized for theta generation, so phasic signalling characterized elsewhere may not generalize directly to the septo-hippocampal pathway. Direct evidence for phasic cholinergic signalling in the septo-hippocampal pathway remains limited, although robust aversive-stimulus-evoked responses have been recorded in cholinergic axons projecting from the medial septum to hippocampal CA1 (ref. 113), consistent with event-locked signalling in this pathway. Confirming that medial septal cholinergic neurons exhibit the full repertoire of state transition prediction error-like dynamics proposed here remains an important goal for future work.

The parallel with dopaminergic reward prediction error signalling is instructive but reveals critical differences. Whereas dopamine provides bidirectional signals for value learning, with firing increasing above baseline for positive reward prediction errors and decreasing for negative prediction errors³⁶, cholinergic neurons show predominantly

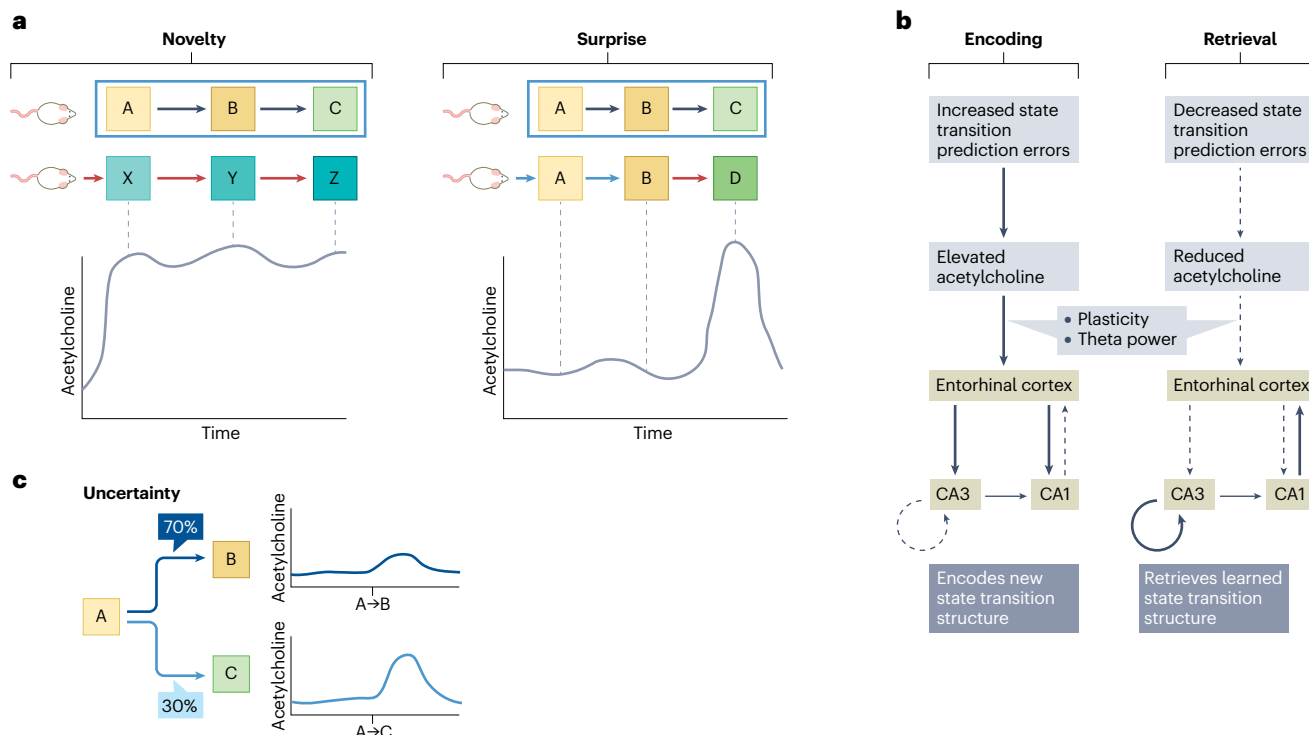


Fig. 2 | Accounting for diverse cholinergic functions. **a**, Novelty and surprise generate distinct state transition prediction error patterns. Exposure to an unfamiliar environment (linear track X–Y–Z) produces sustained acetylcholine elevation (left), whereas unexpected transitions between familiar locations (linear track A–B–C) generate phasic transients (right). **b**, The encoding–retrieval distinction emerges from state transition prediction error magnitude. High prediction errors during encoding trigger cholinergic release that enhances

theta power and plasticity, training CA3 recurrent and CA3 → CA1 synapses to encode new state transition structures and update the internal world model. During retrieval, accurate state transition predictions minimize acetylcholine, allowing these same circuits to retrieve learned state transition structure. **c**, In environments with stochastic state transitions, prediction errors scale with state transition unpredictability, producing graded acetylcholine release that tracks environmental uncertainty.

unidirectional signalling, increasing firing for prediction violations but maintaining baseline activity for accurate predictions^{105,107}. This asymmetry makes computational sense: although both positive and negative reward errors are behaviourally relevant, only violations of expected state transitions necessitate updates to the internal world model. However, accurately updating it requires two complementary synaptic changes. When an animal experiences an unexpected sequence of states, STDP⁷² acting on theta sequences⁸⁴ strengthens connections corresponding to the new state transition²⁹, whereas heterosynaptic depression weakens connections supporting the expected state transitions that do not occur^{114,115}. These same mechanisms naturally accommodate the incorporation of novel states into existing state transition structures: strengthening connections to newly encountered states while weakening incorrect predictions inherited from familiar states – both updates following from a single, unidirectional cholinergic signal.

Having set out how acetylcholine could signal state transition prediction errors and drive the resulting plasticity, we now turn to a broader implication: that a single principle may unify diverse cholinergic functions – from novelty and uncertainty to the enhancement of encoding over retrieval – that have so far been studied in isolation.

Unifying diverse cholinergic functions?

Decades of research have revealed two fundamental but seemingly distinct roles for acetylcholine in hippocampal function. First, the

influential framework from Hasselmo and colleagues proposed that acetylcholine biases hippocampal dynamics towards encoding new information over retrieving existing memories^{1,13,14,116}. This occurs through both circuit-level and synaptic mechanisms. Acetylcholine selectively suppresses excitatory feedback connections^{117,118} – particularly the recurrent collaterals in CA3 (ref. 119) and the Schaffer collaterals to CA1 (ref. 12) – while preserving or even enhancing feedforward input from the entorhinal cortex¹. Simultaneously, acetylcholine directly enhances synaptic plasticity, facilitating long-term potentiation, and STDP during theta oscillations⁷³. This differential modulation creates optimal conditions for encoding: reducing interference from previously stored patterns while maintaining sensitivity to new sensory input. The state transition prediction error framework provides a computational interpretation of this switch: prediction errors trigger acetylcholine release that suppresses CA3 recurrent collaterals, allowing sensory-driven entorhinal input to update these same synapses with new state transition structures (Fig. 2b). The extensive recurrent collaterals in CA3, which support pattern completion and sequence learning^{120,121}, are a primary substrate for encoding these state transition structures³⁰. Additional sites may include the CA3 to CA1 Schaffer collaterals that could convey predictions forward²⁹, and subicular circuits that might integrate these representations for behavioural output^{35,122}. In the case of spatial navigation tasks, states are encoded by place cells^{48,123} and other spatially modulated cells^{124–127}, with the

connections between them encoding the state transition structure of the spatial environment^{22–25,29,35}. These circuit-level mechanisms, combined with the direct enhancement of synaptic plasticity^{73–76}, align precisely with what would be expected of a signal that tracks state transition prediction errors and selectively enables structural learning when world models must be updated.

Second, extensive work has established the cholinergic system's crucial role in modulating theta oscillations. Optogenetic stimulation of septal cholinergic neurons suppresses sharp wave ripples (synchronized bursts of hippocampal activity essential for memory consolidations)¹²⁸ and enhances theta oscillations in the hippocampus¹⁵, creating network dynamics associated with encoding¹. Pharmacological studies demonstrate that cholinergic blockade with scopolamine disrupts both the amplitude and phase dynamics of theta oscillations^{129,130}, whereas cholinergic enhancement increases theta power and frequency¹³¹. Acetylcholine modulates hippocampal theta oscillations through both muscarinic and nicotinic receptors acting on pyramidal cells and interneurons^{130,132}, via both direct and indirect pathways. Septal cholinergic neurons project directly to the hippocampus to modulate theta phase and amplitude dynamics, but also act on GABAergic neurons within the septum, which provide the rhythmic pacing of theta oscillations through phasic inhibition of hippocampal interneurons^{133,134} – generating the ~100-ms theta cycle within which theta sequences are organized and plasticity is timed.

Although both functions are clearly important for hippocampal processing, these roles of acetylcholine have typically been studied as parallel phenomena. We propose that these two aspects of cholinergic function are intimately connected through a common computational principle: state transition prediction errors drive cholinergic release that simultaneously biases hippocampal dynamics towards encoding and modulates theta oscillations to support plasticity. However, direct evidence for cholinergic signalling of state transition prediction errors – such as increased acetylcholine release when animals encounter unexpected state transitions – remains to be demonstrated. Task designs that manipulate state transition probabilities between equally familiar states, while controlling for state novelty itself, can dissociate state transition prediction errors from state novelty responses and provide a direct test of this hypothesis.

The state transition prediction error framework provides a unified account of the diverse functions that have been attributed to acetylcholine in the context of hippocampal processing: novelty detection^{6–8,45,46}, the selective enhancement of encoding over retrieval^{1,13,14,116,135,136}, tonic and phasic responses to environmental unpredictability^{9,41,96,97,107}, and hidden state inference^{11,17,44,137,138}. Each function emerges from different patterns of state prediction error. Beginning with novelty detection, when an animal encounters a genuinely novel environment, every state transition violates expectation because the current internal world model lacks representation of these new states (Fig. 2a, left). This generates maximal state transition prediction errors, driving the robust cholinergic release consistently observed during exploration of novel environments^{6–8,17,45,46}. However, novelty encompasses more than just new locations – it includes familiar states connected in unexpected ways. A known room accessed through a previously blocked passage, or familiar landmarks appearing in unusual configurations, generates state transition prediction errors despite the individual states being recognized. This broader conception predicts cholinergic responses not only to absolute novelty but also to familiar elements in novel arrangements. Consistent with this view, empirical studies show that acetylcholine

release scales with the degree of prediction violation: completely novel state transitions producing the greatest sustained elevation that diminishes progressively with familiarity^{6,103–105,107}. This graded response suggests a structural learning signal consistent with state transition prediction error magnitude, allowing new information to be incorporated into existing internal world models while maintaining stable representations of well-learned environmental structures.

During encoding of new experiences, state transition prediction errors are high as the brain encounters novel state transitions or updates its internal world model – conditions that trigger cholinergic release to gate synaptic plasticity in these proposed circuits (see 'The state transition prediction error hypothesis' section)^{14,15,29,73–76}. However, during retrieval of well-learned information, the brain operates with accurate internal models of the world that generate minimal state transition prediction errors¹ (Fig. 2b, right). State transitions unfold as expected, resulting in limited cholinergic release and requiring little updating of the state transitions encoded in CA3 recurrents and CA3–CA1 connections^{6,29,30,103,116}. Accordingly, cholinergic antagonists such as scopolamine profoundly impair learning of new state transition structures¹⁰, with dose-dependent effects¹³⁹, while leaving intact the ability to generate predictions from already-learned internal world models^{1,3,10,14,140}. Conversely, cholinergic enhancement reopens plasticity in these hippocampal circuits for further optimization of even well-learned internal world models^{139–141}. Such error-based gating of structural learning resources prevents both catastrophic forgetting and the persistent use of outdated state transition estimates.

Uncertainty arises in environments with inherently stochastic state transitions – mazes containing repeated identical rooms¹⁴², moveable barriers that reconfigure spatial connectivity^{28,143} or social contexts in which conspecifics create unpredictable path blockages. As lower-probability state transitions generate larger prediction errors, individual state transitions in such environments evoke graded cholinergic transients scaled by their improbability (Fig. 2c). We predict that the accumulation of these recurring transients maintains tonically elevated acetylcholine, sustaining the enhanced plasticity that allows internal world models to be continuously updated, consistent with observations of sustained cholinergic activity during uncertainty^{6,41,107}. By contrast, surprise occurs when low-probability transitions happen in otherwise predictable environments – a change in a previously stable sequence of states such as a familiar landmark suddenly moving, or a reliable path becoming blocked. We expect these events will generate large, phasic prediction errors and corresponding cholinergic transients (Fig. 2a, right). The distinction is computationally important: uncertainty requires sustained structural learning readiness whereas surprise demands rapid revision of internal world models. These distinct computational demands align with observations that cholinergic signalling operates on multiple timescales^{9,41,96,97,107} – tonic elevation during uncertain environments plausibly reflects either accumulated phasic state transition prediction errors or a distinct expected uncertainty signal^{9,47}, whereas phasic transients mark individual prediction violations.

Cholinergic release also scales with movement speed during navigation, persisting even in highly familiar environments^{104,144}. Rather than posing a difficulty for this framework, this observation is a quantitative prediction of it: state transition prediction errors should never reach zero unless state transitions are both entirely deterministic and perfectly learned. As the internal world model encodes probability distributions over future states whereas observations are categorical, a residual error persists on every state transition, even for

high-probability paths. These individually small errors accumulate faster at higher speeds, because states are encountered more rapidly, producing the speed-correlated cholinergic signal evident in familiar environments^{104,144}. Importantly, this speed-correlated cholinergic signal coexists with separable phasic responses to genuinely unexpected events¹⁴⁴, consistent with a single system encoding both residual errors per state transition and large phasic acetylcholine signals driven by prediction violations. The distinction between phasic and tonic cholinergic signalling may be further supported by acetylcholine receptor-subtype-specific readout. Nicotinic receptors, which operate on faster timescales than muscarinic receptors¹³⁰, are well suited to transduce rapid per-state transition residual error signals, modulating theta dynamics through their effects on hippocampal GABAergic interneurons^{130,132}. By contrast, slower muscarinic signalling could integrate over multiple state transitions, contributing to the tonic modulation of hippocampal network state and plasticity that characterizes uncertain environments. In both regimes, we propose the specificity of synaptic updating for structural learning is ultimately determined by STDP acting on theta sequence content^{29,72,84} – acetylcholine scales the magnitude of these updates^{73–76} rather than selecting which synapses are modified.

Hidden state inference represents a sophisticated form of learning in which the brain must update representations of hidden (latent) variables that cannot be directly observed^{11,61,137,145}. Consider an animal that learns two distinct behavioural contexts across locations in the same physical environment: foraging versus escape¹⁴⁶. Each behavioural context has different optimal actions: optimal foraging requires a random walk spanning different sections of the environment in search of food, whereas optimal escape probably involves running for shelter along the shortest possible route to escape a potential threat. The transition between these hidden states (food versus threat) generates state transition prediction errors because the same location now predicts different outcomes (searching for food versus searching for shelter), even when the environment remains unchanged. We propose the cholinergic system responds to these behavioural context switches with increased cholinergic release, enabling the hippocampus to update its representation of the current hidden state^{11,61}. This mechanism might extend to social scenarios¹⁴⁷ in which others' intentions are hidden states, or to tasks requiring maintenance of multiple hypotheses about environmental structure¹³⁷. Empirical support comes from converging lines of evidence. Studies show elevated acetylcholine during task stages in which contexts change, necessitating behavioural shifts based on hidden rules¹²⁸. In parallel, cholinergic antagonists impair processes that rely on detecting such changes that cannot be directly observed: they reduce sensitivity to belief-updating sensory stimuli¹⁰ and prevent hidden state inference from ambiguous sensory cues¹⁴⁸. These findings suggest that state transition prediction errors drive cholinergic release when representations of hidden variables require updating.

Thus, the state transition prediction error framework builds on and extends existing accounts of cholinergic function rather than replacing them. Hasselmo and colleagues introduced an influential framework describing how acetylcholine biases hippocampal dynamics towards encoding over retrieval^{11,13,14}. The state transition prediction error framework offers a computational complement to this account: it proposes that the magnitude of prediction failure determines the degree of cholinergic release, providing a graded trigger for what has previously been characterized as a binary encoding and retrieval switch (Fig. 2b). This predicts that cholinergic release should scale continuously with prediction violation magnitude, even within encoding

contexts. Uncertainty-based accounts^{9,11,44,47} contribute the important insight that acetylcholine tracks the reliability of predictions, with elevated release in uncertain environments (Fig. 2c). The state transition prediction error framework shares this core intuition but proposes a finer-grained mechanism: discrete prediction errors on individual state transitions drive phasic cholinergic release, with the tonic elevation observed in uncertain environments emerging from the accumulation of such frequent phasic errors.

A third class of model is also subsumed. Unsigned prediction error accounts of cholinergic firing^{98,105,106} capture the observation that cholinergic responses are valence independent – a property the state transition prediction error framework reproduces directly: reinforcement events are themselves state transitions, so unexpected rewards or punishments generate state transition prediction errors, while the framework additionally predicts cholinergic release driven by unexpected transitions in the absence of any reinforcement. These predictive modelling accounts converge in many situations, but the state transition prediction error framework generates distinct predictions. Most notably, encountering familiar states connected in an unexpected sequence – such as a well-known room accessed through a novel corridor – should produce robust cholinergic release despite involving no state novelty, no change in environmental uncertainty and no categorical shift between encoding and retrieval. Experiments that manipulate state transition structure while holding these other variables constant can therefore arbitrate between computational accounts of cholinergic firing as an unsigned prediction error (Box 1).

Although we have developed this framework through spatial navigation, the underlying principle generalizes to belief updating more broadly. Bayesian surprise – the divergence between prior and posterior beliefs – provides a general theoretical measure of belief updating that converges with state transition prediction errors in many situations. It quantifies how an entire probability distribution over possible states is revised in light of new evidence: a high-dimensional comparison of prior against posterior across all hypotheses. The state transition prediction error captures the same intuition with a single quantity – the degree to which an observed transition departed from the predicted one. In our account, beliefs about environmental structure are embodied in the learned state transitions of the internal world model, so updating a belief is updating its connections. The scalar state transition prediction error reports the need for such an update and, through cholinergic gating of plasticity, drives it – just as the divergence between prior and posterior would in a Bayesian scheme. The framework can thus be understood as a mechanistically constrained instantiation of Bayesian surprise, trading the generality and precision of a full distributional comparison for a signal that is biologically realizable and cheap to compute. Finally, the state transition prediction error framework subsumes older theories positing CA1 as a comparator region^{118,149,150}. Those accounts address state identification – whether sensory input matches memory – but operate on individual states rather than sequences of states. The state transition prediction error framework extends this logic to the level of trajectories, evaluating whether transitions between states unfolded as predicted, with CA1 state comparisons potentially feeding the septal computation of successive state transition prediction errors.

Having set out what the state transition prediction error computes and how it subsumes existing accounts, we now turn to its implementation: how predicted and observed transitions might be represented and compared in the brain. We propose that the theta rhythm provides the temporal scaffold on which this computation unfolds.

Box 1 | Testable predictions of the state transition prediction error hypothesis

The hypothesis makes specific, testable predictions spanning behaviour, physiology and circuit function. For each, we outline an experimental approach feasible with current methods and the outcome the framework predicts. Together they offer a programme for evaluating — and potentially falsifying — the central claim that acetylcholine reports state transition prediction errors.

Cholinergic release scales with state transition prediction error magnitude

- Experimental approach: combine genetically encoded acetylcholine sensors (such as GRABACH) with tasks that parametrically vary transition predictability while controlling for state novelty. Compare acetylcholine release when animals experience expected transitions, unexpected transitions between familiar states or novel states.
- Expected outcome: cholinergic release should be minimal for expected state transitions, elevated for unexpected transitions between familiar states and maximal for novel state sequences. Crucially, familiar states in unexpected contexts should produce release comparable to that for genuinely novel states.

Cholinergic signalling is necessary for updating internal world models

- Experimental approach: use optogenetic silencing of medial septal cholinergic neurons during environmental changes (such as barrier insertion or a shortcut opening) in well-learned environments. Probe subsequent navigation behaviour and whether place cell representations update appropriately.
- Expected outcome: silencing during environmental change should impair behavioural adaptation and prevent appropriate updating of place cell representations, with animals persisting on outdated trajectories. Silencing during stable navigation should have minimal effect.

Cholinergic signalling is sufficient to gate internal world model updating

- Experimental approach: use closed-loop optogenetic stimulation of septal cholinergic neurons time locked to specific state transitions in stable environments. Assess whether artificial cholinergic activation induces plasticity at otherwise stable synapses.
- Expected outcome: stimulation paired with specific state transitions should induce place field changes or route-preference shifts, even in well-learned environments. Unpaired stimulation should have weaker or no effect.

Theta sequences reflect learned state transition probabilities

- Experimental approach: record hippocampal ensembles during navigation in environments with experimentally controlled state transition statistics (such as probabilistic barriers or one-way doors). Decode theta sequence content at choice points.
- Expected outcome: theta sequence content should be biased towards higher-probability state transitions, and should update as animals learn new state transition statistics, with the rate of updating scaling with cholinergic tone.

Cholinergic release signals evidence for updating latent state estimates

- Experimental approach: record hippocampal acetylcholine dynamics during tasks requiring hidden state inference, in which the same sensory input requires different behavioural policies depending on unobservable context.
- Expected outcome: cholinergic release should scale with state transition prediction errors computed over hidden states — mismatches between expected and observed outcomes given the currently inferred context.

Theta oscillations as an implementation mechanism

Theta oscillations may provide a temporal scaffold upon which structural learning unfolds in the hippocampus. During active behaviour, hippocampal place cells fire in organized sequences within individual theta cycles (Fig. 3a), compressing extended behavioural trajectories into ~100–120-ms windows⁸⁴. These sequences sweep from behind to ahead of the animal's current location, representing more than simple recapitulation of recent experience or the specific path the animal will take. Rather, they seem to sample the space of possible available paths^{53–55} (Fig. 3a); a phenomenon that occurs on both constrained tracks and in the open field¹⁵¹.

Other authors have observed that this temporal compression may provide a computational function: theta sequences compress state transitions that unfold over seconds into neural patterns within STDP windows^{84,152,153} (Fig. 3b). We extend this framework by proposing that theta sequences serve two distinct computational functions for structural learning. First, theta sequences provide the substrate for structural learning of the internal world model itself. Recent computational work demonstrates that STDP acting on theta sequences is sufficient to learn successor representations²⁹ — predictive maps

encoding state transition probabilities between states represented by spatially modulated cells^{22,25,35} (Fig. 3c). As animals navigate, repeated theta sequences combined with STDP naturally build and refine these predictive models²⁹. Second, theta sequences may provide a mechanism for calculating state transition prediction errors. As the animal moves forward, locations that were represented as predictions in one theta cycle become increasingly sensory defined in subsequent cycles (Fig. 3a), allowing comparison between predicted and observed state transitions.

Acetylcholine exerts profound modulatory control over both the power and phase dynamics of theta oscillations^{14,15,129,135,154,155} and thus is perfectly placed to facilitate structural learning of the internal world model. Cholinergic activation enhances theta power through direct effects on hippocampal interneurons and pyramidal cells, with muscarinic receptors increasing neuronal excitability and nicotinic receptors synchronizing network activity^{16,132}. Beyond simple amplitude modulation of the theta oscillation, acetylcholine shifts the theta phase relationships between different hippocampal subregions, optimizing the network for encoding new information^{135,156}. Thus, elevated cholinergic tone, driven by large state transition prediction errors, enhances theta power^{15,135} and shifts the network activity in the hippocampus

towards encoding mode^{13,14,116}, facilitating the incorporation of new state transitions into the internal world model^{13,156}. This modulation creates a dynamic system in which the temporal structure of hippocampal activity adapts to the magnitude of state transition prediction errors, allocating computational resources precisely when internal world models need revision. When state transition prediction errors occur, cholinergic release plausibly amplifies the resulting plasticity, either directly^{12,73,74,76,157} or by modulating the theta phase of place cell activity^{14,129,135,154,155}, ensuring synaptic weights update in proportion to state transition prediction error magnitude.

Equally, the computation of state transition prediction errors may also be facilitated by theta sequences. Hippocampal output reaches the

septum through direct and indirect pathways^{77,78}, where septal circuits are well placed to compare predictions with observations. Each theta cycle provides predictions about upcoming states (see the 'The state transition prediction error hypothesis' section)^{62,84}. Critically, at the start of a theta sequence, predictions about proximal locations are constrained by current sensory input, whereas later in the sequence predictions about distant locations rely increasingly on the internal world model. As the animal moves forward, locations that were previously represented as distant predictions become sensory defined, providing the means to compare expectations and observations. Hence septal circuits may compute transition prediction errors by comparing how states were represented in different theta sequences. This framework

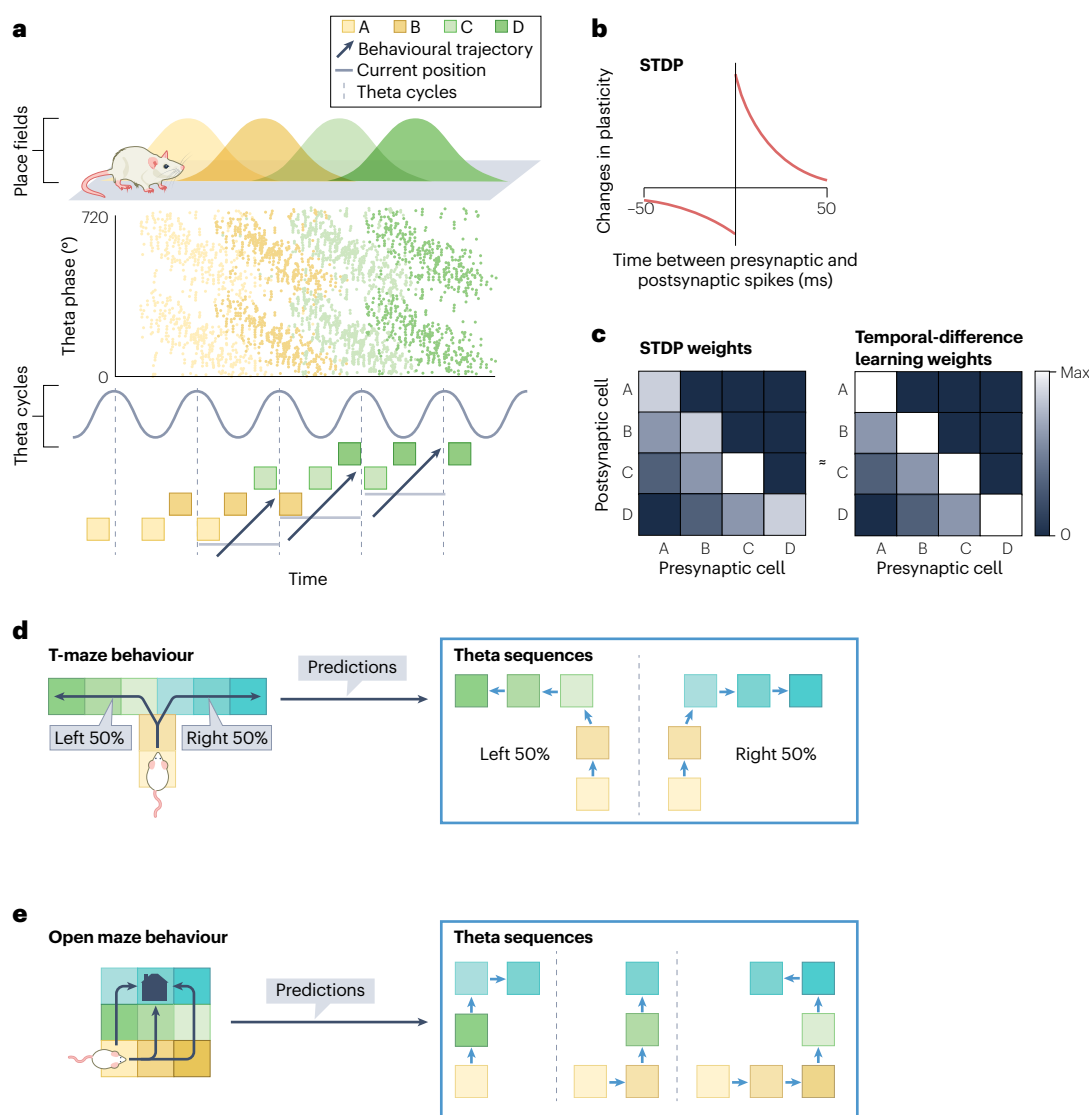


Fig. 3 | Proposed role of theta sequences in predictive learning of state structure. During active navigation, place cells fire in organized sequences that sweep from past through current to upcoming locations within individual ~100-ms theta cycles, compressing extended behavioural trajectories into windows compatible with synaptic plasticity (part **a**). Spike-timing-dependent plasticity (STDP) is sensitive to the millisecond-scale temporal relationships achieved

by this compression (part **b**). STDP acting on theta sequences learns state transition structure resembling internal world models, such as the successor representation (part **c**). Theta sequences should reflect learned state transition probabilities: sweeping towards remembered goal locations on an alternating T-maze task⁸⁵ (part **d**) or biased towards frequently traversed trajectories in open environments⁶³ (part **e**).

Glossary

Behavioural policy

An animal's strategy for selecting actions in each state — where it tends to go next from a given location. As predictive representations of state structure are learned from the state transitions an animal's actions produce, the sequence of states predicted depends not only on location but also on the behavioural policy the animal has followed during learning.

Disinhibition

The release of a neuron or pathway from ongoing inhibition, achieved by suppressing an inhibitory interneuron that normally constrains it. The net effect is excitatory: inhibiting an inhibitor increases the activity of its target.

Heterosynaptic depression

A reduction in synaptic efficacy at inactive synapses following strong activation of a separate, converging input onto the same postsynaptic neuron.

Hidden state inference

The cognitive or computational process of estimating unobservable (hidden) environmental states or contexts by analysing observable cues and outcomes.

Internal world models

Brain representations of environmental structure that encodes which states exist and the probabilities of transitions between them — across spatial, sensory, temporal and abstract task domains — supporting prediction of upcoming states and revised by prediction errors when environments change.

Pattern completion

The reconstruction of a stored neural ensemble pattern from partial or noisy input, via recurrent network dynamics.

Place cells

Hippocampal neurons that fire at specific locations and show prospective activity representing expected future positions, serving as fundamental units for encoding spatial state spaces.

Place field

The receptive field of a place cell. A region of an environment in which a hippocampal place cell fires at elevated rates.

Predictive learning

A learning framework in which organisms build internal world models predicting future events (state transitions and rewards), contrasting with associative learning that links stimuli to responses without predictive models.

Reward prediction errors

Dopaminergic teaching signals encoding the difference between expected and received rewards, driving value learning — the estimation of which states are rewarding.

Sequence learning

The encoding of ordered sequences of neural activity patterns representing successive experiences or locations.

Spike-timing-dependent plasticity

(STDP). Synaptic plasticity that depends on precise spike timing: presynaptic activity shortly before postsynaptic firing strengthens connections, whereas the reverse order weakens them. The ~20–100-ms timing window for potentiation aligns with theta-compressed sequences.

State space

The set of all possible states (locations, contexts or task variables) that an organism can represent, with transitions between states defining environmental structure.

Structural learning

Learning the structure of an environment — which states exist and how they connect, as distinct from their value — by updating the internal world model in response to state transition prediction errors.

Successor representation

A predictive representation that encodes each state by the states expected to follow it — weighted by their proximity and frequency under current behaviour — rather than by its immediate features, allowing future states to be predicted directly.

Temporal difference learning

A computational framework that learns predictions by computing differences between successive estimates, enabling learning from step-by-step prediction errors rather than waiting for final outcomes.

Theta cycle skipping

A firing pattern in which neurons fire on alternate theta cycles rather than every cycle, observed in some hippocampal and entorhinal neurons.

Theta oscillations

A prominent 8–10-Hz rhythmic oscillation in hippocampal field potentials during movement and REM sleep, with acetylcholine modulating its power and phase to support encoding versus retrieval.

Theta phase precession

The phenomenon whereby a place cell's firing shifts to progressively earlier phases of the hippocampal theta oscillation as an animal traverses the cell's place field.

Theta sequences

Organized place cell firing within individual ~100–120-ms theta cycles. These sequences compress extended behavioural trajectories into brief temporal windows, sweeping from current to future locations and aligning with spike-timing-dependent plasticity timescales.

predicts theta sequences should recapitulate behavioural trajectories that mirror learned state transition probabilities. For example, at a choice point on a T-maze where both paths are taken with equal frequency, theta sequences should alternate between sweeping left and right in roughly equal proportions across successive cycles⁸⁵ (Fig. 3d). However, in scenarios where a particular route is more reliably taken, such as one leading to a goal, sequences would become biased towards that path^{54,55,63} (Fig. 3e).

The alignment between place cell activity within theta sequences and STDP windows suggests how state transition prediction errors could drive structural learning at the level of synaptic weights^{72,73}. While place cells representing upcoming locations fire milliseconds after

those representing current position^{53,84,152,153}, creating suitable temporal relationships for strengthening weights between connected states in the internal world model²⁹, we propose that cholinergic modulation adds a critical computational dimension to this established mechanism. Specifically, rather than simply gating plasticity^{74–76}, acetylcholine may scale synaptic updates proportional to state transition prediction error magnitude. This would link the phase-dependent properties of theta cycles^{154,155} — encoding at peaks, retrieval at troughs — to the computational demands of structural learning: stronger plasticity when state transition predictions fail, minimal change when they succeed. Theta-nested beta and gamma oscillations¹⁵⁸ may provide finer temporal structure at the timescale of plasticity itself: their ~15–30-ms periods

fall within the windows over which STDP operates, organizing sequence elements at the resolution at which synaptic change is actually induced. Complementing existing proposals that encoding and retrieval alternate within single theta cycles^{13,156,159}, with cholinergic tone – updated across theta cycles – setting the gain on plasticity organized by within-cycle phase dynamics^{12,14,73,74,76,129,135,154,155,157}. The alternation between forward and reverse theta sequences within single cycles⁶² is particularly intriguing in this context. Forward sequences at troughs could generate predictions whereas reverse sequences at peaks might enable comparison with recent experience, potentially allowing the septo-hippocampal circuit to continuously compute state transition prediction errors. If cholinergic release indeed scales with these computed errors, this would provide a biologically plausible mechanism for the error-driven weight updates proposed by temporal difference algorithms.

Importantly, theta sequences represent just one potential mechanism for implementing state transition prediction errors. Our core claim – that acetylcholine signals these errors – may be realized through alternative pathways. For example, the septum might compute state transition prediction errors through direct comparison of hippocampal and sensory inputs, independent of theta oscillations^{77,78,81}. Indeed, recent computational work demonstrates successor representation learning can be accomplished without theta sequences, using Hebbian plasticity with eligibility traces or replay events^{30,31,71,160,161}. Identifying which mechanisms the brain actually exploits, and whether it engages multiple strategies in parallel, is therefore a key goal for future experimental and theoretical studies. Notably, theta-paced sequential activity also persists during rapid eye movement (REM)

sleep, with recent evidence showing that hippocampal–entorhinal sweeps continue with flexible, attention-like modulation of their direction and width^{151,162}. This raises the possibility that state transition prediction errors are computed over internally generated sequences during sleep, with elevated cholinergic tone maintaining an encoding-like state conducive to internal world model revision during consolidation.

Testable predictions

The framework outlined above generates specific, testable predictions that distinguish it from alternative accounts of cholinergic function (Box 1). Cholinergic release should be quantitatively predictable from computational models – specifically, acetylcholine levels should scale with the magnitude of state transition prediction errors calculated as the difference between predicted and observed state transitions, with familiar states in unexpected contexts (a known room accessed from the wrong corridor) generating comparable acetylcholine release to genuinely novel states. Cholinergic blockade should prevent animals from updating their internal world models when state transition probabilities change, such as when a familiar path is blocked or a new connection opens. Enhancing cholinergic transmission specifically when state transition prediction errors occur should improve memory formation, particularly in disease models in which endogenous acetylcholine signalling is compromised. Cognitive training paradigms that systematically induce state transition prediction errors should produce more robust learning than errorless approaches. These four predictions can be tested using emerging technologies, particularly real-time

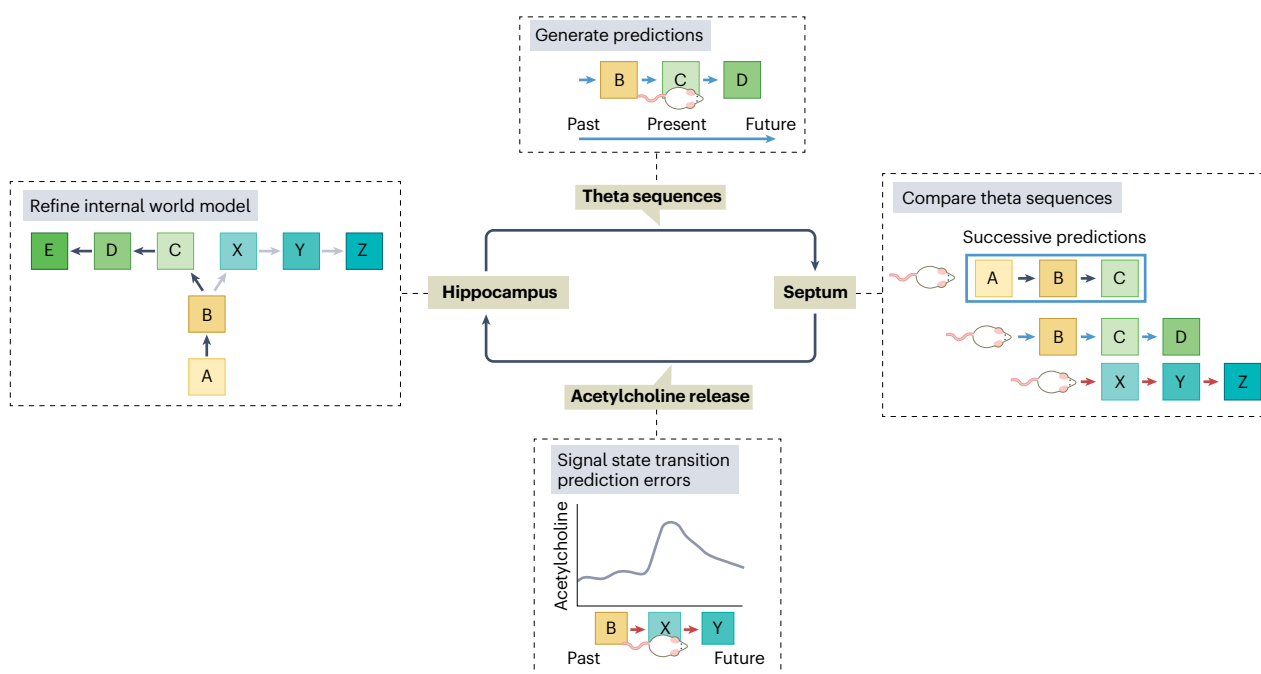


Fig. 4 | Proposed hippocampal–septal circuit for computing state transition prediction errors. The hippocampus generates predictions about upcoming states via theta sequences – compressed trajectories that sweep from past through present to future locations within each ~100-ms theta cycle⁶². These sequences are relayed to lateral septum^{93,94}, allowing successive state transition predictions to be compared. When predicted and observed state transitions match (blue), cholinergic output remains low, reflecting minimal state transition

prediction error. When they diverge (red) – because the animal encounters an unexpected state – we propose cholinergic neurons in medial septum release acetylcholine proportional to the state transition prediction error, potentially via disinhibitory mechanisms⁹². This cholinergic feedback returns to the hippocampus, gating plasticity to refine the internal world model and improve future predictions^{12–14}.

measurement of cholinergic dynamics using genetically encoded sensors combined with closed-loop optogenetic manipulation (Box 1).

Testing these predictions will require methodological advances in both animal models and humans. Virtual reality environments offer unprecedented control over state transition probabilities¹⁶³, enabling systematic manipulation of state transition prediction errors while monitoring behavioural and neural responses. Closed-loop systems that detect hippocampal state transition prediction errors and trigger appropriately timed cholinergic stimulation could provide a powerful tool for establishing the causal role of error-driven cholinergic release.

The framework's core predictions are amenable to validation across species, from rodent navigation to human spatial memory. Critical tests will require paradigms that dissociate state transition prediction errors from other variables such as reward, novelty and arousal – challenging but feasible with careful experimental design. The conservation of septo-hippocampal circuitry and cholinergic modulation across mammals suggests that state transition prediction error signalling may represent a fundamental principle of vertebrate brain function, although its specific implementation probably varies across species and cognitive domains. Cross-species validation will be essential for establishing whether the computational principles identified in rodent navigation extend to the complex internal world models that humans use for abstract reasoning and social navigation.

These predictions have clinical relevance. Basal forebrain cholinergic degeneration occurs early in Alzheimer's disease and predicts cortical pathology spread^{164,165}. Under the state transition prediction error framework, this degeneration specifically impairs the brain's ability to signal mismatches between predicted and observed state transitions, leading to progressive failure in updating internal world models. This may explain why spatial disorientation is among the earliest symptoms^{166,167} – reflecting not simply forgetting locations but inability to update predictive models when environments change – and why episodic memory is disproportionately affected, given the high state transition prediction errors required to link states in novel temporal sequences¹⁶⁸. Current cholinesterase inhibitors provide modest benefit^{169,170}, arguably because tonically elevating acetylcholine cannot restore the precise temporal dynamics of state transition prediction error signalling. Future therapeutic strategies informed by this framework might instead focus on restoring the timing and specificity of cholinergic signals, whether through closed-loop stimulation, selective receptor modulation or behavioural interventions that enhance natural state transition prediction error signalling. Longitudinal studies tracking state transition prediction error responses alongside cognitive decline could establish whether preserving prediction error signalling delays dementia onset.

Outlook

The state transition prediction error framework offers a potentially unifying account of hippocampal acetylcholine function, proposing that acetylcholine signals mismatches between predicted and observed state transitions to guide structural learning about environmental dynamics. From novelty detection to hidden state inference, the framework suggests diverse cholinergic functions can be understood as expressions of a single computational principle: signalling state transition prediction errors to drive structural learning when internal world models fail to predict experience. Our central hypothesis is that acetylcholine carries these state transition prediction errors, and in parallel we advance a concrete mechanistic hypothesis in which theta sequences relay hippocampal predictions to the septal complex

for error computation, while the same theta-compressed sequences engage plasticity in hippocampal circuits to update the predictive internal world model (Fig. 4).

This linkage between a normative structural learning signal and synapse-level implementation makes the framework experimentally tractable and, we argue, particularly powerful, yet these mechanistic proposals remain logically independent of the core claim: that acetylcholine reports state transition prediction errors, and the mechanisms by which this happens could be revised without undermining the central theory. Critically, the framework makes predictions that could challenge its core claims: if cholinergic release were shown to be entirely insensitive to the predictability of state transitions, or if cholinergic manipulation had no effect on structural learning, or if familiar states connected in an unexpected sequence failed to elicit cholinergic release, the central hypothesis would require substantial revision.

Positioning acetylcholine as the structural learning counterpart to the dopaminergic role in value learning suggests a fundamental division of computational labour in the brain, with dopamine teaching what is valuable and acetylcholine teaching how the world is structured. This perspective could transform our understanding of cholinergic dysfunction in Alzheimer's disease – from a neurotransmitter deficiency to a fundamental breakdown in the ability to update internal models of the world – and suggests that successful therapeutic interventions must restore not just cholinergic levels but the computational functions that allow people to learn from state transition prediction errors. If acetylcholine does serve as a fundamental learning signal – as essential for building predictive world models as dopamine is for learning values – this could provide a principled foundation for understanding the mechanisms of memory and the devastating consequences when these systems fail.

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