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Episodic Memory on the Path to Alzheimer's Disease

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Abstract

This review is focused on specific circuits of the medial temporal lobe that have become better understood in recent years for their computational properties contributing to episodic memory and to memory impairment associated with aging and other risk for AD. The layer II neurons in the entorhinal cortex and their targets in the dentate gyrus and CA3 region of hippocampus comprise a system that rapidly encodes representations that are distinct from prior memories. Frank neuron loss in the entorhinal cortex is specific for AD, and related structural and functional changes across the network comprised of the entorhinal cortex and the dentate/CA3 regions hold promise for predicting progression on the path to AD.

Introduction

Disorders that impair mental capacities are among the most feared outcomes of aging. Dementia, with Alzheimer's disease (AD) accounting for the vast majority of cases, exacts a staggering toll on individuals, families, and society. Much progress is being made in understanding the pathophysiology of AD, which ultimately causes massive neurodegeneration and a devastating loss of mental faculties. Still, the slow progression of AD runs its course over many years, and biomarkers relevant to the pathophysiology of the disease appear long before a clinical diagnosis. As recently reviewed elsewhere [1,2,3,4,5], new data coming from the Alzheimer's Disease Neuroimaging Initiative and other sources support the existence of AD pathology in the brain for at least a decade before clinical diagnosis is typically made. Defining the earliest boundary of AD, when interventions could be most effective and beneficial, is a topic of great interest and yet a significant challenge.

Although the devastation of dementia is clinically unmistakable in the end, the earliest symptoms are barely noticeable to patients, families and physicians. Failures in the ability to remember events of daily living are easily dismissed as normal aging. In clinical practice, the diagnosis of AD is only made when such memory loss accelerates and other cognitive and behavioral symptoms emerge, reaching criteria for dementia as a progressive syndrome [6]. New criteria to define an earlier boundary for AD are under investigation for research purposes, combining evidence for the hallmark of episodic memory impairment with supportive biomarkers indicative of the pathophysiology or topography of AD in the brain [4,7,8]. Here, we focus on specific components of the neural circuitry essential for episodic memory that have become better understood for their computational properties and for how dysfunction in this network contributes to memory loss (see Figure 1). New opportunities

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for in vivo assessment of biomarkers within this circuitry may contribute to the set of measures that are clinically useful for early AD diagnosis and to assess disease modification in therapeutic trials.

Distinctive effects of early AD and aging on neurodegeneration in the medial temporal lobe

The structures of the medial temporal lobe (MTL) in the mammalian brain are critical for memory functions that give us a record of our experience, in acquiring new facts and preserving information about the events in our lives, the latter commonly referred to as episodic memory. This system, comprised of the hippocampus and its interconnections with cortex, undergoes changes during aging in circuits that are highly susceptible to neurodegeneration in AD. Here, however, a clear distinction exists between the effects of aging and AD. We have known for awhile that by the time of AD diagnosis, marked neuronal loss has already occurred in the entorhinal cortex (EC), the brain's interface between the hippocampal formation and neocortex. In their classic study using unbiased stereological methods, Gómez-Isla and colleagues [9] reported that brains from mild AD patients (with a Clinical Dementia Rating of 0.5) exhibited more than 50% loss of layer II entorhinal neurons, while numbers of those neurons were maintained in healthy aged brains. Since then, stereological studies have widely confirmed that numbers of neurons are largely preserved in the MTL system over the course of aging in humans and other species (e.g., primate and rodent) [10,11,12,13,14], while significant neuronal loss affecting EC is already evident in the earliest stages of clinically diagnosed AD [15,16]. These findings are consistent with structural changes in the volume of EC, not only over its clinical course but also on the path to AD prior to diagnosis [17,18*,19,20]. Still, the overall atrophy of a region is likely to underestimate the magnitude of degeneration that affects a specific subset of neurons. As expected, a structural measure of cortical thinning, which could reflect layer-specific neuron loss in EC, shows greater sensitivity in structural MRI compared to differences in the overall volume of EC [21,22**,23,24*,25**].

Given the evidence just described, the use of improved methods in diffusion tensor imaging (DTI) and tractography applied to the perforant path would seem to hold promise as an early biomarker with great specificity for AD. Because the perforant path, which innervates the dentate gyrus (DG) and CA3 region of the hippocampus, is comprised of the projections from layer II entorhinal neurons, measuring the integrity of those connections could have particular sensitivity for the earliest neurodegeneration in AD. Ex vivo imaging of this pathway in the human brain was recently conducted to validate tractography methods with histological procedures [26*]. In another recent application of in vivo microstructural DTI, imaging of the perforant path provided evidence of decreased integrity in older subjects compared to young adults [27**]. Notably, as a control, the temporoalvear path, showed no corresponding difference between the age groups, suggesting a circuit-specific basis for signal change. To the extent that such methods prove sensitive to neurodegeneration in EC, a biomarker based on perforant path integrity might perform even better than structural measures of EC itself. Moreover, the specific neurons that give rise to this pathway are closely tied to the pathophysiology of AD in both descriptive studies of AD brains and experimental research [15,28,29*,30*].

Role of the perforant path and its targets in episodic memory

The computational functions contributing to episodic memory have become better defined for subregions and circuits in the MTL. The input from layer II of EC to the DG and CA3 is especially critical for encoding distinctive representations of experiences that share overlapping elements with prior memories, a process referred to as pattern separation.

Consistent with earlier predictions based on its anatomy and physiology, studies in laboratory animals have confirmed that the ability of the hippocampus to assign distinct representations to similar inputs emerges in the DG and CA3 regions [31,32,33,34]. This feature of information encoding is due, at least in part, to the fact that relatively few dentate gyrus granule cells, among the very large number of granule cells, are activated by a pattern of cortical input.

The generality of this function has been extended from studies of the encoding properties of DG and CA3 neurons in rodents to a corresponding function in humans localized to DG/CA3 with high-resolution fMRI [35,36]. Moreover, studies of memory performance, both in animal models of aging and elderly human subjects, have shown substantially reduced pattern separation, with changes in behavioral performance coupled to altered function in the DG/CA3 network in the aged brain [37,38,39*,40,41,42,43*]. Relative to age-matched controls, a progressive worsening of this condition is detected in amnesic mild cognitive impairment (aMCI) patients [44*], who have memory impairment greater than would be expected for their age and who are at increased risk for AD. Thus, dysfunction in this subsystem of the MTL appears to make a significant contribution to the clinical condition affecting memory on the path to AD. Although task related activation using fMRI has potential limitations as a biomarker, functional connectivity measures in resting state fMRI may be more amenable to clinical applications [45*, but see 46*] and can be used to assess functional connectivity in the EC/DG/CA3 circuit [47*], complementing structural approaches using DTI and tractography as described above.

Apart from a distinctive effect of AD on frank degeneration of EC neurons, aging itself could confer vulnerability to AD in its effects on those neurons most susceptible to degeneration in the disease. Aged rats that do not suffer from neuron loss in the MTL nonetheless have a decrease in the synaptic input from EC specifically affecting the layer II connections in animals that age with memory loss [48]. Together with a weakened perforant path input, a condition of excess activity associated with the CA3 neurons in those animals shifts the EC/DG/CA3 network from pattern separation to pattern completion, which is mediated by CA3 recurrent associational connections [40]. Thus, rather than creating distinctive representations, CA3 neurons are more likely to retrieve previously encoded information. This condition of network dysfunction is consistent with behavioral and fMRI data in humans with age-related memory impairment. In behavioral tasks that tax pattern separation, errors in memory judgments exhibit a shift from responses indicative of good pattern separation to greater pattern completion [38,39*], and during task performance, fMRI reveals excess activation in the MTL that is restricted to the DG/CA3 region [43*]. Such observations made in aged individuals are also further magnified in aMCI [44*].

Some of the features described above resemble conditions that can be caused or augmented by the pathophysiology of AD [49*]. Consistent with the view that synaptic failure precedes neuronal loss in the degenerative cascade of AD brain, degradation of perforant path connections (from layer II EC neurons) occurs in the brains of AD mouse models overexpressing amyloid precursor protein (APP) [50,51]. Excess hippocampal excitability has also been observed in APP transgenic mice with changes in many molecular markers affecting DG/CA3 circuitry [52]. To the extent that greater hippocampal activation is not compensatory in a beneficial sense, there is growing concern that excitation in the brain, particularly in the hippocampus, could be a driver on the path to AD [53,54**,55,56*].

Apolipoprotein E (apoE) and vulnerability in the EC/DG/CA3 network

Apart from aging itself, apoE is the most important known genetic risk factor for sporadic AD, with the apoE4 allele conferring dramatically increased risk in a dose-dependent

manner. A memory/MTL phenotype is characteristic of ApoE4 carriers with AD [57**]. Studies of asymptomatic apoE4 carriers also report alterations in the EC/DG/CA3 network prior to an AD diagnosis. In comparison to older heterozygote carriers and non-carriers, e4 homozygote carriers have greater deficits in episodic memory tasks [58], and e4 carrier status is associated with greater longitudinal decline in memory performance evident by the sixth decade of life [59*]. Consistent with data on memory performance, apoE4 carriers exhibit reduced structural measures of EC, both in cross-sectional comparisons and longitudinal assessments [60,61*,62]. It is possible that this morphometric change reflects neuronal degeneration in EC, which is uncharacteristic of normal aging, and instead could represent a signature of prodromal AD in affected individuals.

Another finding described in many studies of ApoE4 carriers is increased fMRI activation in the hippocampus [63,64,65,66], a phenomenon that has often been interpreted as compensatory recruitment to support memory performance. In contrast with that view, recent research has demonstrated a detrimental loss of hippocampal inhibitory function in animal models used to study ApoE4. Andrews-Zwilling and colleagues [67**] report that ApoE4 causes age- and tau-dependent impairment of GABAergic neurons in the hilus of the hippocampal formation and that this loss of inhibitory function underlies learning and memory deficits both in ApoE4 knock-in mice and in transgenic mice producing neurotoxic fragments of ApoE4. Contrary to the notion that increased hippocampal activation is beneficial, as discussed in reference to fMRI findings, memory was improved by treatment with the GABA_A receptor potentiator, pentobarbital, in ApoE4 mouse models. Similar to the benefit reported in these ApoE models, improvements have been obtained in memory-impaired aged rats by targeting hippocampal overactivity associated with neurocognitive aging [68].

In the context of the hippocampal subsystem considered here, it is particularly noteworthy that the impact of ApoE4 on inhibitory neurons in mouse models was regionally restricted within the hippocampal formation, with an effect observed on interneurons in the hilus that was not seen in CA1. In a recent report examining morphometry within subregions of the hippocampus, ApoE4 carrier status during aging was specifically associated with volume loss in the CA3/DG relative to non-carriers [69,70]. The prominent effect on EC and its targets in ApoE4 carriers could not only account for greater episodic memory impairment but also set a background contributing to AD vulnerability.

Conclusion

The ability to make an earlier diagnosis of AD will likely depend on a set of measures that together provide high discrimination for the disease and are clearly relevant to the clinical condition of those on the path to dementia. Memory impairment is a recognized hallmark of AD that shows progressive worsening and has undisputed clinical significance for patients. Here, we have focused on specific components of MTL circuitry that have become better understood in recent years for their computational properties contributing to episodic memory. Although aging affects the condition of this system apart from AD, EC is a site of neurodegeneration that does not occur in healthy aged brains. In addition, structural and functional measures of the EC/DG/CA3 network register a progressive change on the path to AD, yielding biomarkers topographically-relevant to the core clinical presentation of memory loss that could be suited for clinical trials of therapies aimed at modifying disease progression.

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- of special interest
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Highlights

- Diagnosis and intervention at earliest boundary of AD will be most effective.
- Specific MTL circuits contribute to memory impairment in aging and AD.
- Neuron loss in the entorhinal cortex is specific for AD but not aging.
- Improved structural and functional measures of MTL circuitry to track path to AD.

Figure 1.

Schematic of the circuits in the hippocampal formation. The entorhinal cortex (EC) provides cortically processed information, via layer II neurons, to the dentate gyrus (DG) and distal dendrites of CA3 principal pyramidal neurons. CA3 afferents, in addition to innervation of CA1, form a massive autoassociative input to CA3. Recurrent CA3 input produces generalization/pattern completion. EC input, which is weakened in aging and comprises a significant early lesion in AD, is essential for pattern separation/specific new encoding.