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Review article

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Maintaining and regaining episodic memory in Alzheimer disease: a circuit-based perspective

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Abstract

Losing track of personal experiences is a defining feature of Alzheimer disease (AD), arising from the spread of AD pathology through the brain circuits that support episodic memory. In this Review, we explore strategies to improve the function of episodic memory circuits in AD by leveraging the optimized use of neural resources. We introduce the circuit utilization framework, which builds on evidence that synaptic dysfunction, maladaptive responses and deficient adaptive plasticity contribute to episodic memory impairment. The circuit utilization framework posits that by optimizing the utilization of circuit resources, episodic memory function can be partially regained. Our focus includes mitigation of hypoactive and hyperactive synaptic dysfunction, reduction of maladaptive processes and enhancement of brain and cognitive reserve. The circuit utilization framework is grounded in circuit-specific hypotheses that link the component processes of episodic memory to clinical symptoms of memory impairment and AD progression. Its overarching aim is to guide the development of interventions that support episodic memory in people with AD, complementing disease-modifying treatments such as anti-amyloid antibody therapies.

Sections

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Key points

- Brain circuits that support episodic memory — that is, the ability to recollect personal experiences — are affected early in the course of Alzheimer disease.
- The hippocampal formation is a crucial convergence region of the episodic memory network, which includes the retrosplenial, parietal, orbitofrontal and medial prefrontal, parahippocampal, temporal and perirhinal cortices and the Papez circuit with its thalamic structures.
- Alzheimer disease induces maladaptive plasticity, resulting in suboptimal resource utilization in episodic memory circuits.
- Adaptive plasticity mechanisms, such as brain and cognitive reserve, can support resource utilization in episodic memory circuits.
- The circuit utilization framework proposed in this Review aims to enhance our clinical and mechanistic understanding of memory impairment in Alzheimer disease and to stimulate the development of interventions to reduce maladaptive plasticity and strengthen adaptive reserve mechanisms.

Introduction

Impairment of episodic memory[1] — that is, the ability to recollect personal experiences — is an early cardinal symptom of Alzheimer disease (AD)[2–4] that profoundly affects life participation and independence. New anti-amyloid drugs such as donanemab and lecanemab[5,6] have been shown to slow cognitive decline in people with AD[5,7], and these should accompany interventions focused on regaining lost functionality in episodic memory circuitry.

In this article, we consider how disease-modifying treatments could be complemented by interventions intended to maintain and even regain lost episodic memory capacity more effectively. We focus on the amnestic variant of AD, which accounts for around 80% of AD cases. We organize our research questions into a common framework that we term the circuit utilization (CU) framework. The core premise of this framework is that episodic memory impairment in AD includes a regainable component stemming from the suboptimal utilization of brain circuits, and we highlight how targeting this suboptimal CU could potentially support both maintenance and recovery of lost function.

The CU framework builds on our current understanding of how clinically observable memory deficits relate to the component processes of episodic memory, their circuit-level functional anatomical organization and the anatomical progression of AD (Table 1 and Fig. 1). It considers synaptic dysfunction and neuromodulatory dysregulation caused by AD and maladaptive and adaptive plasticity, including targetable mechanisms of brain reserve and cognitive reserve for episodic memory. We synthesize these aspects into potential interventions targeting suboptimal CU using pharmacological and non-pharmacological approaches, such as brain stimulation and cognitive training. Our aim is to provide a research agenda to remedy the suboptimal utilization of memory circuits in people with AD, and we believe that the principles of the CU framework can also offer a path towards earlier diagnosis and more precise monitoring of disease progression, both in AD and in other neurodegenerative diseases.

Episodic memory

Definitions and main features

Episodic memory binds, retains and retrieves the spatial, sensory, emotional, social and affective details of personal experiences[1]. It not only enables us to relive past experiences, as beautifully described in Marcel Proust's recall of childhood memories triggered by a madeleine, but also allows us to draw new insights from personal events and to anticipate the future through mental simulation[8,9] — aspects that are underappreciated in AD research and care. Episodic memory is also likely to have a key role in extending self-awareness beyond the 'here and now' to the past and the future. Despite our increasing understanding of episodic memory, no unified theory currently exists. In this Review, we present a circuit-based model of the impact of AD pathology on episodic memory (Table 1 and Fig. 1), incorporating features of different frameworks and theories (Box 1) and emphasizing aspects that might be compromised by inefficient resource use in AD.

Association and separation. Episodic memory can accomplish two seemingly opposing goals — association and separation. It can associate the elements that belong to an experience and separate similar experiences so that they do not interfere with each other. Association in episodic memory relies on pattern completion[10], which in turn has an important role in recollection, just like the remembrance of childhood memories triggered by a madeleine. The key process that enables separation of similar experiences is termed pattern separation[11]. Although episodic memory is traditionally considered to be a form of long-term memory, pattern separation processes can be engaged over shorter time frames that are more typical of working memory. Replay mechanisms associated with episodic memory have also been implicated in working memory[12,13], thereby blurring the traditional distinction between episodic and working memory.

The balance between association and separation in episodic memory changes with age. With advancing age, our behavioural repertoire shifts from being exploratory to being more 'exploitative' of our known and trusted environments[14,15]. At the same time, our internal model of the environment in which we live is being refined, and synaptic plasticity for new sensory learning seems to decrease[16]. Thus, the burden on episodic memory shifts from the associative memorization of new experiences to the separation of familiar experiences in predictable environments. This aspect of episodic memory might be particularly impaired in the early stages of AD[3,17].

Schemata, prior knowledge and preplay. Experiences that are committed to episodic memory are embedded in prior knowledge and schemata[18,19]. Unsurprisingly, episodic memory processes are intricately interwoven with mechanisms that enact prior knowledge, planning, prediction and preplay[20]. This relationship is relevant for our understanding of the neural mechanisms that enable cognitive reserve (discussed later).

Gaining insights from different personal experiences. Any experience or episode unfolds as a chain of associated elements that need to be integrated (a phenomenon termed integrative encoding[21]), and at the same time experiences need to be linked across different episodes[21,22], for example, to remember the social hierarchy of the same individuals when encountered at different events[23]. The ability to integrate information across episodes is relevant for our understanding of the clinical impact of episodic memory impairment in AD.

Table 1 | Hypotheses based on the circuit utilization framework

Memory capacity	Everyday example	Circuit-level processes	Clinical impairment
Distinguishing similar events from each other	"We talked about this when we met in the supermarket and not when we met in the library"	Perirhinal and parahippocampal representation of object and spatial context information; entorhinal cortex projections to DG and hippocampal subfield CA3; pattern separation in DG and CA3	Memory confusions; false memories
Distinguishing memories with overlapping feature combinations (conjunctions)	"This is the entrance door to my neighbour's flat but not my flat"	Perirhinal feature representations; pattern separation in DG and CA3	Interference
Remembering an event when only a cue is available	"This picture reminds me of a lunch we had last week"	Pattern completion in CA3 and cortical back-projections in CA1; hippocampal projections to cortical layer I	Forgetting; inability to recall; mind going 'blank'
Association of successive elements in events	"First I heard a loud roar, then I saw a child dropping his ice cream"	Associative binding throughout the medial temporal lobe	Forgetting causalities; inability to recall a storyline
Integration of common elements across episodes	"I realized that Joe and Jill go to the same restaurant on different days"	Integrative encoding, big-loop recurrence	Lack of insight
Reliving past experiences	"I feel like I am reliving that moment; this makes me very emotional"	Autonoetic awareness; hippocampus and limbic system	Impaired awareness of one's own past
Orienting to novel events	"This never happened before during a football game"	Novelty detection in CA1; prediction error processing; neuromodulatory systems (dopamine, noradrenaline)	Blunting of attention to novel events; indifference; excessive novelty owing to hippocampal hyperactivity could cause anxiety because familiar environments feel novel
Keeping track of context changes and linking information across successive contexts	"I liked how the first scene of the movie gave a clue about the last scene"	Event-boundary processing in the hippocampus; linking elements across event boundaries	Inability to follow and keep track of a narrative
Curiosity and explorative drive	"I like to meet new people and visit new places"	Emotional and motivational responsiveness; amygdala; neuromodulatory systems (dopamine, noradrenaline)	Lack of motivation to explore novel content
Unitizing objects, spaces and multisensory information	"I am sure that this used to be exactly here"	Perirhinal unitization of object and space information and multisensory information	Failure to get accustomed to new environments; feeling overwhelmed with information in one's habitat

This table presents hypotheses, based on the circuit utilization framework, for how the functional anatomical organization of episodic memory, its neurocognitive component processes and the anatomical progression of pathology of the amnestic form of Alzheimer disease (and potential co-pathologies) results in impaired circuit function and related clinical impairments. DG, dentate gyrus.

Underlying brain circuitry

The hippocampal formation is a crucial convergence region[24] of the episodic memory network, which includes the retrosplenial, parietal, orbitofrontal and medial prefrontal, parahippocampal, temporal and perirhinal cortices[25,26] and the Papez circuit with its thalamic structures[27–29]. Here, we focus on components of this network that are likely to be particularly relevant in the context of AD (Table 1 and Fig. 1). In this respect, the hippocampal formation, which comprises the subiculum, the dentate gyrus (DG), subfields CA1 and CA3 of the hippocampus proper, and the entorhinal cortex (EC), is of major interest. The EC acts as a gateway for sensory input to the hippocampus through two (or possibly three[30]) pathways that originate in EC layers II and III. The indirect pathway, which originates in pyramidal neurons of EC layer II, and the direct or 'temporoammonic' pathway, which originates in stellate excitatory neurons in EC layer III, both target hippocampal subfield CA1[31,32]. In humans, both pathways have to 'perforate' the subiculum and are, therefore, referred to as perforant pathways.

The indirect pathway first targets the DG and distributes input from the EC onto a substantially larger granule cell population in the DG. This dispersion can reduce overlap between neural representation patterns originating from the EC, thereby enabling pattern separation. Representations that have been pattern-separated in the DG reach CA3 through the thinly myelinated axons of DG granule cells, known as mossy fibres[33]. Projections from CA3 then reach CA1 through the Schaffer collaterals. CA3 axons also have highly recurrent collateral connections into CA3 neurons, thus enabling autoassociation[34]. During encoding, this promotes binding of different elements of an experience. During retrieval, autoassociation allows the recall of memories if only partial information is available at the EC, thereby enabling pattern completion. Behaviourally, episodic memory readouts that tax either pattern separation or pattern completion more strongly are uncorrelated to some extent[35,36].

Recollection and reinstatement. The autoassociated pattern in CA3 is reinstated in a corresponding activity pattern in subfield CA1 and is associated with other features of an experience through reactivation of cortical representations[29,37]. This cortical reinstatement requires long-range interactions between the hippocampus and cortical regions, which are partly guided through the EC[38] but also through

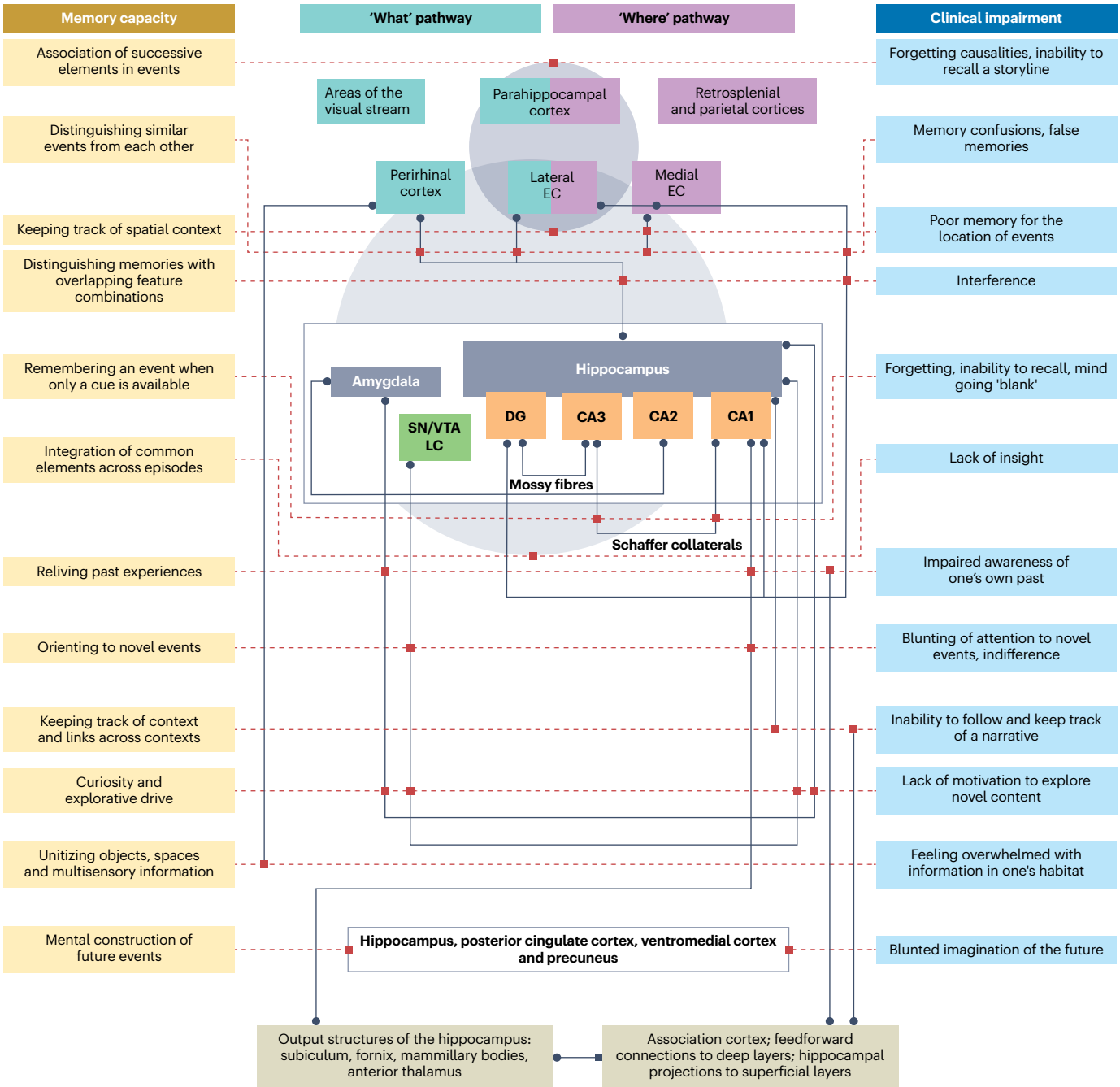

Fig. 1 | Organization of episodic memory processes. The figure provides an overview of the circuit-specific organization of episodic memory processes (left column) and the putative clinical symptoms caused by their impairment (right column). Red dashed lines connect memory processes and clinical symptoms to specific circuitry components (red squares). Red squares intersecting with circles denote the larger network of regions linked to memory processes and clinical symptoms (Table 1). This overview is incomplete, and additional information is provided in the main text. CA1, CA2 and CA3, hippocampal subfields; DG, dentate gyrus; EC, entorhinal cortex; LC, locus coeruleus; SN/VTA, substantia nigra/ventral tegmental area.

the fornix, the mammillary bodies and the anterior thalamic nuclei[39–41]. Pyramidal neurons in CA1 do not possess such recurrent collateral connections and might linearly link CA3 input to cortical representations to enrich reactivation[37]. Neocortical cue information is estimated to trigger hippocampal recall within 100 ms, fast enough for hippocampal back-projections to reach neocortical information before it decays and to allow recollection within a few hundred milliseconds[33].

Context–feature binding. The hippocampus predominantly targets layer I of the neocortex[42,43]. Superficial cortical projections could enable

context information to be integrated with deep layer feedforward projections of feature information[43]. Inhibitory neurons in layer I[44,45] might have a key role in shaping and modulating the effects of hippocampal projections on long-term neocortical memory formation[43]. This layer is affected early by amyloid-β (Aβ) pathology, which causes impaired inhibition[46].

Content of episodic memory. The rich and multifaceted content of personal experiences is committed to episodic memory through hippocampal cortical networks that partly map onto the 'where' and 'what' pathways[25,47–50]. The 'where' pathway conveys representations of spatial information through the retrosplenial, parietal and parahippocampal cortices, the medial and lateral EC and the presubiculum[33,51]. The 'what' pathways convey information about objects through early visual areas, the temporal, perirhinal and parahippocampal cortices and the lateral EC[33,52]. Cross-projections are observed from the parahippocampal cortex towards the perirhinal cortex and lateral EC, and object and scene information converge in the lateral but not the medial EC[52]. The retrosplenial cortex projects to the medial EC and, like the parahippocampal cortex, is part of the scene-processing stream (for example, involved in scene translation[51]). Consistent with this segregation, grid-like space coding is accomplished by grid cells[53] and object–vector cells in the medial EC that fire at specific distances and directions from objects[54]. Together, these data indicate a vector code for location in the medial EC and coding of object identity in the lateral EC. The lateral EC is also implicated in coding of episodic time[9]. Emerging ultrahigh-precision imaging in humans might reveal an even more fine-grained parcellation of the perirhinal cortex and EC on the basis of their cortical connectivity patterns[55].

Additional forms of content-specific representation include social relationships, discrimination and aggression, for which the ventral hippocampal CA1 (ref. 56) and CA2 (refs. 33,57) subfields seem to be particularly well suited. CA2 neurons are directly excited by the lateral EC[58], and they also receive projections from the DG[30] and disinhibit CA1 neurons[59]. CA2 might mediate social components of memory regulated by oxytocin[58]. The amygdala may also be needed to encode social aspects of an episode and extract social information, such as social hierarchies, across episodes[23]. In addition, the amygdala is part of an anterior medial temporal lobe (MTL) network that includes the anterior hippocampus and the perirhinal, temporopolar and lateral orbitofrontal cortices[25,60,61].

Taken together, the evidence suggests that different regions (anterior versus posterior) and subfields of the hippocampus harbour engrams that represent different aspects of an episode[49], and that different representations related to a hippocampus-dependent memory can be selectively manipulated[49,62]. These findings raise the possibility that over the course of AD, some contents of episodic memory are affected earlier than others, depending on how the pathology spreads through these regions[3].

Schemata and prior knowledge. A new episodic memory is both a multisensory and a constructed experience to which the hippocampus, posterior cingulate cortex, ventromedial cortex and precuneus contribute[63]. The medial prefrontal cortex is likely to have an important role in the rapid assimilation of new experiences into existing schemata[18,19], and the hippocampus might be involved in the rapid encoding of knowledge-based prediction errors[19]. Midline neocortical–hippocampal connectivity, in turn, seems to be relevant for the successful memory encoding of new paired associates embedded into pre-existing schemata[19].

Integration and segmentation. Prior knowledge might also be crucial to recognize boundaries between experiences[64]. Without boundary segmentation, experiences could lack the necessary temporal and contextual coherence to be recalled. The posterior hippocampus and the posterior medial network are activated by event boundaries, and the activation level decreases with ageing[65]. Functional magnetic resonance imaging (fMRI) using naturalistic videos showed that the anterior temporal network represented information about specific people in different contexts, whereas the posterior medial network represented the context shared by different people[65]. The medial prefrontal cortex represented the same schema across events, whereas the hippocampus maintained event-specific information[65].

Mechanistically, integration of information across different episodes is likely to involve big-loop recurrence in the hippocampal–cortical circuitry[23]. According to this view, entorhinal deep layer outputs can be recirculated as new input to superficial layers of the EC. This mechanism allows cortical reactivation of event features triggered by successful pattern completion in CA3 and CA1 to be associated with new episodic memories[66].

Unitization. Although an important feature of episodic memory is to flexibly associate anatomically distributed and multisensory representations, there is also a need for computational efficiency by uniting representations into single entities. An example is the unitization of object and space information in familiar environments to reduce the curse of dimensionality for making choices, selecting action policies or forming new episodic memories in known environments[67].

Novelty detection. The direct pathway from the EC to CA1 could serve several purposes. It could enrich pattern-separated and autoassociated information from the indirect pathway with additional event information during encoding[68]. In addition, autoassociation in CA3 might be used to compute a memory-based prediction error or novelty

Box 1 | Theories of episodic memory

Several neurocognitive frameworks and theories guide research into episodic memory:

- Representation-based theories such as the trace transformation theory[203], which emphasize reconstruction and change over time
- The complementary systems theory and its recent modifications[204], which distinguish episodic memory from slow cortical learning
- The pattern separation theory[205], which emphasizes distinct hippocampal representations as a fundamental principle of episodic memory
- The levels of processing framework, which emphasizes the role of attention and information processing during encoding[206]
- Theories that emphasize the role of signal detection and the distinction between recollection and familiarity[207]
- The theory of autonoetic awareness, which emphasizes the role of conscious awareness and the ensuing experience of remembering an event or just knowing that it must have happened[73]

signal against sensory CA1 input from the direct pathway[69]. The resulting memory-based novelty detection could then lead to an orienting response, trigger encoding and enhance consolidation through activation of dopaminergic midbrain regions (via hippocampal projections to the nucleus accumbens) and ensuing dopamine release in the hippocampus[69,70].

Episodic memory impairment in AD

Clinical presentation

The clinical presentation of episodic memory impairment in people with AD is an amnestic syndrome of the hippocampal type, characterized by poor free recall despite controlled encoding, that is, when sufficient attention and the use of appropriate learning strategies is ensured[71,72]. In these individuals, recall shows limited benefit from cueing with semantic cues or recognition prompts[72]. This pattern is seen as evidence of a true storage failure, as opposed to retrieval deficits seen in other conditions such as depression or frontotemporal dementia.

Clinical neuropsychological assessment of episodic memory impairment in AD does not yet incorporate our current understanding of the component mechanisms of episodic memory outlined above and is not anatomically targeted or circuit-related. Closing this knowledge gap could enable progress on several fronts. First, the abovementioned neurocognitive aspects of episodic memory could help us to gain a more complete understanding of the clinical presentation of AD, which includes content-specific forgetting; impairments in future thinking and event segmentation; impoverished insight generation and integration; and novelty-related anxiety. Second, by making clinical assessment anatomically targeted and circuit-related, neurocognitive information about anatomical disease progression could be obtained and anatomically targeted interventions could be deployed. Third, we could gain insights into the experiential nature of memory impairment in AD and how the contents of memories are impoverished in terms of content and the autonoetic[73] nature of awareness. Last, a circuit-level understanding of episodic memory impairment could open up a path towards establishing a clinical phenotype for very early AD, when tau pathology is restricted to a few circuits.

Our rationale to assign anatomically confined AD-related impairments of circuit-specific functions to specific component deficits in episodic memory is supported by human case studies. Following the famous case of H.M.[74], who developed memory impairment following experimental neurosurgery, specific-lesion–memory-deficit relationships have been described for bilaterally selective hippocampal lesions[75], as well as selective CA1[76], DG[77], perirhinal cortex[41,78] and fornix lesions[79], to name just a few examples.

Clinical staging

The pathological hallmarks of AD include aggregation of soluble forms of Aβ into insoluble plaques, intracellular accumulation of hyperphosphorylated tau in the form of neurofibrillary tangles, and neurodegeneration, which is evident in neuropil loss or neuronal death[80,81]. AD pathology can be assessed using imaging biomarkers — positron emission tomography (PET) for Aβ and tau, and PET and MRI for neurodegeneration — and fluid biomarkers in blood and cerebrospinal fluid[81].

The Alzheimer's Association[82] and the International Working Group[83] have proposed clinical staging schemes for AD based on legacy neuropsychological tests and functional impairments in activities of daily living. Both frameworks recognize mild cognitive impairment (MCI) as the first relevant clinical manifestation of AD. MCI with fluid or imaging biomarker evidence of Aβ and tau pathology is classed as stage 3 by the Alzheimer's Association and prodromal AD by the International Working Group. MCI is characterized by significant (usually >1.5 s.d.) cognitive impairment in at least one cognitive domain — episodic memory in 80% of cases — compared with an age norm. Independence in everyday life is preserved, although minor impairments in complex tasks such as managing financial affairs, mild difficulties pursuing hobbies and intellectual interests, and very mild problems in orientation and time perception are often reported[84,85]. In the International Working Group framework, Aβ-positive individuals with less impairment are staged as asymptomatic at risk if tau pathology is still confined to the MTL and as presymptomatic AD if tau pathology extends beyond the MTL. The Alzheimer's Association framework distinguishes an asymptomatic stage 1 from stage 2 with subtle cognitive decline that can be accompanied by subjective memory complaints.

Episodic memory circuit dysfunction

AD pathology shows progression through the episodic memory circuitry. In this section, we hypothesize how circuit dysfunction owing to Aβ and tau pathology is related to component processes and features of episodic memory impairment (Table 1 and Fig. 1).

A meta-analysis of tau PET imaging data[86] revealed that among people aged 60–80 years, 17.4–22.2% of Aβ-positive participants without cognitive impairment showed abnormally high (2 s.d. above the norm) tau accumulation in medial and lateral parts of the temporal cortex (tau PET positivity). In participants with MCI, rates of tau PET positivity were 68.0% at 60 years of age, compared with 52.9% at 80 years of age. These data indicate that lower levels of tau pathology are sufficient to cause MCI in old age, whereas higher levels of tau pathology are needed to cause MCI earlier, possibly reflecting higher reserve at younger ages. Tau positivity was more frequent in the EC than in lateral temporal regions in both cognitively unimpaired individuals and people with MCI, and was also more frequent in apolipoprotein E (*APOE*) ε4-homozygous individuals than in those with other *APOE* genotypes. Therefore, the extent to which the circuit-related symptoms outlined in Table 1 and Fig. 1 occur at the pre-MCI or MCI stages of AD is likely to depend on the extent of tau pathology, combined with age and reserve mechanisms (see below).

Memory confusions, recall failure and false memories. The transentorhinal region, EC and hippocampus (including the subiculum and CA1) are among the first areas ('epicentres') to be affected by tau pathology in EC layer II, which is followed by formation of neurofibrillary tangles and cell death[87,88]. The DG and CA3 are affected later by trans-synaptic spread[60,89], as corroborated by human imaging studies[90]. Input of mnemonic information from the EC to the DG might be compromised by noise and degraded perceptual fidelity early in AD, which, in turn, could impair the ability of the DG and CA3 to pattern-separate similar memories, leading to memory confusions, particularly if the corresponding representations are subject to decay[91] (Table 1). Spread of tau pathology from the transentorhinal to the perirhinal cortex could contribute to memory confusions by disrupting unitization (Table 1, Fig. 1). Better preservation of pattern completion than pattern separation in CA3 can have both positive and negative consequences: on the one hand, pattern-completion biases can help to compensate for loss of memory detail, but on the other, such biases can be maladaptive and increase the propensity for false memories, which are often encountered in AD[92,93] (Table 1).

Remote versus recent memories. Individuals with AD are often suggested to have relatively preserved remote episodic memories, whereas more recent memories tend to be disproportionately affected[94]. However, meta-analyses show that patients with AD also have clear autobiographical memory deficits[94], and the mere ability to report such memories does not indicate that they are retrieved through episodic memory processes. Instead, preserved remote autobiographical memories could be schematic memories (akin to semantic memory), as described in the multiple-trace theory of episodic memory consolidation[95].

Reduced motivational drive and emotional responsiveness. The distribution of neurofibrillary tangle pathology along the hippocampal long axis is not uniform, with the anterior and the most posterior regions showing the strongest accumulation[96] — the latter mirroring the connectivity profile of the anterolateral EC[52,60,97]. Anterior hippocampal neurofibrillary tangle accumulation is mediated through privileged connectivity to the amygdala[60], and early involvement of the amygdala could impair emotional responsiveness and reduce motivational drive and curiosity for novelty (Table 1, Fig. 1). Of note, the level of Aβ pathology correlates with hyperphosphorylated tau levels in the EC and the individual hippocampal subfields, with the exception of CA2 (ref. 98). This sparing of CA2 is possibly related to the relative preservation of the social interaction facade in the early stages of AD.

Impaired context recollection and learning across contexts. Hippocampal projections to the cortex reach superficial cortical layers[43], which show the earliest signs of Aβ-related synaptic dysfunction (impaired inhibition) in humans[46]. Therefore, long-range hippocampal–cortical reverberations could be affected early in AD, leading to impairments in the ability to code and retrieve context[43] and to extract commonalities across episodes (Table 1 and Fig. 1). Indeed, learning by temporally spaced repetition across days is thought to be particularly sensitive to Aβ pathology early in the course of AD[99], possibly owing to the effects of this pathology on hippocampal–cortical projections.

Content-specific impairment. Clinical assessments of episodic memory are currently performed largely independently of the representational content of memories. Established tests such as the Doors and People Test[100], the Wechsler Memory Scale[101], the Face–Name Associative Memory Exam[102] and the Free and Cued Selective Reminding Test[103] involve a wide range of material, including faces, words, images, spatial information and visual, auditory and story content. This content-agnostic approach is questionable, because different modalities and contents are segregated in the circuitry of episodic memory (Fig. 1). Indeed, verbal and picture-based versions of the same test are not equivalent when assessing cognitive deficits[103]. Object mnemonic discrimination is affected earlier in the AD course than scene mnemonic discrimination, and both of these processes are differentially related to tau pathology in the anterior temporal region and Aβ pathology in the retrosplenial region[3,104–106]. Spatial disorientation with impairments in path integration — that is, the ability to continuously track one's position and orientation relative to a starting point — are early symptoms of AD that have been related to dysfunction of spatially tuned cells in the MTL[107–109]. Whether object mnemonic discrimination impairment, spatial disorientation and path integration deficits reflect successive stages of tau spread in the MTL or whether they reflect different phenotypes of tau spread[60] is unclear.

Capacity reduction. A core clinical feature of episodic memory impairment in AD is an apparent loss of capacity. Factors that might limit memory capacity include the number of CA3 recurrent collateral connections for autoassociation, the number of back-projection connections from the CA1 to cortical neurons via the EC, and the number of associatively modifiable synapses made by EC neurons onto each CA3 neuron[33]. The intricate regulation of the plasticity of CA3–CA1 synapses to couple sparse CA3 patterns with information-rich CA1 representations might be an important determinant of the capacity to store a large number of similar episodic memories without interference[37]. In the future, a combination of ultrahigh-resolution imaging and synaptic-density mapping with PET[110] could provide individual in vivo estimates of memory capacity by quantifying these connections. We note that a reduction in encoding owing to impaired novelty orienting and novelty-related activation of the hippocampus[111,112] could mimic reduced memory capacity in people with AD (Table 1).

Impaired dual-tasking and sensorimotor integration. Striatal pathology could lead to impaired motivational drive and sensorimotor integration and problems with the motor and cognitive demands of dual tasking. These impairments are likely to be particularly relevant in situations where bodily cues — such as head position, vestibular inputs, posture and proprioception — need to be integrated with motion perception and with scene and object processing to form multidimensional representations of objects and space to guide navigation[113] at the interface with episodic memory.

AD subtypes and co-pathologies. The progression of AD pathology through the episodic memory circuitry shows interindividual differences, and various subtypes of AD can be distinguished, including limbic-predominant and hippocampal-sparing subtypes[114–116]. In subtypes that initially spared the MTL, tau pathology was found to spread into this region at later disease stages[116]. Because the AD subtypes show different rates of disease progression[114], the abovementioned impairment of episodic memory component processes might follow different temporal sequences.

Co-pathologies represent an additional stratification criterion. In individuals presenting with AD, the MTL frequently harbours protein aggregates that are typical of other conditions, most notably TAR DNA-binding protein 43 (TDP43) and α-synuclein, which are associated with frontotemporal and Lewy body dementia, respectively[117,118]. Both TDP43 and α-synuclein pathology have a predilection for subfield CA2 and might be associated with impaired social cognition and memory. Post-mortem studies indicate that the frequency of these co-pathologies increases with advancing age and can be as high as 30%[118].

The circuit utilization framework

We propose a CU framework, which posits that episodic memory impairment in AD has a reversible or regainable component as a result of suboptimal neurocognitive CU (Fig. 2). The CU framework outlines how beneficial adaptations can be identified and strengthened while non-beneficial or maladaptive responses are attenuated. We propose that the optimal utilization of neural resources of episodic memory in people with AD depends on several interconnected factors (Fig. 2), including synaptic and circuit dysfunction (hypoactivity and hyperactivity) owing to AD pathology; maladaptive circuit-level network reorganization; maladaptive neurocognitive biases and overutilization and underutilization; and adaptive plasticity (brain and cognitive reserve).

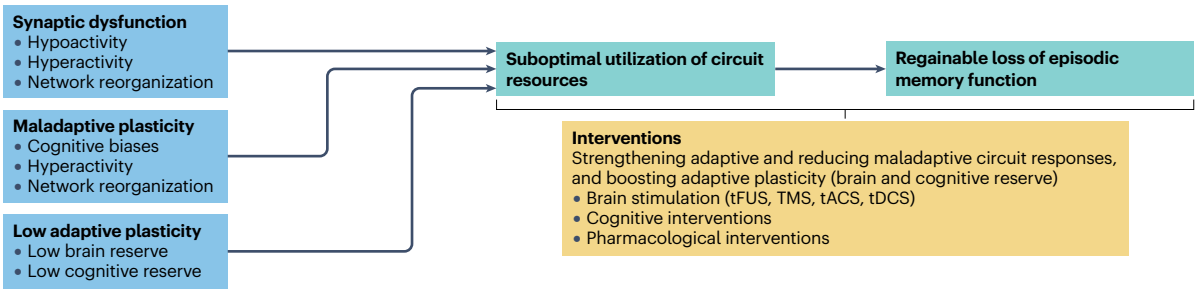

Fig. 2 | The circuit utilization framework in Alzheimer disease. The figure shows how the circuit utilization framework might be used to improve episodic memory function in people with Alzheimer disease through recovery of reversible (regainable) aspects of episodic memory circuit impairment. tFUS, transcranial focused ultrasound; tACS, transcranial alternating current stimulation; tDCS, transcranial direct current stimulation; TMS, transcranial magnetic stimulation.

The CU framework rests on two fundamental hypotheses. First, the suboptimal utilization of episodic memory in AD is multidimensional, resulting from a combination of circuit-specific hypoactive and hyperactive synaptic dysfunction and a lack of adaptive and an excess of maladaptive plasticity. Second, interventions targeting episodic memory dysfunction in AD should also be multidimensional and circuit-specific, with hypoactive and hyperactive circuits and adaptive and maladaptive circuit plasticity being targeted in parallel.

Synaptic dysfunction

AD starts as a synaptopathy, characterized by local synaptic dysfunction, before progressing to synapse loss and neurodegeneration[119]. Soluble oligomeric Aβ induces deterioration of synaptic function in AD even before overt signs of dementia and plaque formation[120–122]. A plethora of studies have addressed how Aβ pathology in conjunction with accumulation of hyperphosphorylated tau in spine synapses induces dysfunction of synaptic neurotransmission and impaired synaptic plasticity[123], and clear evidence from mouse models of tau and Aβ pathology indicates that cognitive impairment is reversible in AD[124,125]. Synaptic dysfunction is also related to glial function and is intimately linked to chronic sterile neuroinflammation, which is a hallmark of ageing and is more pronounced in AD[126,127]. The complex interplay of astrocyte and microglial function with the local inflammatory status in small neuronal circuits is one of the first overt cellular changes associated with Aβ pathology[127]. Increased production of pro-inflammatory cytokines alters synaptic function and gene expression in glial cells, and is largely detrimental for the expression of synaptic plasticity[128]. These changes, in turn, are likely to influence the dynamics of the tripartite synapse, which consists of synaptic junctions and glial endfeet that are instrumental for glutamate reuptake following synaptic release.

Synaptic hyperexcitability. An early phenotype of AD is neuronal hyperexcitability caused by suppression of glutamate reuptake[129]. At this disease stage, inhibition of glial glutamate uptake causes increased ambient glutamate levels, which, in conjunction with binding of Aβ to the NMDA receptor (NMDAR) subunit GluN2B, results in detrimental activation of extrasynaptic NMDARs[130]. Interestingly, synaptic phenotypes that are caused by initial hyperexcitability occur before or at the onset of cognitive decline[131] and before synaptic depression induced by oligomeric Aβ. As a consequence, interventions that target early synaptic dysfunction within this time window hold promise for the treatment of cognitive symptoms of AD at disease onset. A study published in 2024 suggests that scavenging of Aβ monomers, which prevents formation of synaptotoxic Aβ oligomers, can suppress early neuronal hyperactivity and ambient glutamate accumulation[132]. This approach is of particular interest because the invention of synaptic-density PET[110] has now put systematic analysis of synaptic phenotypes in people with AD within reach (Box 2).

Hippocampal hyperactivity might be coupled to the degree of clinical impairment and cognitive decline[131,133–135]. Preliminary evidence suggests that in individuals with amnestic MCI, targeting of hyperactivation with the antiepileptic drug levetiracetam can normalize hippocampal activity levels and improve mnemonic discrimination (by tapping into pattern separation), possibly through modulation of synaptic vesicle glycoprotein 2A (SV2A)[136,137]. In the Hope4MCI trial, a levetiracetam-related modified SV2A modulator specifically designed to reduce hyperactivity in hippocampal subfield CA3 yielded promising results in terms of slowing down EC neurodegeneration and cognitive decline[138] in *APOE* ε4 non-carriers[136].

In humans, network hyperactivity can be indirectly measured using fMRI[104,131,135,139,140]. However, unlike in animal models, with fMRI it is challenging to discern the extent to which hyperactivation in an individual patient with AD is an adaptive, maladaptive or aberrant response (Box 2). In the context of the default mode network, Aβ drives hyperexcitability within the MTL[135]. Hyperexcitability in both the default mode network and the MTL, in turn, is related to the rate of tau PET signal accumulation in the EC[135]. These data converge with animal models in indicating that Aβ disrupts the local excitatory–inhibitory balance (Box 3).

Synaptic depression and hypoexcitability. Collectively, the current evidence points towards early synaptic dysfunction as an accessible entry point for interventions. Oligomeric Aβ induces synaptotoxicity and compromised synaptic plasticity by inhibiting NMDAR-mediated Ca^{2+} signals[141–143] and long-term potentiation — a key form of plasticity that is essential for learning and memory[141,144,145]. Over longer timescales (several weeks) in animal models of AD, a shift of the threshold to preferentially induce long-term depression has been consistently reported[4]. Synaptic depression was shown to precede dendritic spine loss and synapse elimination in these models[4].

Interestingly, whereas high levels of Aβ deposition are associated with brain network hyperexcitability, hyperphosphorylated tau deposition leads mainly to brain network hypoexcitability in

transgenic AD mouse models[146]. In cerebrospinal fluid from $A\beta_{42/40}$-positive individuals on the preclinical and prodromal AD spectrum, novelty responses (that is, the contrast in activity between highly familiar and novel images) in the hippocampus decreased with increasing levels of hyperphosphorylated tau in cerebrospinal fluid[111]. No such relationship was found for Aβ-negative individuals, indicating that Aβ has a permissive role in tau-related hippocampal dysfunction.

Hypoactivity can also be observed in the functional connectivity of the MTL. Aβ-positive individuals without cognitive impairment showed decreased functional connectivity between the perirhinal cortex and EC and the medial prefrontal cortex[140], and as the level of tau pathology increased, functional connectivity between the bilateral perirhinal cortex and EC, the anterior hippocampus and posterior–medial regions decreased further[140]. Lower MTL–cortical functional connectivity was associated with reduced memory performance and more rapid longitudinal memory decline[140]. At the MCI stage, Aβ-positive individuals showed reduced connectivity between the anterior hippocampus and the posterior cingulate cortex but hyperconnectivity within the MTL[140].

Synaptic dysfunction and noise accumulation. Noisy neural representations could accumulate in episodic memory as activity cycles through hypoactive and hyperactive parts of the hippocampal–cortical circuitry. Evidence from a mouse model of AD indicates that noise can accumulate owing to aberrant activity and epileptiform discharges[147]. Noise might accumulate in sensory representations of memories; through temporal jitter in the interplay of different hippocampal subfields, direct and indirect path convergence in CA1, hippocampal and perirhinal back-projections to cortical layer 1, and big-loop recurrence; and in the EC itself, for instance, in grid cell coding[109]. In the context of navigation, the path-integration process in mice has been shown to accumulate errors in its estimate of movement direction during the course of a journey when relying on self-motion cues alone[109,148,149]. Neural oscillations have an important role in structuring neural activity[150], such as the coding of place and direction of movement[151], head direction and rotation-related movement[152], and disambiguation of stimuli[153,154]. Noise in neural oscillations can degrade these representations and processes, and it represents a potentially tractable cause of memory failure and a promising target for interventions to remedy suboptimal CU. In humans, noise could be measured using representational decoding of brain activity.

Maladaptive plasticity

As outlined above, episodic memory is not only a record of multisensory experience but also a constructive process in which prior knowledge determines the need for new encoding and shapes the resulting memory engram. Once formed, memories are subject to ongoing transformation[155], in which they are shaped and distorted by current

Box 2 | Readouts for synaptic dysfunction in humans

Definition

In the circuit utilization (CU) framework, we define synaptic dysfunction as a disease-related local brain activity change (cross-sectional or longitudinal) that cannot be explained by local neurodegeneration. This definition follows the rationale from animal research, where synaptic dysfunction is conceptualized independently from synapse loss.

Brain activity measurement

Local brain activity within the episodic memory network can be measured using functional magnetic resonance imaging (fMRI), electroencephalography (EEG) and magnetoencephalography (MEG). EEG and MEG have lower spatial resolution and anatomical precision than fMRI. Ultrahigh-resolution MRI at 7T can measure brain activity with submillimetre, layer-resolved precision.

Neurodegeneration

Morphometric MRI, such as volumetric data and structural connectivity, can be used to estimate the degree of neurodegeneration at the same location as brain activity. Neurodegeneration can be measured by 7T MRI with submillimetre, layer-resolved precision. Quantification of synapse density is not possible with MRI; however, synaptic-density PET can provide an estimate. By statistically accounting for localized neurodegeneration through MRI or synaptic-density PET, brain-activity measures can be used to estimate the circuit dysfunction that best reflects synaptic dysfunction.

Hyperactivation and hypoactivation

Hyperactivation-like and hypoactivation-like patterns have been observed in task-based fMRI studies in people with Alzheimer disease (AD), although fMRI measures are not specific to hyperactivity and hypoactivity. Attempts to identify aberrant hyperactivity patterns with EEG and MEG are ongoing. The CU framework criteria for hyperactivity and hypoactivity as indices of synaptic dysfunction are as follows:

- Increased or decreased brain activity compared with individuals with less AD pathology
- Correlated with biomarker pathology, that is, increasing hyperactivity with increasing amyloid-β and/or tau pathology
- Not explained by neurodegeneration
- Not explained by a neurocognitive mechanism

Hyper-recruitment

Synaptic dysfunction within the episodic memory circuitry can have downstream or upstream neurocognitive consequences that are associated with increased brain activity. These activity increases do not reflect local synaptic dysfunction and therefore do not qualify as hyperactivity elicited by synaptic dysfunction. Instead, they reflect hyper-recruitment of a brain region. The CU framework criteria for hyper-recruitment are as follows:

- Increased brain activity related to a specific cognitive strategy
- Maladaptive (non-beneficial) recruitment of additional neurocognitive resources (attempted compensation)
- Adaptive (beneficial) recruitment of additional neurocognitive resources: cognitive reserve
- Mobilization of circuit components: brain reserve
- Computational modelling, such as dynamic causal modelling, is compatible with task-based interactions between regions

Box 3 | From research to real-world benefits

Episodic memory loss is one of the most disabling and distressing symptoms of Alzheimer disease (AD), and developing translational strategies to partially restore its function remains challenging. The circuit utilization (CU) framework presented in this Review focuses on the specific neural circuits and component processes that support episodic memory and how these processes are disrupted as AD pathology spreads through the brain. By linking the organization of memory circuits with patterns of pathology and clinical symptoms, the CU framework provides a mechanistic explanation of potentially reversible dysfunction.

According to this framework, memory impairment is driven not only by irreversible neurodegeneration but also by suboptimal utilization of surviving neural resources. Hypoactive and hyperactive circuit states, maladaptive plasticity and insufficient adaptive plasticity (or reserve) can all reduce the efficiency of episodic memory networks in ways that might be amenable to intervention. This perspective enables a multi-scale translational strategy aimed at improving the function of remaining circuit capacity, rather than focusing exclusively on slowing disease progression.

Interventions inspired by the CU framework could form the basis of circuit-centred rehabilitation programmes that combine multimodal training, neuromodulation, enhancement of designated brain reserve and cognitive reserve mechanisms, and lifestyle approaches. These programmes could complement disease-modifying treatments, including anti-amyloid therapies, with the aim of maximizing everyday functioning, independence and quality of life.

Key challenges in translating this research into practice include identifying reliable biomarkers of CU, determining the optimal timing of interventions and tailoring treatments to individual patterns of pathology and reserve. The next steps are longitudinal, multimodal studies to validate CU-based markers, early-phase trials of combined pharmacological and circuit-targeted interventions, and the development of scalable rehabilitation protocols. These efforts could enable mechanistic insights into memory circuits to be converted into practical strategies to help people with AD to maintain and potentially regain meaningful aspects of episodic memory.

knowledge, beliefs and feelings[156]. The constructive and reconstructive nature of episodic memory can lead to false memories when actual events are schema-incongruent because of a schema-dependent pattern-completion bias[17].

Degradation of pattern separation together with a bias towards false memories in AD[93,157] can cause clinical problems in everyday life that go beyond mere forgetting[92]. False memories in AD are more frequent for specific details than for gist[158], supporting a combination of impaired mnemonic detail representation and pattern-completion bias. In the early stages of AD, patients tend to have a liberal response criterion for familiarity[157]. Evidence indicates that MTL but not prefrontal dysfunction[93,157] is related to false memories and liberal response criteria. In tasks that tap into pattern completion, older adults show a bias towards 'false' pattern completion[159] — a phenomenon that is under investigation in people with AD.

The novelty-detection circuitry in the hippocampus and the hippocampus–ventral tegmental area loop[69] could create 'novelty' noise in familiar environments as a result of hippocampal hyperactivity. Aberrant hyperactivity might lead to increased dopaminergic stimulation, causing a feeling of novelty in a person's familiar setting, which in turn could lead to anxiety and fear. This situation could be targeted by reducing hippocampal activity through non-invasive inhibitory hippocampal stimulation — an approach that might be particularly relevant in the later stages of AD.

Adaptive plasticity

People with AD pathology can be cognitively normal, and rates of decline vary considerably between individuals, presumably reflecting interindividual differences in reserve capacity[160–165]. The aforementioned observation[86] that younger age at MCI symptom onset is associated with more distributed tau pathology is compatible with a reserve framework, whereby decreasing reserve with age lowers the pathology threshold needed to produce clinical symptoms. As outlined in the Collaboratory on Research Definitions for Reserve and Resilience in Cognitive Aging and Dementia criteria[166], brain reserve and cognitive reserve are distinct forms of coping with pathology. Brain reserve refers to 'neural capital', and cognitive reserve refers to adaptive reorganization of cognition, both of which enable individuals to cope with pathology.

The Collaboratory on Research Definitions for Reserve and Resilience in Cognitive Aging and Dementia consensus explicitly encourages a circuit-based research approach to uncovering the mechanisms of brain and cognitive reserve[166]. Within the CU framework, we hypothesize that reserve is not merely an empirically observable state but can be strengthened and mobilized by circuit-based interventions, once their neural underpinnings and their link to the functional anatomy of episodic memory have been identified in empirical and longitudinal studies of AD[162,164].

Brain reserve. Brain reserve refers to the capital of neural resources, such as numbers of neurons and synapses, with which individuals are equipped when being challenged by a pathology or perturbation[166]. The volume of a brain region can be related to brain reserve by affording better than expected cognitive performance at a given state of brain pathology. For example[162], older adults who had no memory complaints despite having Aβ pathology were shown to have larger CA1 subfields than their Aβ-negative peers or Aβ-positive individuals with memory complaints (subjective cognitive decline, AD stage 2)[163]. These findings indicate that brain reserve — that is, higher capital of neural resources in the hippocampus — enables some individuals to avoid memory complaints despite having Aβ pathology[162].

Neuroanatomical data from people with exceptional memory performance are also informative. Post-mortem data from individuals over 80 years of age who had the memory capacity of people 20–30 years younger showed that their layer II EC neurons had larger somata than those in typical agers[167]. These so-called super-agers also had fewer neurofibrillary tangles in EC layer II than their cognitively average peers.

Cognitive reserve. The adaptive properties of cognitive reserve[166,168] include compensation, which is the use of an alternative network from the one affected; flexibility, which is the optimization of how an affected network can be used; and efficiency, which is the ability to reduce the demand on the affected network[166]. These adaptations moderate the relationship between age-related brain changes or pathology and cognitive decline over time[168].

Several fMRI studies have investigated cognitive reserve mechanisms[169]. In people with AD, cognitive reserve against Aβ, tau and hippocampal atrophy was reflected in more pronounced expression of novelty responses in the anterior cortex and inferior temporal regions, including the fusiform gyrus[164]. Cognitive reserve was also associated with better preserved segregation of resting-state functional networks despite increasing levels of tau pathology[170]. In addition, higher connectivity of the inferior frontal junction was associated with greater cognitive reserve against the impact of brain pathology, including tau[171], in people with sporadic or familial AD[172]. Lifelong experiences can be a proxy of cognitive reserve moderating the association between connectivity and cognition in people with AD[173,174].

The potential neurocognitive mechanisms through which episodic memory might be supported by cognitive reserve are summarized in Table 2. Semantic memory — that is, performance in naming or word-generation tasks — is relatively preserved in early amnestic AD. Evidence suggests that semantic proficiency is linked to educational attainment and can provide cognitive reserve for episodic memory[166], and educational attainment has often been used as a proxy for cognitive reserve[166]. Knowledge in the form of pre-existing schemata is likely to be associated with a U-shaped benefit for episodic memory as a function of congruency of new experiences with prior knowledge[175]. Events that are related to or conflict with our knowledge of the world (termed schemata and novel events, respectively) are both better remembered than unrelated events[175]. Low educational attainment could blunt the memory benefit at both sides of this U-shaped curve.

Reduced utilization of prior knowledge and prediction could lead to capacity overflow and confusion. For instance, in our daily trip to the supermarket, the familiar environment through which we navigate does not need to be encoded again every day, unless the store layout changes, leading to prediction errors. Efficient schema-based recruitment of pre-existing engrams can reduce the memory storage capacity that is needed to adapt to such changes. Artificial intelligence approaches with large language models that incorporate a person's environment offer the possibility of leveraging this form of cognitive reserve in people with AD. A related mechanism is unitization of associated elements into single representations. Schemata can enhance the unitization of new information by the perirhinal cortex[176], which might assist with reducing the storage capacity required for new episodic memories. Prior knowledge might also preactivate neural ensembles in episodic memory, thereby enhancing the signal-to-noise ratio in afferent inputs to reduce noise accumulation.

Enactment of these potential knowledge-based reserve mechanisms requires the involvement of multiple cognitive domains, including attention and context-dependent and schema-dependent facilitation of multi-object and feature tracking; parallel planning; time estimation and temporal prediction, including knowledge and schema predictions based in semantic memory; cognitive control and effort; motor control of balance and posture; and cognitive flexibility (Table 2). These auxiliary cognitive domains are viable targets for interventions to strengthen cognitive reserve (Table 2). Of note, CA1 neurons project to the prefrontal cortex, amygdala or nucleus accumbens depending on task demands[49,177], and this flexibility raises the possibility that cognitive training can influence the routing of hippocampal–subcortical or hippocampal–cortical outputs.

Interventions based on the circuit utilization framework

The CU framework points towards interventions for improving the use of circuit resources for episodic memory by reducing the impact of synaptic dysfunction and maladaptive plasticity while strengthening adaptive plasticity (Fig. 2). In combination with disease-modifying treatments for AD, such interventions could provide a pathway to regaining episodic memory impairment caused by suboptimal utilization. Our hypothesized circuit-specific interventions include inhibitory and excitatory non-invasive brain stimulation, specific forms of cognitive and bodily training to support cognitive reserve for episodic memory, and pharmacological interventions that target neurocognitive mechanisms[136,138,178].

Reducing maladaptive and enhancing adaptive plasticity

New non-invasive brain-stimulation technologies, including low-intensity transcranial focused ultrasound (tFUS) and focused transcranial electrical stimulation[179–183], can reach deep brain regions such as the medial temporal and midline cortical regions of the episodic memory circuitry. Both of these technologies can achieve the anatomical precision in the centimetre and sub-centimetre range that is required for the CU framework, and they can promote either excitatory[179,184] or inhibitory drive[185,186]. Low-intensity tFUS protocols have lasting effects that seem to extend beyond 60 min after stimulation[185,186], thereby offering the potential for sustained benefit through intermittent application. As of October 2025, nine trials of low-intensity tFUS and over 15 trials of non-invasive electrical stimulation for the treatment of cognitive impairment in AD were registered on ClinicalTrials.gov.

We hypothesize that stimulation that causes excitation of a circuit can be used to target MTL hypoactivity caused by synaptic dysfunction, in particular as a result of interactions between Aβ and tau pathology (see above); enhance EC functional connectivity to improve crosstalk between the hippocampus and cortical regions; enhance perirhinal multisensory integration and unitization (see below); and target brain regions known to be important for brain reserve and cognitive reserve (see below). By contrast, inhibitory stimulation might be used to target aberrant hyperactivity in retrosplenial regions and the MTL, and in superficial cortical layers of brain regions that show strong connectivity to hippocampal output regions to inhibit early hyperexcitatory cortical responses to Aβ deposition.

Targeting brain reserve

We hypothesize that mobilization of brain reserve involves circuit-specific activation of neurons that are silenced, have reduced synaptic plasticity, are functionally unavailable owing to aberrant network activity, are energetically compromised owing to vascular pathology or cannot be recruited into ensemble activation. We propose that brain reserve regions that have been identified in cohort studies[162] can be stimulated with excitatory non-invasive brain-stimulation protocols (Table 2).

A key challenge for mobilizing brain reserve is to recruit neurons in the episodic memory circuitry that have been silenced by disease pathology. A study published in 2023 showed that reinstatement of excitation–transcription coupling using the small molecule nitarsone

Table 2 | Hypothetical interventions to improve circuit-specific aspects of episodic memory in early Alzheimer disease

Circuit dysfunction (target)	Goal[a]	Interventions		
		Behavioural	Brain-stimulation targets	Pharmacological
Noise in spatial coding of episodic events and movement perception	Improving afferent signals that are required for grid-cell coding and egocentric and allocentric spatial processing	Training vestibular processing, balance, gait, head position perception and visual acuity; training spatial attention; training dual tasking (e.g., talking while walking)	Entorhinal cortex, basal ganglia, motor regions	Cholinergic agents[198,199] and dopamine receptor D1/D2[200] and noradrenergic[201] neuromodulation to enhance sensory attention and perception
Noise in visual perception of episodic details	Improving perceptual detail in MTL afferents	Visual perception and discrimination training (expertise) for relevant percepts (e.g., faces); reward-based enhancement of perception[202]	Early visual brain areas and motion perception	Cholinergic agents[198,199] and dopamine receptor D1/D2[200] and noradrenergic[201] neuromodulation to enhance sensory attention and perception
Noise in multimodal integration of episodic details	Improving perceptual accuracy in auditory, visual and tactile perception	Training auditory, visual and sensory attention and discrimination; training cross-modal association, integration and unitization	Visual, auditory and somatosensory regions, perirhinal cortex	Cholinergic agents[198,199] and dopamine receptor D1/D2[200] and noradrenergic[201] neuromodulation to enhance sensory attention and perception; reducing hyperactivity (SV2A modulation[138])
Timing 'jitter' of afferent episodic event information	Improving coordinated convergence of episodic details; improving crosstalk across hippocampal subfields and between hippocampus and cortical regions	Pacing information with external entrainment such as sensory flickering or music	Oscillatory entrainment of MTL–cortical crosstalk	Cholinergic agents[198,199]
Stimulus-triggered hyperactivity	Reducing hippocampal drive of dopaminergic regions by certain stimuli, such as novelty	Meditation; anxiety reduction	Inhibitory stimulation of hippocampus and retrosplenial regions	Reducing hyperactivity (SV2A modulation[138])
Aberrant associations during encoding, interference	Improving coding of event boundaries and contextual segregation	Whether context segregation can be trained behaviourally is unclear	Inhibitory stimulation of MTL and retrosplenial regions and cortical components of the episodic memory network	Reducing hyperactivity (SV2A modulation[138])
Failure to integrate across elements of an episode	Improving crosstalk between hippocampus and neocortex (big-loop recurrence) to learn from regularities across episodes	Gamified training of cross-episode integration	Improving big-loop circulation and crosstalk between MTL and cortical regions through entorhinal cortex stimulation	Cholinergic agents[198,199] and dopamine receptor D1/D2[200] and noradrenergic[201] neuromodulation to enhance sensory attention and perception
Maladaptive pattern-completion bias	Reducing bias for false pattern completion (false memory)	NA	Inhibitory stimulation of episodic memory network components	NA
Noise in cortical context–feature integration	Improving crosstalk between hippocampus and cortex and across cortical layers	NA	Inhibitory stimulation of superficial cortical mantle to reduce impairment of inhibition	Cholinergic agents[198,199] and dopamine receptor D1/D2[200] and noradrenergic[201] neuromodulation to enhance sensory attention and perception; reducing hyperactivity (SV2A modulation[138])

[a]Assessed using behavioural, functional magnetic resonance imaging, electroencephalography and magnetoencephalography readouts. MTL, medial temporal lobe; NA, not applicable (no hypothesis could be formulated at this point); SV2A, synaptic vesicle glycoprotein 2A.

restored synaptic plasticity and hippocampus-dependent cognition in transgenic mouse models of AD[130]. Through this pharmacological intervention, the excitability of neurons that would otherwise be silenced in a neuronal network can be increased. Moreover, this example shows that brain reserve can be mobilized in neurons undergoing synaptic depression[130]. Several peptides that sustain synaptic connections or re-establish synaptic circuits are currently under investigation[187,188]. Although the field of synaptic engineering is still in its infancy, it holds promise for the development of interventions that target specific brain regions and synapses[188].

Another promising approach is to target the firing set point of a neuron in a given circuit. At present, the extent to which single-cell dynamics contribute to the firing rate set point in hippocampal circuitry is unclear, but data published in 2024 indicate that aspects of neuronal function might be regulated differently[189]. Therefore, setting the threshold for action potential firing might be the most relevant

target for interventions aimed at preventing initial hyperexcitability in the hippocampus. If so, molecular and pharmacological interventions become more feasible, because the impact of Aβ pathology at the level of single neurons can be neglected. New AD treatment strategies that go beyond targeting of Aβ and tau pathology, such as restoration of cellular homeostasis by using blarcamesine to activate muscarinic and sigma-1 receptors[190], by improving glucose metabolism in the hippocampus by inhibiting indoleamine-2,3-dioxygenase[191] or by reducing hyperactivity in the hippocampus[136], could further enhance this approach.

In addition to developing novel compounds, repurposing of existing drugs with known safety and tolerability profiles[192] could be a viable strategy to target synaptic dysfunction. Computational approaches, including in silico modelling, might help us to identify relevant candidate proteins and processes. Beside molecular interventions, cardiovascular exercise has been shown to increase hippocampal volumes in old age and could increase brain reserve through neurogenesis in the hippocampus and rewiring of hippocampal pyramidal cells with MTL structures[193–195].

Targeting cognitive reserve

We hypothesize that non-invasive stimulation of brain regions that were identified in longitudinal cohort studies as contributors to cognitive reserve[164], such as the anterior cingulate cortex or the fusiform gyrus, could improve cognition. Another possibility guided by the CU framework is to target the potential cognitive reserve mechanisms outlined above. Several approaches can be envisaged. First, individualized contextual guidance and prior knowledge could be provided for environments that a person is using, such as the supermarket. Second, the representations of bodily cues that are needed to construct context representations and for orienting and navigation in space could be enhanced, for example, by training head position control and balance, improving gait and vestibular functions, and alleviating medical conditions that impair proprioceptive signalling in gait and balance. Third, multisensory representations of semantic and perceptual information in the perirhinal cortex and upstream areas might be improved through sensory discrimination training and stimulation of the perirhinal cortex. Last, multisensory unitization of information for prototypical environments that are particularly relevant for an individual could be enhanced. Given the role of the perirhinal cortex in unitization, and the fact that lateral parts of this region are affected later in the course of AD, non-invasive brain stimulation, assistive technology or cognitive training to support schema-based unitization could be a feasible approach.

Targeting false memories and maladaptive biases

A pattern-completion bias can be maladaptive in that it contributes to false memories through prior knowledge and pre-existing schemata.

Glossary

Autobiographical memory
Memory for personally experienced events that integrates episodic detail with self-referential and semantic knowledge.

Autonoetic
Autonoetic awareness is a self-referential mode of conscious experience that enables virtual re-living of personal events.

Big-loop recurrence
Re-entrant information flow between the hippocampus and neocortical regions that supports memory association and generalization across memories.

Curse of dimensionality
The exponential increase in representational or computational demands as the number of encoding variables grows, challenging efficient learning and generalization.

Default mode network
A set of interacting cortical regions that are preferentially active during internally oriented cognition, such as autobiographical memory and future simulation.

Engrams
Functional ensembles of neurons, the activity patterns of which encode and store a specific memory.

Event boundaries
Perceptual or conceptual transition points that segment continuously unfolding experiences into discrete memory episodes or contexts.

Feature information
Discrete representational elements (for example, sensory, spatial, semantic or contextual attributes) that collectively compose a memory trace.

Mnemonic information
Any neural or cognitive signal that carries content about stored experiences or learned associations.

Multiple-trace theory
A model proposing that each retrieval of an episodic memory creates a new hippocampal–cortical trace, maintaining lifelong hippocampal involvement in detailed recollection.

Noise
Random or task-irrelevant variability in neural or behavioural signals that degrades the fidelity of information processing.

Paired associates
Stimulus pairings learned through associative binding, usually used to study declarative memory formation.

Pattern completion
Hippocampus-dependent process by which a memory cue triggers retrieval of a stored representation through attractor-like network dynamics (that is, networks of neurons, often recurrently connected, the time dynamics of which settle to a stable pattern).

Scene translation
The transformation of viewpoint-dependent perceptual input into an allocentric, map-like representation supporting spatial memory and navigation.

Schemata
Structured, generalized knowledge frameworks derived from prior experience that guide perception, interpretation and memory encoding.

Schematic memories
Memory representations biased towards generalized knowledge structures, often at the expense of episodic specificity.

Temporal jitter
Variability in the timing of neural signal processing that affects alignment between subcomponents of cognition.

Working memory
A cognitive system that transiently maintains a limited amount of information to support ongoing goal-directed behaviour and decision-making.

Addressing this maladaptive bias through inhibitory brain stimulation or cognitive training could be a viable strategy. However, interventions aiming at reducing false memories might interfere with the aforementioned strategies to improve cognitive reserve on the basis of prior knowledge and pre-existing schemata.

Targeting noise accumulation

As outlined above, several potential sources of noise in AD could affect episodic memory circuits, each of which would require a different type of intervention. Sensory representations could be improved by cognitive training (see above). Temporal jitter could be improved by external pacemaking through oscillatory stimulation[196]. Coding in the EC could be improved by direct electrical[179] or focused ultrasound stimulation, and by overcoming hypoactivation caused by the combined effects of Aβ and tau pathology. In people who experience recurrent anxiety owing to alienation from their familiar environment, aberrant hyperactivity in the hippocampus and the potential ensuing overstimulation of the hippocampus–ventral tegmental area loop[69] could be targeted.

Targeting cortical context–feature binding

Targeting of impaired Aβ-related inhibition in the superficial cortical layer[46] (a target for hippocampal back-projections) with inhibitory brain stimulation could improve context–feature binding in episodic memory. In addition, EC and perirhinal drive could be strengthened through brain stimulation if they show synaptic depression in the face of combined Aβ and tau pathology. This two-pronged approach could also improve big-loop recurrence.

Conclusions and future prospects

The CU framework posits that suboptimal use of circuit resources of episodic memory is a potentially reversible cause of memory impairment that is additive to neurodegeneration in AD. We hypothesize that ameliorating this suboptimal utilization can help individuals to regain episodic memory capabilities. At the core of the CU framework is the circuit-level functional anatomical organization of episodic memory into component processes and their impact on everyday life. Impairment of these processes affects capabilities beyond associative memory and recall, which have dominated the prevailing clinical discourse on AD. In this Review, we have highlighted how AD pathology might affect these component processes, leading to clinically observable deficits. We have synthesized these aspects to formulate hypotheses for multidimensional interventions to reduce maladaptive plasticity and strengthen adaptive plasticity as part of a circuit-centred rehabilitation programme.

Current disease-modifying treatments for AD[5,197] can slow decline but do not reverse existing impairment. We have outlined a translational pathway to ameliorate episodic memory impairment, with the aim of partially regaining lost function. The interventions that we have proposed could be tested as complementary strategies to disease-modifying treatments.

The goal of our CU framework is to facilitate the generation of hypotheses for potential circuit-based, multidimensional interventions at a time point when treatment is likely to be most beneficial. We expect substantial progress in the coming years, as different lines of research come to fruition and several synergies can be exploited to expand current treatment options for AD. However, bringing together knowledge from different areas of research will be challenging. The CU framework aims to provide a synthesis of the data and new perspectives to pave the way for maintaining and regaining episodic memory function in patients with AD, and also to offer a path towards earlier diagnosis and more precise monitoring of disease progression, thereby facilitating timely interventions.

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