**Opinion**

# Remote Memory and the Hippocampus: A Constructive Critique

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**Highlights**

It is widely agreed the hippocampus plays a crucial role in memory encoding.

The question of how long a hippocampal trace is required in order to retrieve a memory is unresolved.

Opposing theoretical accounts advocate either the hippocampus is unnecessary for memory retrieval in the longer-term or that is it required in perpetuity.  There is evidence from animal and human work to support both views and, consequently, extant theories cannot account for these conflicting findings.

We suggest that the hippocampal role in memory retrieval is not simply a question of persistence, but is best characterised as a functional shift over time from retention to reconstruction of the past in the absence of the original trace.

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34 This new perspective accounts for existing data, and offers a means to leverage a clearer

35 understanding of the hippocampal-neocortical interactions that support memory retrieval.

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37 **Abstract**

38 The hippocampus is known to be recruited during the recall of experiences from our distant

39 past, despite evidence that memory traces in this region vanish over time. Extant theories

40 of systems-level consolidation have yet to accommodate both phenomena. We propose

41 that the hippocampus reconstructs remote memories in the absence of the original trace. It

42 accomplishes this by assembling consolidated neocortical elements into spatially coherent

43 scenes that form the basis of unfolding memory events. This reconstruction is likely

44 facilitated by input from the ventromedial prefrontal cortex. This process-oriented approach

45 to hippocampal recruitment during remote recollection is consistent with its increasingly-

46 acknowledged role in constructing mental representations beyond the domain of memory.

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**A Divergent Debate on Hippocampal-Dependent Memory**

Hippocampal damage impairs the formation and recall of recent memories in humans [1], non-human primates [2] and rodents [3]. However, conflicting evidence regarding its necessity for remote memory retrieval has generated two opposing perspectives. There is cross-species evidence of temporally-graded **retrograde amnesia** (see Glossary) – the preservation of older memories following hippocampal damage [4-6]. This reinforces the view of the **Standard Consolidation Theory**, that memories are stored in progressively strengthened cortico-cortical connections – known as **system-level consolidation** – while the hippocampal **memory trace** fades, after which the hippocampus is no longer required for retrieval [7] (Figure 1A).

However, comparably strong evidence also exists to the contrary. Impairment in the recall of memories regardless of their age has been observed following hippocampal damage, particularly where the retrieval of a specific context is essential – **episodic/autobiographical memories** [8, 9]. A resultant reformulation, the **Multiple Trace Theory** (and its recent elaboration the **Trace Transformation Theory**), asserts that episodic memory traces are cumulatively stored in the hippocampus, thus assigning a perpetual role to this region in the retrieval of the original complete representations [10, 11] (Figure 1B). Other prominent accounts of hippocampal functioning also incorporate the notion that memory retrieval involves the reactivation or recombination of consolidated hippocampal memory traces [12, 13].

However, recent compelling evidence in both humans [14] and rodents [15] provides support for the long-standing tenet of the Standard Consolidation Theory that the hippocampus has a time-limited role in memory storage. To reconcile these findings with the seemingly perpetual involvement of the hippocampus in episodic memory retrieval, we

73 propose a reconceptualisation of the hippocampal contribution to remote memory. The

74 hippocampus may reconstruct past experience in the absence of the original trace (Figure

75 1C). In light of this hypothesis, we outline the mounting evidence for systems-level

76 consolidation, and consider the neocortical-hippocampal interactions which may facilitate

77 the reconstruction of remote memories during retrieval.

78

79 **The Evanescent Hippocampal Engram**

80 Theoretical accounts of how memory traces are stored within the hippocampus have been

81 motivated both by its architecture and neural activity. Initial input to the hippocampal

82 circuit generates sparse activity in the dentate gyrus, assumed to reduce interference

83 between similar memories. These distinct patterns are conveyed to CA3, where intrinsic

84 recurrent connections are thought to form a complete memory trace. The resultant output

85 produces a sparse pattern in CA1, and this unique representation is relayed back to the

86 neocortex [16]. This output has been proposed to index neocortical locations relevant to a

87 specific memory [17]. Therefore, tracking the structural and functional integrity of

88 hippocampal memory traces over time is of central importance in resolving the debate

89 about the role of the hippocampus in remote memory.

90 Definitive evidence of a permanent hippocampal trace can best be provided at a

91 cellular level. **Long-term potentiation (LTP) and long-term depression (LTD)** are considered

92 the principal forms of plasticity governing hippocampal information storage. Supporting

93 evidence arises from their enhancement following learning [18, 19] and their association

94 with memory performance [20]. Such methods of plasticity induction provide a means to

95 assess the persistence of memory storage, through repetition of the protocol after a period

96 of time has elapsed. While most studies do not assess LTP changes beyond a 24 hour period,

97    it has been shown to persist for up to one year in the rat dentate gyrus [21]. However, this

98    potentiation can be reversed over just seven days of exposure to an enriched environment

99    [21]. Therefore, under naturalistic conditions of continuous learning, turnover of

100   information in the hippocampus is high [22]. In other words, information only persists in the

101   hippocampus until it is overwritten.

102       A more direct and naturalistic relationship between learning and the permanence of

103   hippocampal memory traces can be studied by examining **place cells**. These cells fire in

104   response to specific locations in a rodent's environment [23], with evidence in monkeys [24]

105   and humans [25] of similar spatially-responsive cells. They represent a useful proxy for long-

106   term memory as their persistence depends on **NMDA receptor** activation [26] and protein

107   synthesis [27]. Furthermore, place cells are sensitive to behaviourally-relevant contexts [28],

108   are predictive of memory performance [29], and reactivate during memory retrieval [30].

109   Measuring place cell activity over time can, therefore, provide insights into the persistence

110   of hippocampal memory storage.

111       Experiments that have recorded from a small number of place cells have yielded

112   mixed results. While cessation or attenuation of spatially-selective firing following extensive

113   [31] or repeated [32] exposure to an environment has been observed, firing fields of

114   individual cells have also been shown to remain stable for up to six months [33]. Given that

115   some place fields form instantly in a novel environment [34], persistent firing patterns may

116   represent an invariant response to spatial topography.

117       Imaging techniques which permit the simultaneous analysis of hundreds of cells are

118   more informative, and reveal the hippocampal code for space is highly transient. The

119   similarity of cell populations firing in the same environment measured five and 30 days

120   following initial exposure, represents an overlap in neuronal ensembles of just 15% between

121    sessions [35]. Importantly, this time window is outside the initial unstable period of place

122    field formation [36]. This disparity also occurs despite equivalent numbers of participating

123    cells, arguing against a reduction in activity. Furthermore, the ability to decode an animal's

124    precise location based on the entire cell population is sustained over time, the locations at

125    which individual cells are most likely to fire are conserved, and the size of observed place

126    fields do not change, implying information content is preserved despite the low neural

127    overlap. These findings suggest that despite repeated exposure to the same location in an

128    environment, prior hippocampal representations are rapidly replaced with new experiences.

129        A likely exacerbating influence on this time-dependent hippocampal instability is

130    that the allocation of place cells to environmental locations is random [37]. In fact, entire

131    sequences of place cell firing appear to be randomly assigned from pre-existing

132    hippocampal sequences which are detectable hours before initial exposure to an

133    environment [38]. Arbitrary allocation of place cells in the hippocampus is especially evident

134    during remapping, the shifting of a neuron's preferred firing field, a phenomenon requiring

135    only brief optogenetically-induced quiescence in order to occur [39]. This mutability in the

136    hippocampal spatial code has implications for the retrieval of remote episodic memories.

137        Is such representational instability evident during remote contextual memory

138    retrieval? The reactivation of hippocampal neurons which support a particular memory has

139    been observed up to 14 days later [40]. **Optogenetic** manipulation of these sparsely

140    distributed functionally-active cells during more remote recall would provide strong

141    evidence of a permanent memory trace. Contextual memory can be temporarily impaired

142    [41, 42], spontaneously induced [43, 44] or rescued from amnesia [45, 46] by tagging and

143    selectively silencing or activating these memory-specific neural representations in the

144    hippocampus. These manipulations simultaneously affect cortical neural reactivation,

145    supporting the hippocampal indexing theory of memory retrieval [41]. Unfortunately,

146    however, to date the majority of studies have only targeted specific memory traces which

147    are at most two weeks old, whereas recent memories in rodents likely persist for at least

148    three weeks (see the section below on structural changes). Temporary optogenetic silencing

149    of CA1 excitatory neurons disrupts recall of four week old memories [47], but this approach

150    is insufficient to disambiguate global disruption of hippocampal functioning from the

151    targeted deactivation of a specific trace.

152    One recent study in mice attempted to revive hippocampal contextual fear engrams

153    that were encoded during infancy and subsequently forgotten, after considerable delays of

154    30 and 90 days [48]. However, despite higher levels of freezing in the trained context during

155    optogenetic stimulation of previously active neurons, this behaviour disappeared when the

156    neuronal stimulation ceased. As hippocampal reactivation in the presence of the original

157    cues appeared insufficient to serve as a persistent reminder of remote memory, it is

158    possible that optogenetic stimulation activated a neural ensemble supporting a general fear

159    response, rather than reinstantiating the specific memory trace which associated the

160    context with a shock.

161    A closer look at the morphology and genesis of hippocampal neurons reveals a

162    structural instability which would make degradation in the integrity of individual engrams

163    over such a long timescale almost inevitable. Dendritic spine production in the hippocampus

164    is altered by both LTP [49] and learning [50]. The resulting changes in synaptic connectivity

165    are thought to facilitate incorporation of a novel memory trace. High resolution *in vivo*

166    imaging of dendritic spines in the hippocampus can therefore provide an insight into time-

167    dependent changes in structural plasticity. The life span of dendritic spines in the mouse

168    hippocampus is just one to two weeks (Figure 2A), with a complete turnover of all spines in

169 three to six weeks [15]. This implies the synaptic connectivity supporting a memory trace in

170 the hippocampus is fully erased over this time. There is no obvious reason to preclude the

171 extrapolation of such an erasure to the human hippocampus.

172 Hippocampal **neurogenesis** in both animals and humans provides further evidence of

173 the transience of memory storage. In rodents, new neurons reach structural and functional

174 maturity after one month [51]. They display high initial plasticity [52], their survival is

175 increased by learning [53], and their elimination impairs long term memory [54]. This

176 suggests a functional integration into pre-existing circuitry in the service of long-term

177 memory. However, their mnemonic contribution is transient. Optogenetic silencing of

178 neurons which are four but not two or eight weeks of age impairs spatial memory retrieval

179 [55]. More importantly, new neurons appear to have a deleterious effect on older

180 memories, as increased neurogenesis following learning actually impairs memory retrieval

181 [56]. Conversely, impairing neurogenesis preserves context-dependent neural patterns in

182 the dentate gyrus [42]. Therefore, the role of neurogenesis in the hippocampus may be to

183 overwrite old memories with new ones.

184 While human neurogenesis remains a contested phenomenon [57], supporting

185 evidence exists [58, 59], with one study concluding that all neurons in the human dentate

186 gyrus are subject to turnover [14]. With an estimated yearly exchange rate of 1.75% (Figure

187 2B), the replacement of all neurons in the dentate gyrus is theoretically possible within the

188 average lifespan. As the dentate gyrus constitutes the initial stage of hippocampal circuitry,

189 is it difficult to envisage how hippocampal memory traces could remain stable over time.

190 The emerging picture of information storage in the hippocampus is, therefore, one

191 of continuous flux. The nature of hippocampal memory traces, whether spatial [60],

192 temporal [61], scene-like [62] or conceptual [63], has received much attention. A more

193    overarching question is, what are the neural processes underlying retention and expression

194    of memory traces once they have disappeared from the hippocampus? To approach this

195    question, we first consider the evidence for systems-level consolidation.

196

197    **A Consensus on Consolidation**

198    Systems-level consolidation is a hypothesised time-dependent process of hippocampal-

199    facilitated strengthening of neocortical neural connections post-learning [64, 65].

200    Supporting evidence in humans arises from hippocampal [66] and neocortical [67]

201    **reinstatement** of activity patterns present at encoding during subsequent quiescence and

202    sleep. This regional activity is synchronised [68], with bursts of hippocampal activity being

203    entrained by slower oscillations in the neocortex [69]. Memory replay is well-characterised

204    in rodents, occurring at high speed in the hippocampus [70], with disruption of this activity

205    impairing **consolidation** [71]. Offline bi-directional connectivity between the hippocampus

206    and neocortex is also observed in animals [72]. The association between sleep architecture

207    and memory consolidation is a focus of ongoing inquiry. Non-REM (rapid eye movement)

208    sleep in humans appears to benefit the consolidation of contextual associations [73], with

209    the replay of neural patterns associated with encoding being predictive of subsequent

210    memory [74]. This activity facilitates ensuing pattern separation processes [75], with the

211    presentation of interfering stimuli actually reducing the likelihood of subsequent wakeful

212    memory intrusions [76]. Conversely, REM sleep seems to promote the extraction of memory

213    regularities [77], with contemporaneous reminders causing subsequent erroneous

214    recognition, a phenomenon attributed to generalisation [78].

215            One neocortical region that is consistently implicated in this consolidation process is

216    the prefrontal cortex. Replay of recent experience occurs here in a highly compressed

217 manner during sleep [79] and wake [80] in rodents. These sequences follow hippocampal

218 **sharp wave ripples** by about 100ms suggesting it is receiving information [81]. This

219 hippocampal input appears to activate prefrontal cells relevant to one context while

220 suppressing others [82], implying its purpose is the consolidation of specific representations.

221 Accordingly, there is evidence that interfering with this process can either disrupt or

222 enhance memory consolidation. Disconnecting the two regions blocks the formation of

223 episodic memories [83], while offline artificial induction of **delta waves** and **spindles** in the

224 prefrontal cortex timed to coincide with hippocampal sharp wave ripples enhances

225 subsequent memory performance [84]. Consistent with the role of replay in long-term

226 memory consolidation, neocortical LTP is enhanced by repeated spaced stimulation, and is

227 enduring [85]. Furthermore, unlike the hippocampus, dendritic spines in the neocortex can

228 remain stable for a lifetime, consistent with permanent storage [86], while their targeted

229 shrinkage eliminates memories [87]. Therefore, it appears that stable memory

230 representations are consolidated in the neocortex over time, and in particular in the

231 prefrontal cortex.

232 How long does this process take? In rodents, replay of an event can be detected 24

233 hours later, whether asleep [88] or awake [89]. Neural replay of learned information can

234 also be decoded during subsequent sleep in humans [90], but in both cases, evidence that

235 more remote events are replayed is lacking. However, animal studies have revealed a critical

236 window in the initial weeks following learning where neuronal silencing of the prefrontal

237 cortex [91], or hippocampus [92] disrupts memory consolidation, suggesting the process is

238 completed relatively quickly.

239 Neuroimaging studies have suggested that the process of memory trace stabilisation

240 in the neocortex takes at most four months in humans [93, 94]. This rapid purge of learned

241 information from the hippocampus and simultaneous consolidation in the neocortex is

242 consistent with the Standard Consolidation Theory, where remote memories are presumed

243 to become hippocampal-independent. Yet there is a persistent problem with this

244 interpretation, which we address in the next section.

245

246 **Reconstruction of the Past by the Hippocampus**

247 Hippocampal damage in humans can impair the recollection of specific autobiographical

248 memories from any period of life before the damage occurred [8, 9] (Figure 2C), and

249 neuroimaging studies in healthy individuals reveal hippocampal engagement during the

250 recollection of both recent and remote autobiographical memories [95]. This implies that no

251 duration of systems-level consolidation will relieve the hippocampus of a role in retrieval.

252 Likewise, hippocampal lesions in rodents yield a flat retrograde amnesia for contextual

253 memory [3, 96](Figure 2D), even after allowing for over 100 days of consolidation before

254 surgery [97, 98]. Given that hippocampal representations are likely to decay over such a

255 lengthy timescale, its role in remote memory requires clarification.

256 Hippocampal-dependent functions beyond memory may illuminate this issue. The

257 capacity to imagine novel scenes and scenarios and to think about the future are

258 compromised following hippocampal damage in humans [99, 100], and hippocampal

259 activation has been shown to predict anticipated stimuli [101]. The rodent hippocampus

260 also behaves in a manner suggestive of planning and imagination, with place cell sequences

261 pre-activating upon observation of a novel route, regardless of whether the path is

262 subsequently navigated [102], or not [103]. Such imagined and anticipatory representations

263 are difficult to accommodate within a simple encoding account of hippocampal functioning.

264 Likewise, the alternative conceptualisation of imagination as a novel recombination of

265 existing hippocampal memory traces [12, 13], in light of evidence presented here, would

266 restrict constructed representations to a limited pool of recent memories. In fact,

267 hippocampal activity during future thinking displays the opposite trend, increasing with

268 temporal distance, when recent memory traces would cease to have relevance [104].

269 Furthermore, such an account could not explain the predictive processing of novel

270 navigation routes for which no trace exists.

271 Adopting a more wide-ranging perspective on hippocampal functioning generates an

272 interesting hypothesis on its contribution to remote memory retrieval. Just as the

273 hippocampus is necessary for *de novo* construction of imagined scenarios, it could perform

274 the same function for remote memories long after the original hippocampal trace has

275 decayed. Neocortically-stored elements of remote memories which have become associated

276 throughout the consolidation period are therefore reconstructed into a new hippocampal

277 representation (Figure 1C and Figure 3, Key Figure).

278 One putative supporting mechanism is 'scene construction' [62]. The **Scene**

279 **Construction Theory** proposes that the hippocampus continuously constructs and

280 anticipates scene representations beyond our immediate sensorium. In this context, a scene

281 is a naturalistic three-dimensional spatially coherent representation of the world typically

282 populated by objects and viewed from an egocentric perspective [105, 106, 107]. Scenes

283 represent the fundamental components of unfolding mental events [108], whether recalling

284 autobiographical memories, navigating through environments, forecasting plausible futures,

285 or creating novel, scenarios, all domains in which hippocampal-damaged patients are

286 impaired. Neuroimaging studies have shown a consistent functional overlap across these

287 tasks in the anterior hippocampus [109] (Box 1), highlighting this area as a potential hub for

288 scene construction. Henceforth, in the context of remote memory retrieval, construction

289    will be referred to as "reconstruction" to reflect the recapitulation of prior experiences,

290    although we speculate that the underlying hippocampal neural dynamics are similar to

291    those involved in the construction of novel or future scenarios.

292        An obvious implication of reconstruction in the absence of the original hippocampal

293    trace is that memories would become increasingly vulnerable to inaccuracy and distortion.

294    Alternatively, cumulative hippocampal traces which strengthen over time should generate

295    representations which become stable and resistant to interference. Behavioural evidence

296    favours the former hypothesis. The passage of time has a deleterious effect on recall

297    accuracy [110], without affecting the level of reported detail [111]. The ease with which

298    memory can be distorted via misinformation is well documented; people readily incorporate

299    events that never transpired into a memory if they seem plausible [112] and involve self-

300    relevant information [113]. Furthermore, individuals with exceptional autobiographical

301    memory are even more vulnerable to misinformation [114], suggestive of reconstructive

302    processes.

303        Of most relevance here, susceptibility to distortion increases in accordance with the

304    age of memories [115], with remote life periods highly sensitive to spontaneous fictional

305    [116], or provoked, false memories which can match or exceed the vividness and confidence

306    in recall of real memories [117]. Remote memories can, therefore, be rich and detailed

307    without being veridical, and thus constitute a reinvention of the past rather than faithful re-

308    experiencing. This phenomenon is better accounted for by a hippocampal memory trace

309    which requires reconstruction following its decay, rather than one which stabilises over

310    time.

311        This reconstructive interpretation may also have implications for the well-

312    documented phenomenon of **reconsolidation** [118]. Memories are thought to undergo

13

313   subsequent consolidation upon retrieval, evidenced by a transient vulnerability to

314   disruption [119]. This is because the cellular machinery which facilitated initial consolidation

315   is reengaged and is therefore susceptible to interference [120]. Given that human

316   autobiographical memories are subject to such interference following retrieval [121],

317   reconsolidation provides a putative mechanism through which newly constructed

318   representations can interfere with and distort remotely consolidated memories. This

319   emergent view of consolidation as a continuous phenomenon [122] is congruent with the

320   perspective presented here, that hippocampal representations are constructed and stored

321   in a transient manner (Fig. 3).

322         Clearly, many memories become faded, impoverished and schematic over time,

323   rather than distorted. Existing theories typically associate this phenomenon with decayed

324   hippocampal traces [11]. However, given mounting evidence of universal hippocampal trace

325   transience, all memories should succumb to this fate. Conversely, if the hippocampus

326   constructs a relevant scene from immutable neocortical representations, all remote

327   memories would be richly detailed. Therefore, we propose that remote memory

328   impoverishment is a result of cortico-cortical trace decay, such that insufficient relevant

329   content then exists to reconstruct coherent scene representations via cortical-hippocampal

330   interactions.

331         Our scene construction perspective shares descriptive aspects with others, such as

332   reconstruction in the Constructive Episodic Simulation Theory [12], and the hippocampal-

333   dependence of detailed remote memories in the Multiple Trace Theory/Trace

334   Transformation Theory [10, 11]. We differ fundamentally on the underlying mechanisms.

335   These perspectives propose that remote memory traces remain in the hippocampus [11],

336   and reconstruction relies on their activation and recombination [123]. Our view is novel

337 because it renders these traces unnecessary for remote memory reconstruction, and is

338 compatible with recent neurobiological evidence. We do not dispute the necessity of

339 temporary hippocampal indexes for systems-level consolidation [17], but propose these

340 disappear rapidly and are replaced by different traces during reconstruction [93]. A second

341 unique feature of our perspective is a privileged role for the hippocampus in the processing

342 of scene imagery. In contrast, the Competitive Trace Theory attributes remote memory

343 distortions in the hippocampus to interfering cortical memories [124], whether or not there

344 is a spatial component, whereas the High Resolution Binding account implicates the

345 hippocampus in the precise processing of any complex associations [125].

346      The spatial component of remote memory in hippocampal-damaged patients further

347 illuminates this debate. A range of premorbid topographical information remains spared,

348 with normal performance on general route navigation, map generation, and the estimation

349 of distance and direction [126-129] findings which, on the surface, appear to support the

350 Standard Consolidation Theory. However, specific deficits are present. Patient K.C. failed to

351 recognise all non-salient landmarks in his home neighbourhood [127]. Patient T.T., a taxi

352 driver, was impaired when navigating minor roads [129]. Both patients had previously

353 navigated these environments extensively for approximately 40 years. These deficits have

354 been attributed to a loss of detail in accordance with the Multiple Trace Theory [130].

355 However, an alternative explanation in line with the view presented here, is an impairment

356 in the mental construction of scene imagery. In support of this perspective, patient T.T.

357 could not describe (and by inference envisage) any route he had previously navigated

358 perfectly in a virtual environment [129], nor could he construct in advance the mental

359 scenes of the turns he should take to access the minor roads [108]. Patient K.C. appeared

360 strikingly oblivious to the typical architectural style of buildings in his neighbourhood [127],

361 general schematic knowledge which should be preserved according to both the Standard

362 Consolidation Theory and Multiple Trace Theory/Trace Transformation Theory. The Scene

363 Construction Theory, however, would predict this deficit because of an absence of

364 internally-generated scene imagery against which to compare exemplars.

365

366 **The Remote Control of Memory**

367 Time-dependent strengthening of connectivity between neocortical modules is thought to

368 form the basis of systems-level consolidation. The medial prefrontal cortex becomes an

369 increasingly important hub during this process, with lesions selectively disrupting remote

370 memories in animals [131]. Likewise, in humans, memory-specific activity patterns emerge

371 in the ventromedial prefrontal cortex (vmPFC) over the course of consolidation [93, 94, 132]

372 while vmPFC damage impairs autobiographical memory retrieval [133]. Why does memory

373 reconstruction come to depend on the prefrontal cortex?

374     One perspective is that when the hippocampal memory trace decays, the prefrontal

375 cortex assumes its role as an indexer of memory by linking neocortical modules together

376 [131]. However, consistent hippocampal recruitment during remote memory retrieval

377 suggests prefrontal activation plays a complementary role. One such conceptualisation of

378 vmPFC function is the integration of experiences across time to form a schema, a composite

379 representation which is used to bias memory retrieval in posterior regions [134]. However,

380 opposing evidence suggests that vmPFC-damaged patients have a selective impairment in

381 the recall of specific, rather than general details [133]. Accordingly, vmPFC may directly

382 recruit individual neocortical memory traces prior to hippocampal reconstruction [108].

383     Alternative perspectives propose that vmPFC inhibits the expression of irrelevant

384 memory traces in the hippocampus during retrieval [13], such as representations which are

385  temporally confused [135] or contextually inappropriate [136]. These accounts find support

386  in confabulation - the recollection of temporally or factually inaccurate information arising

387  from vmPFC damage - which can be frequent, florid and held with conviction [137]. One

388  possible mechanism underlying vmPFC control over remote memory retrieval is that return

389  projections to the hippocampus via the entorhinal cortex and thalamic nuclei [138],

390  strengthen over the course of consolidation [139], providing a route to control the flow of

391  information entering the hippocampus and modulate its activity [140].

392      These diverse perspectives furnish numerous testable hypotheses regarding the

393  hippocampal-neocortical interactions that may support the reconstruction of remote

394  memory in the absence of an enduring hippocampal index.

395

396  **Concluding Remarks and Future Perspectives**

397  A proliferation of evidence challenges the notion of permanent hippocampal memory

398  traces. Core assumptions underlying extant perspectives on systems-level consolidation and

399  the fundamental role of the hippocampus may need to be reassessed. The hippocampus is

400  unlikely to be a permanent indexer of memories. Given the extraordinary demands placed

401  upon the hippocampus for continuous encoding of experience, and the required

402  representational flexibility involved in imagination and future-thinking, mnemonic

403  transience is a desirable property. Its fleeting role in consolidation may be subservient to its

404  primary function as a constructor of scenes, whether past, future or fictive.

405      The question for future research is not how the hippocampus retrieves a single trace

406  from the neocortex, but how consolidated elements are flexibly processed to generate

407  diverse mental representations (see Outstanding Questions). To address this in humans will

408  involve tracking the stability of individual hippocampal and neocortical memory traces

during consolidation using high-resolution fMRI, and characterising the electrophysiological dynamics underlying retrieval using source-level magnetoencephalography or intracranial electroencephalography.

We predict that the neural signatures of memory reinstatement in the hippocampus should become increasingly divergent from recent to remote memories [93]. Furthermore, this representational instability should correlate with the degree of memory distortion, independent of subjective vividness or recall confidence. This would have implications for establishing a timeline of reliable memory in applied settings such as eyewitness testimony. Beyond this period, people may erroneously incorporate related elements into their reconstructed scene imagery, as is evident during misinformation [112, 113]. In this context, we further predict that immersion in virtual reality crime scenes would minimise reconstructive errors and yield more accurate remote recollection. In an educational setting, given that we consider scenes to be the scaffold for systems-level consolidation, the use of scene imagery strategies during learning may facilitate subsequent consolidation of information. The contribution of vmPFC to the instantiation or inhibition of remote memories also requires further investigation. We predict that interactions between the hippocampus and vmPFC during the imagination of novel events will closely mirror remote memory reconstruction as they rely on similar mechanisms.

The role of the hippocampus in systems-level consolidation is not simply a question of persistence, but is best characterised as a functional shift over time from retention to reconstruction (Figure 3, Key Figure). Appreciating the pivotal role of the hippocampus across multiple cognitive domains permits us to ask more constructive questions about its recruitment during the retrieval of remote memories.

**Outstanding Questions**

- Precisely how long do hippocampal memory traces persist in humans? Can we gain traction on this question using intracranial EEG?

- What aspects of remote memory are most prone to time-dependent distortion? Given the role of the hippocampus in constructing scene imagery, is this component disproportionately affected?

- Do pattern separation and pattern completion processes only underlie temporary storage, or are they critical online operations for remote memory, imagination and navigation?

- Do the electrophysiological interactions between the hippocampus and neocortex differ between recent and remote memories?

- How do the vmPFC and hippocampus coordinate to facilitate imagination and future thinking? Does this interaction mirror neural activity during remote memory retrieval?

- Given that the posterior hippocampus has been implicated in representing remote memories in humans, what aspects of remote memory necessitate additional processing in the posterior hippocampus?

- The vmPFC is composed of numerous subregions. Do they play different roles in the retrieval of remote memories?

**Glossary**

**Consolidation:** The strengthening of neuronal connections on both a cellular and network level, manifesting as the successful subsequent retention of learned information.

**Delta waves:** Low frequency (1-4 Hz) synchronised neural activity which is prevalent during sleep.

**Episodic/autobiographical memory:** The multisensory mental reconstruction of a personally experienced past event from a particular place and time.

**Long-term potentiation/depression:** The persistent strengthening or weakening of post-synaptic neuronal excitability following pre-synaptic stimulation, and a long-standing model of memory storage.

**Memory trace/engram:** A distributed network of inter-neuronal structural connections which facilitates subjective re-experiencing of a past event when activated.

**Multiple Trace Theory:** The proposed perpetual dependence of detailed episodic memories on traces stored in the hippocampus; its further elaboration is called the **Trace Transformation Theory**.

**Neurogenesis:** The creation of new neurons which occurs throughout adulthood, predominantly observed in the granule cell layer of the dentate gyrus in the hippocampus.

**NMDA receptor:** The *N*-methyl-d-aspartate (NMDA) receptor is a primarily post-synaptic excitatory receptor, gated by glutamate and implicated in learning and memory.

**Optogenetics:** The targeting of photo-sensitive proteins by light, to either activate or silence a neuron which expresses these proteins.

**Place cell:** Hippocampal neurons which increase their firing rate in a particular environmental location, known as a "place field", irrespective of where an animal is looking.

484    **Reconsolidation:** The process by which previously consolidated memories can become

485    destabilised or strengthened upon reactivation.

486    **Reinstatement:** A spatially distributed or temporal neural pattern observed during memory

487    retrieval which was previously present during encoding.

488    **Retrograde amnesia:** An impairment in recalling the past, affecting either all memories (flat

489    gradient), or disproportionately affecting either recent or remote memories (temporal

490    gradient).

491    **Scene Construction Theory:** A proposal that the hippocampal contribution to memory,

492    imagination, prospection and navigation is the construction of naturalistic three-

493    dimensional spatially coherent scene representations of the world typically populated by

494    objects and viewed from an egocentric perspective.

495    **Sharp wave ripples:** Irregular large negative deflections in hippocampal electrical activity

496    (sharp waves), followed by high-speed (110-200 Hz) synchronised activity (ripples), observed

497    during resting states, and which are assumed to be associated with the replay of past

498    experiences.

499    **Spindles:** Periodic transient oscillations between 10-15 Hz observed in the thalamus and

500    neocortex during sleep, and which are thought to facilitate systems-level consolidation.

501    **Standard Consolidation Theory:** A hypothesised time-dependent shift from reliance upon

502    the hippocampus to the neocortex during memory retrieval.

503    **Systems-level consolidation:** The gradual strengthening over time of cortico-cortical

504    connections supporting a particular memory.

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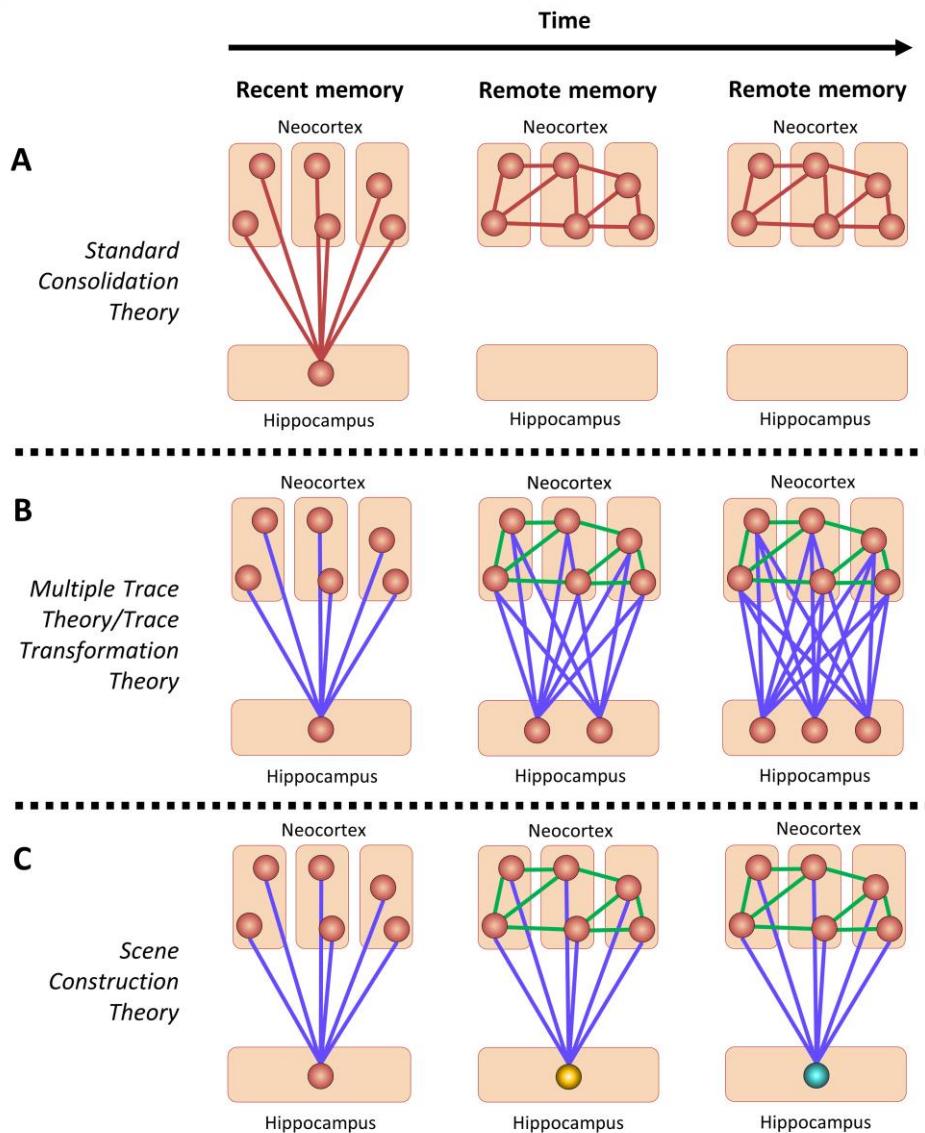
**Figure 1. Three Perspectives on the Hippocampal-Neocortical Connectivity Underlying Systems-Level Consolidation.**

(A) Standard Consolidation Theory [7] proposes that a declarative memory (a past event or factual information) is initially encoded in a hippocampal-neocortical trace (left, red lines and spheres) but, over time, becomes stabilised in a pattern of connectivity between neocortical modules (middle, red lines and spheres, adapted from [131] with permission from Nature Publishing Group). After this consolidation period, the original hippocampal trace is no longer required to reactivate the memory (middle panel). This is true for any subsequent retrieval of this memory (right panel). (B) Multiple Trace Theory/Trace Transformation Theory states that a hippocampal-neocortical trace (left, blue lines and red spheres) is always required for a detailed episodic memory (middle, blue lines and red

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520   spheres), with repeated retrieval of this memory increasing the number of these permanent

521   hippocampal traces (middle and right, red spheres) [10]. The intrinsic neocortical

522   connectivity which emerges over time (middle and right, green lines) supports memories of

523   a more factual and semantic nature, which have been derived from repeated recall [11]. (C)

524   Scene Construction Theory [62] proposes that during the recall of a recent event, the

525   hippocampus constructs a series of coherent scenes from this episode through

526   hippocampal-neocortical interactions (left, blue lines and red spheres). These fade rapidly

527   from the hippocampus as representations are consolidated in the neocortex (middle, green

528   lines). Each time this memory is recalled the neocortically consolidated elements are

529   reconstructed into a new hippocampal trace (middle, yellow sphere; right, cyan sphere) of

530   the sequence of scenes that comprise the past event [108].

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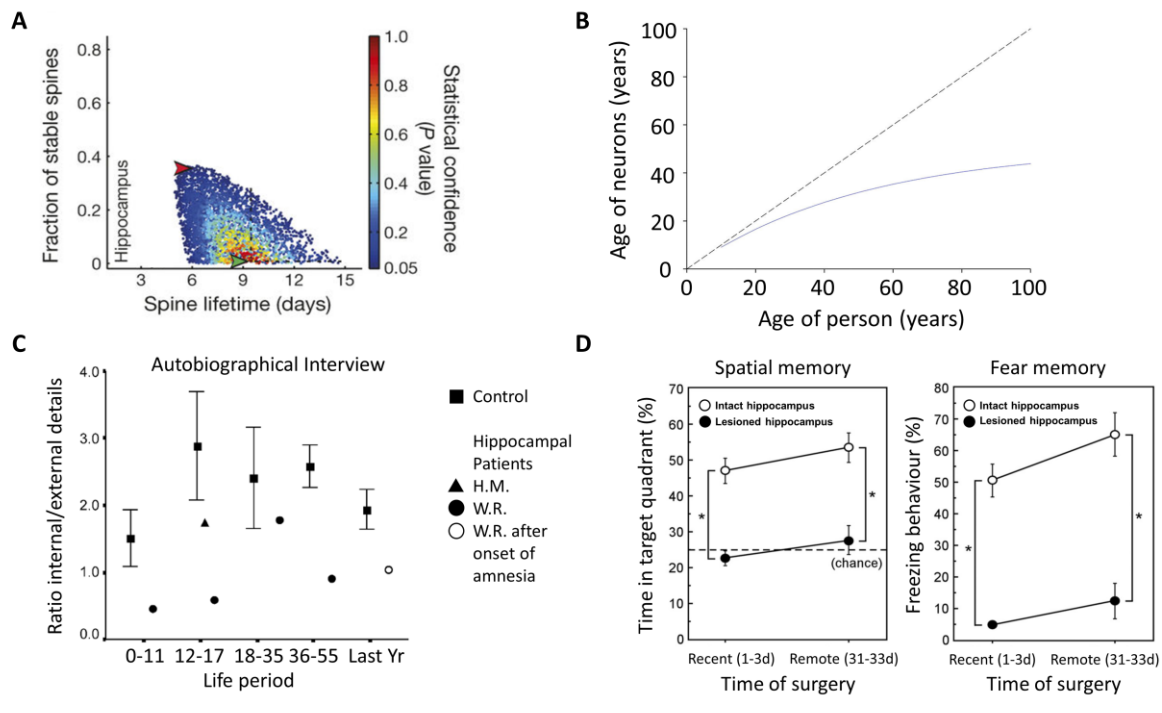
**Figure 2. The Empirical Quandary of Hippocampal-Dependent Memory and Transient Hippocampal Storage.**

(A) The estimated lifetime of mouse hippocampal dendritic spines - the proposed fundamental neural substrates of memory. While models incorporating a stable spine subpopulation cannot be completely rejected (red arrow), the model which best fitted the observed data was 100% impermanent spines with an average lifetime of 10 days (green arrow) [15] (adapted with permission from Nature Publishing Group). (B) In humans, assuming zero neuronal turnover in the hippocampus, neuronal age should be equivalent to that of the person (dashed straight line). Nuclear-bomb test generated $^{14}$C levels in post-mortem hippocampal tissue samples have been leveraged to accurately date the age of neurons, and predicted complete ensemble renewal within the dentate gyrus over a healthy individual's lifespan (full curved line) [14] (reproduced with permission from Elsevier). (C) Despite such structural instability, intact human hippocampi (black squares) were still necessary for retrieval of autobiographical memories from remote life periods, whereas patients with hippocampal damage (circles and black triangle) failed to recall an equivalent level of specific detail from past events, or none at all [9] (adapted with permission from Elsevier). (D) Likewise, in rodents, selective lesions of hippocampal area CA1 (black circles) impaired remote (> 30 day) memories for spatial locations (left panel) and abolished freezing behaviour in an environment where a shock was experienced (right panel) [96]

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552    (adapted with permission from the authors). Consequently, if the hippocampus does not

553    store traces of remote memories, why does it remain essential for their expression?

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**Box 1. Remote Memory and the Anterior-Posterior Hippocampal Axis**

Located deep in the medial temporal lobe, the hippocampus is considered a structurally and functionally heterogeneous structure. This is based on a changing gradient of differential connectivity and gene expression along its longitudinal axis [141]. The anterior hippocampus is preferentially connected to the prefrontal cortex, amygdala, nucleus accumbens and temporal pole, whereas the posterior hippocampus displays stronger connectivity with retrosplenial and inferior temporal cortices [142]. Accordingly, the hippocampus is often parsimoniously segmented into posterior (yellow) and anterior (pink) portions (Figure I) to dissociate their relative contributions. Of most relevance here is whether a functional segregation between these areas exists with regards to the retrieval of consolidated memories.

Remote memories appear to be more distinctly represented in the posterior hippocampus than recent memories [132], a transition which has been observed with individual memory traces over time [93]. This effect has been localised to the dentate gyrus and CA3 [95], hippocampal subregions which appear to coordinate the disambiguation of competing representations during memory recall [143, 144]. From this perspective, remote memories may require additional processing in the posterior hippocampus during their reconstruction. In further support of this idea, increased posterior hippocampus volume is associated with better recollection [145] and extraordinary spatial memory demands [146]. However, the anterior hippocampus also activates strongly during autobiographical memory retrieval [147], and scene construction [148], a recruitment which increases across the earliest stages of consolidation [149]. The precise differential contribution of anterior and posterior hippocampus to memory retrieval remains unclear for now. What is becoming evident, and in striking contrast to the original conceptualisation of systems-level consolidation, is that the passage of time and associated decay of local memory representations, places an increasing burden on hippocampal constructive processes.

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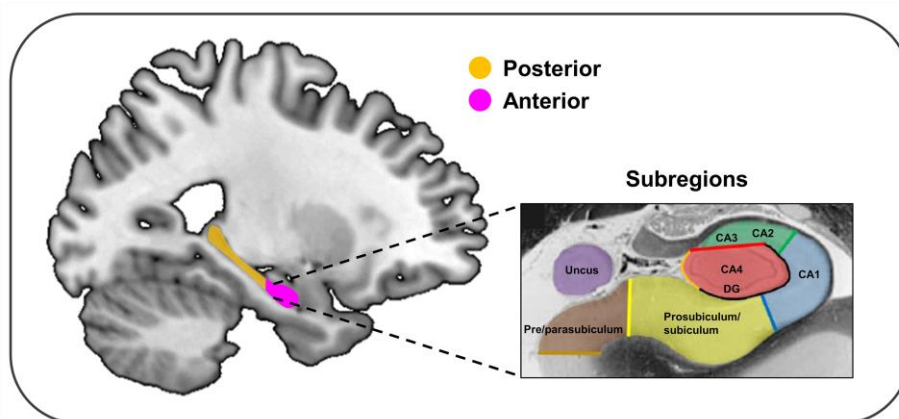
**Figure I. Sagittal and Coronal Views of the Hippocampus and its Subregions.**
The most parsimonious distinction along the hippocampal longitudinal axis is a boundary between posterior (yellow) and anterior (pink) portions, conventionally placed at the apex of the uncus. However, the underlying anatomical and functional differences along this axis are more continuous than discrete in nature. Inset: Coronal slice of the anterior hippocampus with labelled subregions [150] (reproduced with permission from the authors).

**Key Figure**



**Figure 3. A Chronology of Consolidation.**

(A) During the retrieval of a recent memory, experience-dependent traces in the hippocampus reconstruct disparate neocortical elements into a coherent scene which accurately depicts the recent event. (B) With the passage of time, systems-level consolidation creates strong associations between these elements in the neocortex, while the hippocampal scene representation fades. (C) When this experience is recalled some months later, the hippocampus reconstructs a coherent version of the original scene from these consolidated neocortical elements. (D) This scene representation persists for a limited period of time in the hippocampus while its elements are reconsolidated in the neocortex, further strengthening the associations between them. (E) Remote memories are particularly vulnerable to misinformation during retrieval. This can involve the inclusion of semantically-related elements which were not present in the original experience, which are then erroneously incorporated into a reconstructed scene. (F) This altered scene representation in the hippocampus facilitates the reconsolidation and association of both true and false memory elements in the neocortex. This novel interpretation of the hippocampus as a flexible reconstructor of remotely experienced scene imagery is not only consistent with recent evidence of transient hippocampal storage, but also explains the dependence of imagination and future thinking on this brain region which, by definition, occur in the absence of an experience-dependent trace.

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