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REVIEW ARTICLE

Network activity changes in the pathophysiology of Alzheimer's disease: the role of aging and early entorhinal cortex dysfunction

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Abstract

The greatest risk factor for development of the deadly neurodegenerative disorder known as Alzheimer's disease (AD) is advancing age. Currently unknown is what mediates the impact of advanced age on development of AD. Also unknown is what impact activity alterations in the entorhinal cortex (EC) has on the spread of AD pathology such as pathological tau through the brain as AD progresses. This review focuses on evidence in the literature that describes how one potential age-related change, that of glutamate-mediated increases in neuronal activity, may ultimately increase the risk of developing AD and promote the spread of tau pathology in AD-affected brains from the EC to later regions such as the hippocampus and prefrontal cortex. A better understanding of these detrimental alterations may allow for earlier detection of AD, offering a better prognosis for affected individuals.

Keywords Aging · Alzheimer's disease · Tau · Glutamate · Neuronal activity · Entorhinal cortex

Introduction

Alzheimer's disease (AD) is the most common form of dementia, accounting for 60 to 80 percent of all dementia cases (Atri 2019). AD is characterized by three main biological hallmarks, extracellular beta-amyloid plaques, intracellular neurofibrillary tangles containing hyperphosphorylated tau protein, and neuronal death (Hyman et al. 2012). Though there are many risk factors for the development of AD, the greatest is advancing age (Lindsay et al. 2002). The connection between increasing age and AD is of interest because of the aging baby boomer population, which is expected to exacerbate the medical burden of age-related changes in cognition as well as age-related neurodegenerative disorders like AD (Rajan et al. 2021).

While AD ultimately proves fatal for affected individuals, of additional concern is the negative functional impact that the development of AD has on quality of life for these individuals and their caretakers (Isik et al. 2019). Over time, AD affects multiple brain regions as pathology spreads throughout the neocortex, entorhinal cortex, hippocampus, and prefrontal cortex (Braak and Braak 1991). Some of the functional changes that occur, such as deficits in spatial, working, or episodic memory, can be tied to network alterations in the entorhinal cortex (EC) and the hippocampal formation, which consists of the subiculum, the dentate gyrus (DG), and the hippocampus proper (Baddeley et al. 1991; deIpolyi et al. 2007; Greene et al. 1996). The hippocampus in particular has been greatly studied for its role in the progression of AD. In fact, current diagnostic tasks utilized for the detection of AD, such as the mini-mental status exam (MMSE), focus on deficits that become apparent when the functional integrity of the hippocampus and prefrontal cortex has been compromised (Sabuncu et al. 2011). Less understood is the role that the EC plays in the development of AD. This shortcoming is significant because the EC is one of the first areas impacted by tau pathology in the progression of AD and tau pathology beginning in the EC ultimately spreads to the hippocampus and prefrontal cortex as the disease progresses (Braak and Braak 1991). Thus, it is critical to understand the cognitive alterations resulting from pathology in the EC, so as to better detect cognitive deficits resulting from disease-related alterations in this region. Understanding cognitive deficits that result from pathology

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in this region may help identify potential novel therapeutic targets to attenuate the spread of tau pathology throughout the brain. This review will focus on animal and human work that delves into the relationship among aging, AD, and the EC.

Aging and AD

Evidence from the literature suggests that aging is one of the greatest risk factors for the development of AD (Harman 2006; Munoz and Feldman 2000; Xia et al. 2018). There quite a few age-related changes in brain function and activity that likely mediate this risk, one of which regards changes in network activity. Indeed, late-stage AD is associated with a variety of physiological changes but is frequently associated with neuron loss and subsequent network deficits in neuronal activity (de Haan et al. 2012; Hatanpää et al. 1996; Palop et al. 2007). However, there is evidence to suggest that in normal aging, as well as very early stages of AD, some brain regions are hyperactive instead. For example, aging has been associated with increases in hippocampal hyperactivity in both human and rodent models (El-Hayek et al. 2013; Reagh et al. 2018; Yassa et al. 2011). Neuronal hyperactivity, as measured by blood-oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI), is also a characteristic of amnestic mild cognitive impairment (aMCI) (Yassa et al. 2011), a measurable decline in cognitive function that is considered by some to be a risk factor for the development of AD (Mauri et al. 2012). Increased neuronal activity in patients with aMCI is indicative of the rate and possibility of development of AD in these individuals (10 to 15% progression rate annually in clinical samples) (Bakker et al. 2008; Oltra-Cucarella et al. 2018). In addition, hyperexcitability has been associated with cognitive deficits even in older adults that had normal scores on the MMSE (Yassa et al. 2011).

Neuronal hyperactivity is also associated with a number of maladaptive changes in human subjects as well as rodents, including cognitive decline (Reagh et al. 2018), enhanced seizure susceptibility (Cloyd et al. 2006; Stover et al. 2017), and the accumulation of tau but not beta-amyloid (Huijbers et al. 2019). Moreover, reducing neuronal hyperactivity in humans and rodents is sufficient to reduce cognitive deficits (Bakker et al. 2012; Hunsberger et al. 2015b; Koh et al. 2010; Sanchez et al. 2012), suggesting not only an association but a causative relationship between hyperactivity and cognitive decline. Of additional concern is evidence suggesting increased neuronal activity can also lead to excitotoxicity, a pathological process in which neurons are killed due to overactivation (Rudy et al. 2015). Therefore, detrimental changes in neuronal activity levels could serve as potential therapeutic targets to halt or slow the progression from normal aging or aMCI to AD. Of great interest, then, is understanding potential mechanisms that may contribute to these activity alterations and how they may be permissive for the development of AD.

One of the mechanisms that may underlie alterations in neuronal activity is dysregulation of glutamatergic neurotransmission. There is increasing evidence that aging results in enhanced glutamatergic signaling, suggesting one mechanism by which aging might increase the risk for AD. Several animal studies have indicated enhanced glutamate release and/or reduced glutamate clearance in aged rodents (Saransaari and Oja 1995; Stephens et al. 2011). These observations might be due to underlying increases in VGLUT, promoting increased release of glutamate into the synapse (Cheng et al. 2011). In addition, aging is associated with reductions in levels of EAATs, such as GLT-1, resulting in less glutamate clearance from the synapse (Potier et al. 2010; Zoia et al. 2004) leading to increased resting, or tonic, glutamate levels in some cases (Velasco and Tapia 2002). However, other studies have found the opposite, such that aged rodents exhibit decreased glutamate release and/or enhanced glutamate clearance (Mullany et al. 1996). The discrepancies that have been observed may be due to varied ages in the animal models as well as the methods utilized to measure glutamatergic alterations.

In disease states such as AD, glutamatergic signaling also becomes disrupted and these changes have been associated with the presence of tau pathology. Using enzyme-based microelectrode array, our laboratory has observed tau-associated increases in glutamate release and decrease in glutamate clearance in the rTg4510 mouse line, which overexpresses the mutant P301L form of human tau (Hunsberger et al. 2014, 2015a, b). Increases in glutamate release were associated with increased levels of VGLUT, while reductions in glutamate clearance were associated with reductions in levels of GLT-1. Using riluzole to restore these alterations resulted in attenuated cognitive deficits and pathology, which suggests a causative role for increased glutamatergic signaling and cognitive impairment.

These glutamatergic alterations can lead to excess extracellular glutamate, which can initiate cell death-signaling pathways by "spill-over" activation of extrasynaptic NMDARs (Gouix et al. 2009; Potier et al. 2010). Furthermore, an increase in activation of extrasynaptic NMDARs leads to increased tau phosphorylation, which can be reduced by blocking extrasynaptic NMDARs and their associated receptor subunits (Allyson et al. 2010).

Ultimately, enhanced excitatory neurotransmission may create an excitotoxic environment with greater susceptibility to the development and progression of AD. This is critical, because increasing evidence suggests that hyperexcitability can exacerbate the severity of tau pathology and promote its spread in AD.

Tau and AD

While much of the research over the past few decades has focused on beta-amyloid pathology as a therapeutic target for the treatment of AD, therapeutic interventions focusing solely on beta-amyloid have proven largely unsuccessful (Higuchi et al. 2005; Holmes et al. 2008; Honig et al. 2018; Rosenblum 2014; Salloway et al. 2014; Vellas et al. 2013). Additionally, many reports have indicated that the presence of tau pathology more closely correlates with the rate of cognitive decline than does beta-amyloid (Arriagada et al. 1992; Gómez-Isla et al. 1997; Nelson et al. 2012). Though beta-amyloid is thought to initiate tau pathology (Hardy and Higgins 1992; Kowalska 2004), tau pathology once initiated may be self-perpetuating and beta-amyloid independent (Ashe and Zahs 2010; Guo and Lee 2013). Thus, it is equally important to investigate tau as a therapeutic target in the treatment of AD.

One of the aspects that makes tau a unique therapeutic target is the pattern of its progression. Early tau pathology is more localized than early beta-amyloid pathology, beginning in the entorhinal cortex before spreading to the hippocampus and prefrontal cortex as the disease progresses (see Fig. 1) (Braak and Braak 1991; Braak and Del Tredici 2018; Liu et al. 2012). The mechanisms behind this spread are still not well understood. However, increasing evidence suggests that increases in excitatory neurotransmission may mediate the spread of tau pathology across synaptically connected circuits, a process termed trans-synaptic spread. Additionally, there is evidence from the literature that suggests that the presence of pathological tau also results in excess excitatory neurotransmission, indicating a feedback loop between the two phenomena (Bi et al. 2017; Siano et al. 2019). In agreement, knocking down or knocking out tau in rodent or drosophila models resulted in protection from kainic acid-induced seizures, indicating that tau itself plays a role in excitotoxicity in the absence of beta-amyloid (Pallo et al. 2016; Palop et al. 2007; Roberson et al. 2011). Thus, the importance of better understanding the role that tau pathology plays in the progression of the disease and as a potential therapeutic target is clear. An overview of tau protein and the ways in which it becomes dysfunctional in tauopathies like Alzheimer's disease will be discussed below.

Tau is a protein important for the assembly and stabilization of microtubules (Weingarten et al. 1975), which earns it the name microtubule-associated protein tau (or MAPT). Tau is a phosphoprotein, which means it is post-translationally modified by the addition of phosphate groups in a process known as phosphorylation (Mawal-Dewan et al. 1994). Its longest isoform (containing 441 amino acids) has 80 serine or threonine sites on which it can be phosphorylated, though tau protein can be phosphorylated on tyrosine sites as well (Goedert et al. 1989). While tau is highly phosphorylated in fetal brains, this phosphorylation generally decreases throughout development and as the brain ages (Goedert et al. 1989). Changes in the amount of tau phosphorylation as the brain ages are due to alterations in the levels of kinases, enzymes that phosphorylate proteins, and phosphatases, enzymes that dephosphorylate proteins (Mawal-Dewan et al. 1994).

Tau is normally an intracellular protein primarily found in neurons, specifically in the axons (Wood et al. 1986). Besides stabilization of the microtubule, tau is thought to have some other functional roles in a healthy brain. Intracellularly, tau is important for axonal transport of signaling molecules via motor proteins such as kinesin and dynein

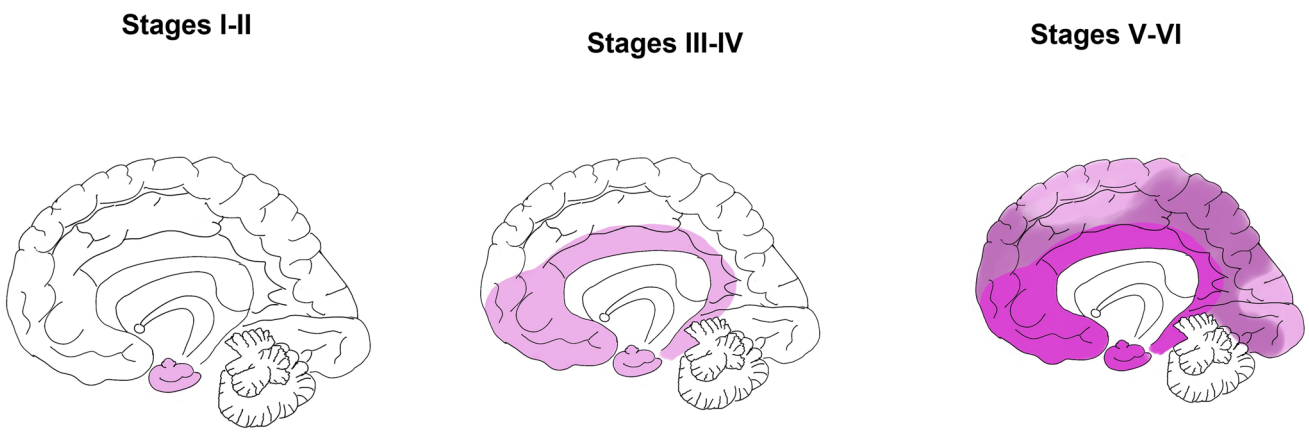

Fig. 1 In comparison to early beta-amyloid pathology, early tau pathology is more localized in most patients. Stages I-II consists of early tau pathology primarily deposited in the EC (LEC, specifically). In stages III-IV, tau pathology has begun to spread to the hippocampus and prefrontal cortex. In stages V-VI, tau pathology has spread into the neocortex. By the time tau pathology reaches these areas, it is severe in the origin areas. Darker shading/coloration indicates more severe pathology progression

(Chaudhary et al. 2018). Tau is also critical for neuronal development, as it plays a role in neurite outgrowth (Wang and Mandelkow 2016). Additionally, though the presence of extracellular tau has been indicated as a major player in tauopathies such as AD (Delacourte and Defossez 1986; Grundke-Iqbal et al. 1986), there is evidence that tau can be found extracellularly in the absence of disease. For example, tau has been found in the interstitial fluid of wild-type mice (Yamada et al. 2011) and in human cerebral spinal fluid (CSF) in the absence of any measurable cognitive changes (Fagan et al. 2009; Handoko et al. 2013; Laws et al. 2017). This evidence appears to suggest that there is a normal, physiological role for extracellular tau. As such, it has been proposed that tau may play an important role in inter-neuronal signaling (Chaudhary et al. 2018). In disease states, however, tau protein becomes dysfunctional in a myriad of ways.

In AD, tau aggregates into paired-helical filaments (PHF), which are the main structural element of neurofibrillary tangles (Goedert et al. 1989). Increased tau phosphorylation, generally termed as hyperphosphorylation, was found to be a key player in the formation of PHFs (Goedert 1993). Additional research determined that in AD, tau is hyperphosphorylated at a rate about three to fourfold higher than in normal brains (Kenessey and Yen 1993; Köpke et al. 1993), which may be due to increased levels of kinases and decreased levels of phosphatases. There are several consequences of these changes in phosphorylation. Hyperphosphorylation of tau negatively impacts its ability to bind to microtubules (Lindwall and Cole 1984). This hyperphosphorylation of tau has been observed to cause mislocalization of tau from axons to somatodendritic compartments leading to synaptic deficits and mediating beta-amyloid toxicity (Hoover et al. 2010; Ittner et al. 2010). In addition to changes in phosphorylation, tau protein can also become misfolded in AD (Tai et al. 2012). This conformational change results in increased propensity of aggregation into neurofibrillary tangles (Tai et al. 2012).

Tau is normally an intracellular protein; however, after pathological tau results in neuronal death, it can accumulate extracellularly as ghost tangles (Bancher et al. 1989). Because of this, it had been assumed that the increased neuronal death that occurs in the disease state may underlie the release of tau into the extracellular space and findings of increased tau in cerebral spinal fluid (CSF) as the disease progresses. However, multiple studies have indicated that the neuron need not die for tau to be released into the extracellular space, and the presence of extracellular tau does not seem to be correlated with markers of cell damage such as LDH activity (Chai et al. 2012; Yamada et al. 2014; Yamada and Iwatsubo 2018). Tau can also be found in interstitial spinal fluid and CSF prior to neurodegeneration (Barten et al. 2012; Yamada et al. 2011). Additionally, the spread of tau seeds precedes neurodegeneration and neither the presence of hyperphosphorylated tau nor tau aggregates are immediately toxic to neurons (Hallinan et al. 2018).

Once tau reaches the extracellular space, regardless of the mechanism, it can be taken up by neighboring neurons, ultimately compromising them as well (Wu et al. 2016). It is in this way that pathological tau is thought to behave in a prion-like fashion along synaptically connected neural networks (Frost and Diamond 2009; Guo and Lee 2011; Kfoury et al. 2012). Prions are misfolded proteins with the ability to transmit their misfolded shape onto normal variants of the same protein. Supporting the prion tau-spread theory, human pluripotent stem-cell models have been utilized to demonstrate that pathological tau released from initially infected cells into the medium can thereafter be taken in by previously unaffected recipient cells. Further, aberrant tau can be released by these recipients and taken in by new recipients, indicating a cell-to-cell propagation (Wu et al. 2016). The prion-like propagation of tau pathology has also been demonstrated in vivo. Injection of brain homogenates from mice expressing mutant tau into mice expressing wild-type tau results in the assembly of the wild-type tau into NFTs and neuropil threads (NTs), and this pathology spreads to synaptically connected brain regions (Clavaguera et al. 2015). Additionally, injection of brain extract from older mice expressing mutated tau (Ahmed et al. 2014; Peeraer et al. 2015), or synthetic pre-formed fibrils from full-length or truncated tau (Iba et al. 2013) into the brains of younger mice expressing mutant tau (prior to expression of tau pathology) also resulted in enhanced prion-like spread of tau pathology along synaptically connected circuits.

The latter finding, that of the spread of tau from brain region to brain region, has also been of great focus in the literature. Tau can spread along mono-synaptic (across one synapse) or trans-synaptic (across more than one synapse) circuits (Liu et al. 2012). Mice expressing mutant P301L tau restricted to layer II of the EC also exhibit propagation to connected regions such as hippocampal subregions and the cingulate cortex (de Calignon et al. 2012). This spread of tau is not limited to pathological or mutant tau, as wild-type tau also can spread along axonal connections to distal brain regions (Dujardin et al. 2014). The trans-synaptic pathology spread suggests that propagation of tau pathology is an active process that is synaptically-linked and not solely limited to targeting nearby neurons.

The entorhinal cortex, tau, and AD

The literature suggests that the EC is one of the first regions in the brain to develop tau pathology (Braak and Braak 1991; Kaufman et al. 2018; Welikovitch et al. 2018). However, compared to the hippocampus, the functional role of

the EC in cognition as well as in the progression of AD is relatively poorly understood. In order to target maladaptive alterations that are EC-dependent, this region needs to be further studied. An overview of the EC and its role in the spread of tau in AD is discussed further, below.

The entorhinal cortex, so named because it is partially enclosed by the rhinal sulcus, is located in the medial temporal lobe between the transentorhinal area and the hippocampal formation. In mice, the EC consists of the medial and lateral entorhinal cortices (MEC and LEC, respectively), whereas in humans, the EC is divided into the anterolateral (front and to the side) and posteromedial (to the back and at the center) entorhinal areas (Maass et al. 2015).

The EC can be separated into six layers. Layer I of the entorhinal cortex receives olfactory input and projects to the presubiculum, perirhinal cortices, and amygdala. Layer II projects to the dentate gyrus (DG) and cornu ammonis 3 (CA3) subregions of the hippocampus, whereas Layer III projects to the cornu ammonis 1 (CA1) and subiculum subregions of the hippocampus. The Layer II and III hippocampal projections are referred to as the perforant pathway. In turn, the deeper layers (Layers IV and V) of the EC receive input from the CA1, a pathway called the third synaptic connection (see Fig. 2). Information processed via the third synaptic connection eventually projects to the striatum, amygdala, and thalamus. Layer VI is still not well understood (Canto and Witter 2012). The projections between the EC and hippocampus are impacted in both early AD and aMCI, causing disruptions in neuronal signaling (see Fig. 2).

Generally, the hippocampus is most commonly denoted as the neurobiological source for episodic memory (Desgranges et al. 1998). However, it is also clear that the entorhinal cortex plays a significant role in episodic memory (Wilson et al. 2013b). Memory tasks that assess performance in regard to this type of contextual information have been purported to represent a rodent model of episodic memory (Eacott and Easton 2010). Briefly, components of this model include information regarding objects within a given environment, information regarding the spatial aspects of the objects in that environment, and aspects of the environment itself.

The combination of processing non-spatial and spatial information as described above is important for a type of memory known as associative memory. Associative memory tasks involve altering two or more aspects (object recognition, object location, and contextual properties) of the environment in order to assess an animal's ability to detect novelty. For example, a task may involve exposing the animal to a specific environment and then either altering the objects within the environment, the locations of said objects, the context itself, or some combination thereof. The combinations are thus referred to as associative memory, as proper performance on these tasks requires the animal to remember the association between the object, locations, and context to which the animal has been previously exposed. Lesion studies have determined that while LEC-lesioned rodents are able to detect changes in object or object location alone, these animals are unable to detect changes in tasks that involve associative memory, such as object-object location, object location-context, or object-object location-context combinations (Hunsaker et al. 2013; Wilson, et al. 2013a, b).

To our knowledge, there are no currently existing animal studies examining the impact of tau (or beta-amyloid) pathology within the EC on EC-dependent cognition. However, evidence from human literature sheds some light on what impact AD-associated changes, such as alterations in excitotoxicity has on EC-dependent cognitive performance. For example, hypoactivity in the EC and hyperactivity of hippocampal DG and CA3 subregions, as

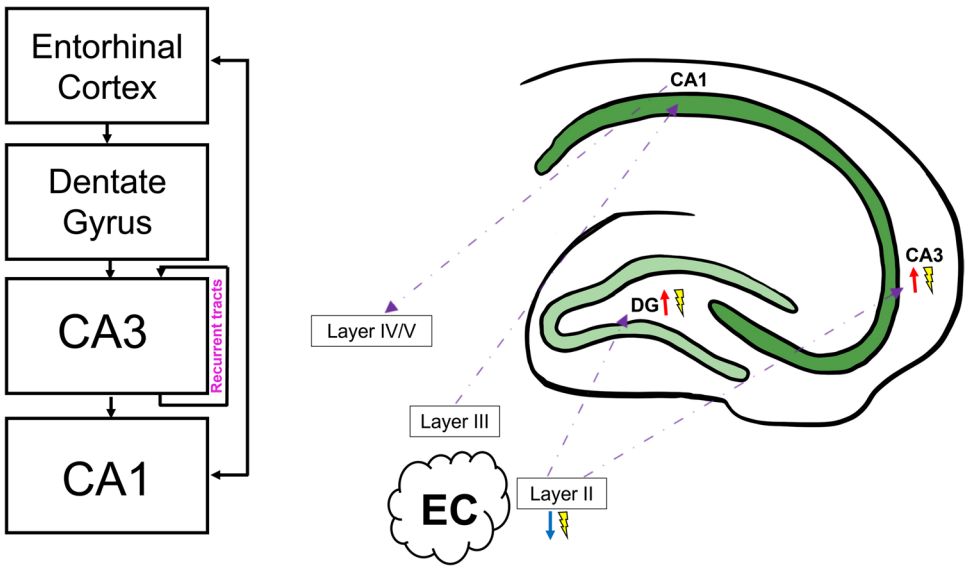

Fig. 2 The entorhinal cortex projects to the dentate gyrus (DG) and CA1 hippocampal subregions (referred to as the perforant pathway). The dentate gyrus projects to the CA3 hippocampal subregion (referred to as the mossy fiber pathway). The CA3 has autoassociative (or recurrent) tracts that project onto itself. The CA3 also projects to the CA1 via the Schaffer collateral pathway, and the CA1 projects back to the entorhinal cortex (third synaptic connection). Evidence from the literature suggests that alterations such as hypoactivity (blue arrow) in the EC are associated with increases in activity (red arrows) in the DG and CA3

identified by changes in fMRI blood-oxygen level dependent (BOLD) activation, is associated with a shift toward responses indicating pattern completion rather than pattern separation (Bakker et al. 2012), which is not observed when the task has a spatial component (i.e. objects within a specific location in an environment) (Reagh et al. 2018). Recent studies have identified the anterolateral entorhinal cortex (alEC), rather than the posteromedial entorhinal cortex (pmEC), as the specific subregion of the entorhinal cortex that is hypoactive in older adults (Berron et al. 2019; Reagh et al. 2018) and that this dysfunction is associated with higher levels of tau in cerebrospinal fluid.

The functional imbalance observed in these cases may well have to do with the projections from EC to DG and CA3 hippocampal subregions via the perforant pathway. The projections between the EC and hippocampus are impacted in both early AD and aMCI, causing disruptions in neuronal signaling (see Fig. 2). What is unknown is the directionality of these alterations in human studies. That is, whether it is the EC hypoactivity that is causing DG/CA3 hyperactivity, or the reverse. It has been theorized that CA3/DG hyperactivity could lead to retrograde degeneration of the perforant pathway in human subjects (Reagh et al. 2018). It has been also been theorized that the disrupted EC signaling leads to inadvertent activation of the CA3 recurrent tracts, promoting a state of hyperexcitability (Reagh et al. 2018). Studies assessing the role of early EC activity in humans are lacking, potentially due to the degradation of this region by the time hippocampal-dependent changes are apparent.

Volumetric changes in the alEC are also predictive of ability to process repeated versus similar objects (Yeung et al. 2017). As volume decreases are also observed in the LEC in preclinical AD (Yeung et al. 2017), these region-specific changes and resultant impact on object-recognition memory may represent a precise target for development of a diagnostic task sensitive to early AD alterations.

In addition, because hippocampal subregions receive major excitatory input from Layer II of the EC, it has been proposed that changes observed in cognitive aging and aMCI are likely resultant from a disruption in EC-hippocampal afferents (Smith et al. 2000). Indeed, evidence has shown that input from Layer II of the EC is reduced with increasing age (Geinisman et al. 1992; Scheff et al. 2006). Additionally, synapses that project from Layer II of the EC to the CA1 hippocampal subregion undergo degeneration in AD mouse models (Shih et al. 2016). The EC is also one of the first areas to undergo neuronal loss in early AD. For example, by the time individuals affected by cognitive aging or aMCI have progressed to even mild AD, they can exhibit 60% neuron loss in Layer II of the EC compared to a normal individual (Gómez-Isla et al. 1996; Kordower et al. 2001). In conjunction, the EC is significantly atrophied in AD compared to other brain regions (Kordower et al. 2001; Van Hoesen et al. 1991).

While there are several studies examining the role of EC in cognition via EC-lesions, as well as studies assessing the impact of EC activity alterations on cognition, there is a gap in the literature regarding the impact of pathological tau in the EC on EC-dependent cognitive tasks.

Conclusion

The key to better understanding the pathophysiology of AD, and therefore offering a better prognosis for affected individuals, is understanding one of the major regions that AD pathology originates from. It is clear from the evidence in the literature, as disseminated in this review, that aging and early AD result in alterations in network activity in the EC and hippocampus. These alterations create an environment of excitotoxicity which is then permissive to promote and propagate the spread of tau pathology. In turn, pathological tau deposition, once initiated, begets further tau pathology as well as mediating both beta-amyloid toxicity and exacerbated excitatory neurotransmission. While these observations have been documented in the literature, not much focus has been given to the impact of early AD pathology within the entorhinal cortex on EC-related cognitive function. This review hopes to offer a comprehensive starting point in terms of the currently known information and the gaps that need to currently be filled. In addition, understanding what changes that occur in this region lead to the spread of pathological tau, such as hyperactivity, is fundamental in the advancement of the field.

Author contributions Sharay E. Setti performed the literature search and drafted the review. Miranda N. Reed critically revised the content of the review article.

Declarations

Conflict of interest The authors report no conflict of interest.
The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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