Hypothesis

Which Memory System is Impaired First in Alzheimer's Disease?

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Abstract. Diagnosis of Alzheimer's disease (AD) in its earliest stages becomes increasingly important as disease modifying agents are being developed. In this area of research, many clinical and neuroimaging studies focus on markers of hippocampal dysfunction. However, during the "transentorhinal stage" of AD, neurofibrillary tangles (NFT), related to tau protein pathology, develop in the anterior subhippocampal (perirhinal/entorhinal) cortex before the hippocampus. NFT are tightly correlated with clinical symptoms. Therefore, an accurate understanding of the behavioral correlate of transentorhinal dysfunction could critically contribute to the early diagnosis of the disease. Recent findings from studies in animals and human brain-damaged patients suggest that the anterior subhippocampal region, functionally integrated into an anterior mesiotemporal network, is involved in object based context-free memory. In this article, we evaluate the hypothesis according to which tau deposition in the anterior subhippocampal region during the earliest stages of the most common form of AD, with predominant MTL dysfunction, will lead to dysfunction of neural networks implicated in context-free memory. We challenge the view that impaired episodic memory is the hallmark of early AD. Instead, a model that integrates the localization and temporal sequence of NFT within the mesial temporal lobe (MTL) is proposed. Paralleling the development of NFT in anterior subhippocampal areas, impaired context-free, object-based, memory could be the first detectable sign in AD. In a subsequent, "hippocampal" stage, context-rich, episodic and spatial memory, becomes altered as well. The question as to the "episodic" nature of "episodic memory tasks" is also addressed.

Keywords: Alzheimer's disease, amnesia, entorhinal cortex, hippocampus, memory, mesial temporal lobe, perirhinal cortex

"By the time I wrote Elements of Episodic Memory [1], it had become possible to entertain the thought that the heuristic distinction was useful for the simple reason that it corresponded to biological reality. I proposed, therefore, that episodic and semantic memory represented two functionally separable memory systems. In Elements I also made a confession: I had been wrong in 1972 when I had assumed that the traditional, Ebbinghaus-inspired, study/test laboratory experiments of verbal learning and memory had dealt with episodic memory. They had not. Two important features of episodic memory were missing. One had to do with the contents of what the subjects in

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the experiments had to learn. Episodic memory is about happenings in particular places at particular times, or about "what", "where," and "when" [2, 3]. Traditional laboratory experiments, however, were almost invariably concerned with "what." Subjects are asked, "What do you remember of the presented material?" They report their knowledge in tests such as free recall, cued recall, or recognition. Subjects' memory for "where" and "when" was hardly ever examined. (. . .)" Endel Tulving [4].

INTRODUCTION

During the earliest stages of many neurodegenerative diseases, like amyotrophic lateral sclerosis, Parkinson's disease, or multisystem atrophy, clinical symptoms are clearly related to the disruption of one anatomo-functional system. There is evidence that large scale human brain networks involved in cognition present a selective vulnerability in neurodegenerative disease [5, 6]. In Alzheimer's disease (AD), findings from neuropathological studies indicate that the integrity of neural systems related to memory is compromised by the loss of projections between and among the entorhinal cortex (ERC), the hippocampus (H), and the amygdala, as well as subcortical nuclei and paralimbic cortices such as the temporo-polar cortex (TPC) [7]. The general idea developed in this hypothesis article is that studies that focus on the function of neural networks affected by pathological lesions in the earliest stages of AD could improve the understanding of clinical signs of predementia AD.

A better understanding of memory systems affected early in AD equally has important implications for early diagnosis. The current development of disease modifying therapeutic agents requires reliable identification of patients when neuropathological changes are minimal. Despite major advances in the development of structural/molecular neuroimaging and cerebrospinal fluid (CSF) biomarkers, adding results from the cognitive assessment considerably contributes to the identification of AD in patients with mild cognitive impairment (MCI) [8]. However, which type of cognitive dysfunction should be looked for and which tasks should be used remains controversial [9].

AD is characterized by amyloid and tau deposition, as well as neuronal and synaptic loss. Neurofibrillary tangles (NFT), related to tau protein pathology and associated with clinical signs [10–12], first develop in the mesial temporal lobe (MTL) [13–14]. This brain
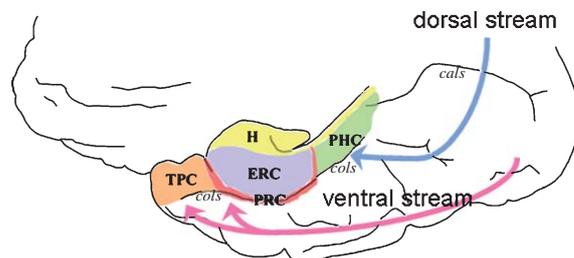

Fig. 1. Medial view of the right temporal lobe, along with a schematic representation of MTL structures. H: hippocampus; ERC: entorhinal cortex; PRC: perirhinal cortex; TPC: temporopolar cortex; PHC: parahippocampal cortex; cols: collateral sulcus; cals: calcarine sulcus. The posterior limits of the H and PHC are not represented. Note that the PRC lies mainly within the collateral sulcus. Adapted from Barbeau et al. [38].

region is crucial for declarative memory [15]. Within declarative memory, a distinction between episodic and semantic memory was introduced by Tulving [16]. Many studies report that anterograde episodic learning is impaired in patients with predementia AD (see [17, 18] for reviews). Moreover, it was recently suggested that impaired episodic memory is a core symptom that should be integrated into the diagnosis of predementia AD [19]. However, recent advances on the function of subcomponents of the MTL are rarely taken into account.

The MTL is composed of several subregions that contribute to declarative memory, the H as well as the perirhinal (PRC), ERC, and parahippocampal cortices (PHC). Henceforth, the PRC and the ERC will sometimes be referred to as "anterior subhippocampal" structures for the sake of simplicity. These subcomponents are interconnected with distinct cortical association areas, thus forming distinct mesiotemporal networks. There is increasing evidence for a differential contribution of these subcomponents of the MTL to declarative memory. Anterior subhippocampal structures play a crucial role in "context-free memory", or long term memory of learned information which is dissociable from the context of learning when required to be recalled or recognized (memory for objects, facts and concepts), while the H plays a critical role in "context-rich memory" or long term memory of learned information that is embedded into a context (like spatial and episodic memory) [20–23]. If the role of each of these structures is specific, the resulting memory dysfunction in AD should depend on the topographical distribution of NFT. In this way, the different neuropathological stages, which initially affect a subregion of the PRC, then the ERC before spreading to the H [13, 14], should result in distinct types of

memory impairment. Our hypothesis is that tau deposition in the anterior subhippocampal region during the earliest stage of AD will lead to dysfunction of neural networks implicated in context-free memory.

Early AD and the subhippocampal stage

NFT, which are composed of abnormally phosphorylated tau protein that develops in the nerve cell body and are associated with cognitive deficits [10–12], initially appear in the MTL in the most common form of AD (∼85% of the cases [24]), spreading through its subcomponents in a sequential fashion. Several studies demonstrate that NFT initially develop in the medial portion of the PRC, the transentorhinal cortex (TERC, or BA35) [25], then progress to the ERC, before reaching the H in the limbic stage and later affect the temporal neocortex [13, 14, 26]. Within the H, NFT first appear in the CA1 subfield, mainly represented in the head of the H [27]. Although the topography, as well as the inter-personal variability, of these anterior subhippocampal structures (PRC/ERC) makes the neuroimaging assessment of this brain region difficult, potential non-invasive diagnostic tools that could reliably detect subtle pathological changes at the "subhippocampal" stage of AD are currently receiving increasing interest. Using MRI, several studies demonstrate atrophy of the ERC in predemential AD [28–32]. Baseline ERC volume has been shown to be a better predictor for decline from MCI to AD than hippocampal volume [28, 30].

Anatomy and connectivity of the MTL

In addition to the H, the MTL consists of several strongly interlinked subcomponents, the PRC (BA35 medially and BA36 laterally), the ERC (BA28), distributed along the anterior part of the collateral sulcus and parahippocampal gyrus, as well as the PHC (parahippocampal cortex) which lies on the posterior parahippocampal gyrus. Furthermore, the medial part of the temporo-polar cortex (TPC) (BA38), functionally part of a wider PRC region, is also viewed upon as an extension of BA36 by some authors [33–36], and hence as part of the "total" PRC for others [37].

The MTL is connected with neocortical and subcortical regions. Studies in monkeys and rodents show that distinct subregions of the MTL are connected to distinct cortical association areas through parallel pathways. Sensory information from widespread areas of the neocortex enters the MTL primarily via projections to the PRC and the PHC. The PRC mainly

receives projections from ventral processing streams, and in particular nearly two-thirds of its cortical inputs from the adjacent ventral-stream visual areas [33]. Compared with the PRC, the PHC receives a far greater proportion of its inputs from dorsal-stream areas, including the posterior parietal cortex, the retrosplenial cortex, the dorso-lateral prefrontal cortex, and the dorsal bank of the superior temporal sulcus [33, 39, 40]. Thus, two major parallel networks are interconnected with the MTL.

Both, the PRC and PHC feed information into the ERC [41, 42]. The PHC projects mainly to the medial entorhinal area, whereas the PRC projects principally to the lateral entorhinal area. The ERC, in turn, projects to the H [43]. Moreover, these parallel pathways are interconnected with projections from the PHC to the PRC, in addition to connections between the lateral and the medial areas of the ERC [33, 40, 44–47].

In the human brain, connectivity studies using functional measurements of resting-state activity on high-resolution MRI recently identified two separate cortical networks that each associate with distinct subregions of the MTL [48]. An "anterior MTL network" involves the anterior lateral temporal lobe, along with the middle temporal gyrus, immediately below the superior temporal sulcus, as well as the PRC and the ERC. This pathway converges on the head of the H. The second network, or "posterior MTL network" involves the inferior parietal lobule, the retrosplenial cortex, the posterior cingulate cortex, and a portion of the ventral medial prefrontal cortex. It includes the PHC, and converges on the body of the H. Overall, the identification of these two pathways in humans provides an anatomic reference for further studies.

Finally, there is also evidence that some segregation is still maintained among the subcortical projections from the MTL since the PRC mainly project to the dorso-median nuclei of the thalamus, while the H mainly projects to anterior thalamic nuclei and henceforth to an "extended hippocampal system" involving posterior cingulate areas and the retrosplenial cortices [22].

Parallel MTL networks involved in declarative memory

That the MTL is crucial for anterograde declarative memory has been confirmed by many studies since the description of the patient HM, a patient who suffered from amnesia after bilateral surgical removal of the MTL for intractable epilepsy [49]. The MTL is crucial for both semantic and episodic memory. Semantic

memory refers to facts (as knowledge of objects, concepts, people, and words). Episodic memory refers to events with a unique spatiotemporal reference that requires mental time travel through subjective time, thus allowing the retrieval of previous experiences [1]. There are two main views of how declarative memory is organized within the MTL. One view argues that the MTL is a set of structures contributing to declarative memory in a rather homogenous way [50]. An alternative view is that subregions of the MTL, although strongly interlinked, make different functional contributions to anterograde declarative memory [20–23].

Over the past years, there has been largely converging evidence for the functional specialization of the different areas of the MTL. Studies in non-human primates indicate that the PRC is crucial for "context-free" memory as assessed by visual recognition memory (VRM) tasks [51]. This brain area is also thought to play a critical role in processes comparable with non-verbal aspects of human semantic memory [52]. By contrast, experimental studies in animals support the evidence that the H is a key node for "context-rich memory" [53–55]. Mishkin and colleagues [20], following a critical study by Vargha-Khadem et al. [56] in three adolescents who had suffered from anoxia, suggested in a "hierarchical model of cognitive memory" that the neural substrate for "context-free memory", could be dissociated from "context-rich memory" in the human brain. Unlike non-human primates, for whom connectivity with the PRC is predominantly visual [33, 34], the PRC in humans receives information that is expanded beyond what is found in macaque, with highly processed signals from large regions of lateral temporal association cortex [48].

Similarly, Aggleton and Brown [57] provided evidence for a distinction between two recognition memory systems involving MTL structures through a dual process model, one system being crucial for familiarity judgments, while the other is thought to be critical for recollection. While familiarity is context-free, giving a sense of prior exposure, recollection is defined as a conscious retrieval of context-rich material and associations. Although these two models significantly differ in many aspects, they converge to the notion that within the MTL, the neural substrate of context-free memory like facts based on familiarity judgment might be segregated from the neural substrate for events based on recollection. Moreover, these two models converge concerning the involvement of brain structures, since context-free memory as well as familiarity, are thought to depend on anterior subhippocampal areas (among which the PRC plays a key role), while context-rich processes such as recollection, is thought to depend on the H. This functional segregation is also supported by neuroimaging (for review, see [58]) and electrophysiological (for review, see [59]) studies.

An increasing number of studies in MTL-injured patients are also in favor of a distinct contribution of the subregions of the MTL to memory [56, 60–64]. Patients with H lesions are impaired on tasks assessing context-rich material, which involve spatial memory, recall for personal events or episodic memory, but show intact memory for context-free material as facts (i.e., semantic memory) or familiarity based recogni-

Table 1
Overview of several studies that provide evidence for different contributions of the subcomponents of the MTL to declarative memory

Reference	Impaired	Preserved
Studies of patients with damage to the hippocampus only		
Vargha-Khadem et al. (1997) Science [56]	episodic and spatial memory	semantic memory and recognition memory
Mayes et al. (2002) Hippocampus [60]	episodic memory	recognition memory
Aggleton et al. (2005) Neuropsychologia [61]	recollection	familiarity in recognition memory
Bastin et al. (2004) Neurocase [65]	recall	Recognition
Barbeau et al. (2005) Hippocampus [62]	visual recall	visual recognition
Lebrun-Givois et al. (2008) Rev Neurol [63]	episodic memory	semantic memory
Tramoni et al. (2011) Brain [64]	context-rich memory (long term)	context-free memory (long term)
Studies of patients with MTL damage leaving the hippocampus (at least partially) intact and/or with impaired familiarity but preserved recollection		
Temple and Richardson (2006) Cogn Neuropsychol [70]	semantic memory	episodic memory
Barbeau et al. (2006) Cogn Neuropsychol [69]	context-free memory	context-rich memory
Bowles et al. (2007) Proc Natl Acad Sci 2007 [67]	familiarity	recollection
Bowles et al. (2010) Neuropsychologia [68]	familiarity	recollection
Barbeau et al. (2011) Hippocampus [66]	visual recognition memory	visual recall
Martin et al. (2011) Neuropsychologia [74]	familiarity	recollection

tion when anterior subhippocampal areas are intact [56, 60, 62, 65].

The reverse dissociation, impaired memory for facts contrasting with intact memory for events is more rarely reported [66–70]. In semantic dementia, a degenerative condition with impaired context-free memory for objects and facts and preserved episodic memory [71], atrophy of both the PRC, the anterior ERC and the TPC, but also the H has been described, PRC volume correlating positively with performance on semantic memory tasks [72, 73].

Taken together, a number of studies in patients suggest that brain damage in regions within anterior subhippocampal areas lead to impaired context-free memory. By contrast, damage to brain regions that are part of a posterior MTL network, like the H, appear crucial for context-rich memory, such as episodic memory and spatial memory. In Table 1, we provide an overview of several studies that provide evidence for different contributions of the subcomponents of the MTL to declarative memory [56, 60–70, 74].

Impaired context-free memory in early stages of AD

In this section, we will provide several examples of the tasks found to be impaired in the earliest stages of clinical AD. The interesting point here is that many of the so-called "episodic" memory tasks that patients fail on in the earliest stages of AD are in fact largely context-free in nature. In particular, most of these tasks mainly evaluate retrograde semantic memory or anterograde learning of single items (such as word lists, pictures of objects, or faces), which can be encoded, stored and later recognized or recalled independently one from the other with no reference to the context of learning.

In studies on asymptomatic subjects at risk for autosomal dominant AD, patients who later developed the disease showed impaired performance on recognition memory tasks using words or faces as early as 6 years before diagnosis [75]. A longitudinal case study of a patient with the APPV717I (London) mutation, clinically presenting with pure progressive amnesia over an extended period of at least 13 years, equally showed impaired performance on tasks assessing context-free memory like the Recognition Memory Tests for single items like words or faces at the predementia stage [76].

Population-based studies in healthy community dwellers, likely to reveal the earliest stages in AD, mainly show deficits on tasks assessing semantic mem-

ory, concept formation, and recall of words [77–81]. Focusing on patients at risk for decline, among the neuropsychological tasks assessing memory that are useful in predicting AD, are the FCSRT (Free and Cued Selective Reminding test) and the RAVLT (Rey's Auditory-Verbal Learning Task) [82, 83]. These tasks all evaluate the ability to recall context-free material like words. In a PET-study, performance on a word list learning task was correlated with glucose metabolism in the entorhinal cortex [84]. In addition, several studies recently consistently demonstrated an impairment of semantic memory in patients at risk for AD, including MCI-patients who later converted to AD [81, 85–92]. Two of these studies found that the neural correlate of this semantic impairment involves anterior subhippocampal structures [93, 92]. Moreover, some studies take the dysfunction resulting from earliest tau-related pathology in anterior subhippocampal regions specifically into account. This issue was more recently addressed by Wolk et al. [94], in patients with a MCI and multi-domain MCI, in a study that assessed familiarity and recollection using recognition memory paradigms, in reference to the dual process model of recognition memory [94]. Familiarity was impaired at least as much as recollection and the authors argued that measuring familiarity, spared in normal aging, could provide a specific marker for pathological changes in AD. Interestingly, the volume of ERC/PRC cortices was more highly related to familiarity, compared with that of the H [95].

In addition, within the theory of binding in the episodic buffer [96], "visual short term memory binding" has been found to be specifically impaired in patients with sporadic and familial AD, as well as in asymptomatic carriers of the mutation [97, 98]. The authors relate no specific neuroanatomical damage to the deficits but speculate that disconnection in AD could explain their findings. However, it is noteworthy that the perirhinal cortex is thought to play a crucial role in the type of intra-item association tasks that were used in the binding paradigm in these studies [23, 96].

In order to evaluate the dysfunction of the anterior subhippocampal region in patients with early AD, our group developed a visual recognition memory task, the DMS48 [38]. This task is thought to evaluate context-free memory and is similar to the paradigm used in the experimental studies with animals [51]. Patients failing on the DMS48 display clinical features of early AD, characterized by reduced delayed free recall and reduced cueing efficiency on the FCSR, indicating MTL dysfunction [38]. Using brain SPECT in MCI patients with impaired performance on DMS48 [99],

we found a functional profile classically reported in early AD [100, 101], with hypoperfusion in the MTL, the posterior cingulate and temporo-parietal cortices. In the same way, using voxel based morphometry, Barbeau and coworkers [102] found a structural profile usually reported in early AD [103–105] with gray matter loss in the MTL and temporo-parietal cortex and a correlation between performance on the DMS48 and grey matter density in anterior subhippocampal structures. Moreover, using proton magnetic resonance spectroscopy, we found reduced MTL NAA/mIno ratios, associated with the severity of pathological changes in AD, only in the MTL of aMCI patients with impaired performance on the DMS48 [106]. In this study, clinical 6-year follow-up data indicated that impaired performance on the DMS48 could predict conversion to AD with a sensitivity and specificity of 81.8%.

Taken together, the tasks mentioned in this section mainly evaluate context-free memory, either through anterograde learning of single items (like words and pictures), but also retrograde semantic memory. Impaired performance is therefore likely to reflect dysfunction of an anterior mesiotemporal network that supports object-based context-free memory.

Concerning list learning tests assessing the recall of words, commonly used in many studies on AD, we argue that they are not "episodic" *per se*, as clearly pointed out by Endel Tulving in the foreword of this article [4]. None of these tasks requires mental travel through time, which is a hallmark of episodic memory. Also, subjects are in the same context during recall as they were during encoding (both spatially, sitting in front of a desk, and even temporally since the neuropsychological examination occurs over a limited period of time). If the specific episode ("when" and "where") of stimulus presentation was tested, the subject would be asked to provide contextual information about "where" and "when" these words were learned. Moreover, it is likely that memory processes like recollection and recall can be dissociated [64, 69]. Recollection is a set of processes activated during retrieval from autobiographical episodic memory which requires remembering contextual details of a specific episode in which these words were learned and are defining features of episodic memory. By contrast, recall is a general competency that allows retrieving any information from memory without necessarily referring to context (e.g., when trying to recall the name the capital of Spain most people will not remember in which context they learned that it is Madrid). Additional evidence to support a relationship between word list learning

and context-free memory comes from a recent study from our group using resting state fMRI that found positive correlations between connectivity of the anterior MTL network, including anterior subhippocampal structures, and performance on word list learning tasks and visual recognition memory tasks (the DMS48) [107]. Therefore, although it is possible that these word-list learning tasks are partly of "episodic" nature, we argue that the largest component is context-free and depends on anterior subhippocampal structures.

Implications for dysfunction of memory systems in predementia AD

To sum up, which memory systems are selectively impaired in predementia AD? Can recent findings on segregated MTL neural networks implicated in declarative memory contribute to the understanding of the memory dysfunction of the earliest stages of AD? Could tau pathology in the earliest stages of the disease interfere with the function of the anterior MTL network and thereby lead to an impairment of context-free memory?

We reviewed studies in rodents, non-human primates, and from human studies in patients with brain damage, as well as more recent findings from connectivity studies using resting-state fMRI, that provide evidence for an anatomical and functional segregation of two distinct parallel neural networks implicating the MTL, initially described in the visual domain, a ventral visual processing stream dealing with perceptive attributes, or "what", and a dorsal visual processing stream, dealing with spatial attributes, or "where" [108]. Anterior subhippocampal structures like the PRC, where NFT first appear, the lateral ERC cortices as well as the anterior H, and the TPC are integrated into an "anterior MTL network" and contribute to context-free memory. By contrast, the medial ERC, the PHC, the posterior H, where NFT appear at the later limbic stage of AD, as well as the posterior cingulate cortex are part of a "posterior MTL network" that plays a critical role in context-rich memory.

It has been suggested that entorhinal lesions in AD lead to the isolation of the hippocampal formation through functional deafferentation "*no less devastating with regard to memory than removal or destruction of the entire structure, thus contributing to the contextual memory defect that is a major component of the amnesia in Alzheimer's disease*" [109]. In contrast with this view, the evidence for distinct MTL networks raises the question of whether NFT in the transentorhinal cortex and the entorhinal cortex could

selectively lead to impaired interaction between the "anterior MTL network" and the H, mainly resulting in deficits of context-free memory. If this was the case, other memory functions of the H, as mediated through the posterior MTL network, and particularly context-rich episodic memory, could remain relatively intact during the very early stages of AD.

We here presented evidence for impaired context-free memory in predementia AD. However, there is also evidence for impaired context-rich memory and for dysfunction of brain regions within the posterior MTL network in patients at risk for AD. In particular, patients with questionable dementia who declined to AD on follow-up were shown to be impaired on a spatial short term memory task, the CANTAB Paired Associates Learning (PAL). It was argued that impaired performance on this task could be a marker of early neuropathological abnormalities in the H [110, 111]. Nestor et al. [112] proposed that amnesia seen in MCI and AD is a consequence of the disruption of critical focal nodes within a limbic-diencephalic network that includes the MTL, mammillary bodies, dorsomedial thalamus, and posterior cingulate [112]. Using brain imaging, additional evidence was presented that impaired episodic memory is associated with dysfunction of this network, thereby arguing that the episodic

memory deficit could not only be explained by the degree of MTL damage alone [113]. In this line of thought, it has recently been demonstrated that aspects of topographical memory are impaired in the earliest stages of the disease [114, 115].

Our suggestion to reconcile these views is to integrate these findings into a model that takes into account the localization and the temporal sequence of the lesions in early AD. Since NFT initially appear in anterior subhippocampal areas, it is possible that the first detectable signs during the transentorhinal stage of AD (i.e., Braak and Braak's stages I and II) lead to a selective impairment of the "anterior MTL network" implicated in impaired context-free memory [107] resulting in impaired performance on tasks assessing familiarity based recognition and word-list learning. When NFT, at the limbic stage of AD (i.e., Braak and Braak stages III and IV), are found in both anterior subhippocampal regions, as well as the H, dysfunction of the "posterior MTL network" may lead to impaired context-rich memory (Fig. 2).

The "transentorhinal" stages I-II may begin years and even decades before the diagnosis of AD [116] and were first considered to be clinically "silent" [13]. However, there is also evidence from clinico-pathological studies that slight symptoms can already
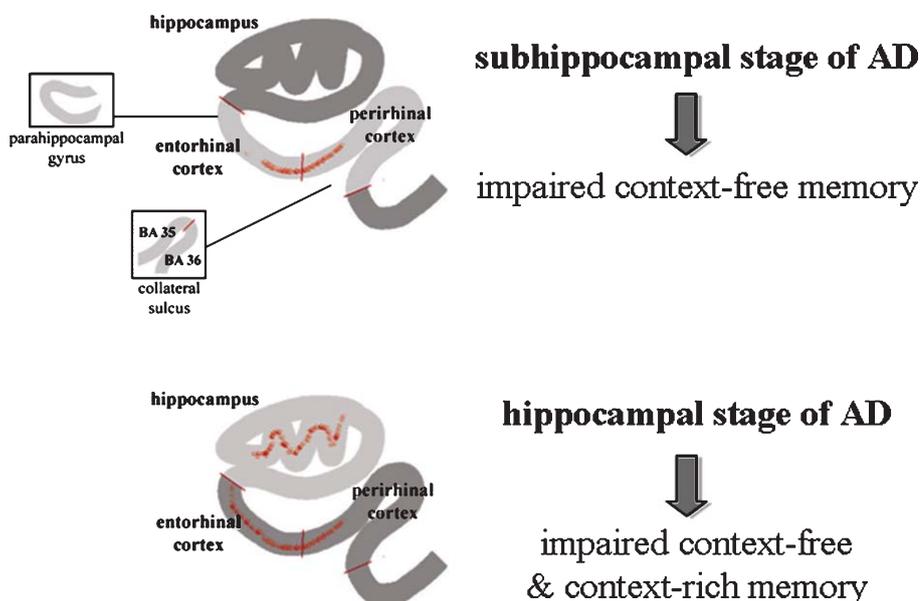

Fig. 2. Successive stages that take into account memory systems as well as the localization and the temporal sequence of the lesions within the MTL in early AD (coronal view). The subhippocampal stage of AD (Braak and Braak's stages I and II) may lead to a selective impairment of the "anterior MTL network" resulting in impaired context-free memory. In the limbic stage of AD (i.e., Braak and Braak stages III and IV), when NFT are found in both anterior subhippocampal regions, as well as the hippocampus, dysfunction of the "posterior MTL network" may additionally lead to impaired context-rich memory. NFT are schematically represented by red dots. MTL = mesial temporal lobe. NFT = neurofibrillary tangles.

be detected [117]. Moreover, prospective neuropathological studies have since shown that several of these individuals were diagnosed with amnestic MCI within a year of death [12, 118]. As a severe deficit in context-free memory has been shown to be compatible with independence in daily life [66, 69], it is possible that difficulties naming people, moderate loss of semantic information, or mild difficulties in learning new factual knowledge leads to consider these patients as being "asymptomatic". By contrast, focal H lesions leading to impaired context-rich memory are known to severely interfere with autonomy [56]. Patients at the limbic stage of AD, with impaired episodic or context-rich memory, leading to memory loss for personal experiences or spatial disorientation, are more likely to be considered as being symptomatic.

The hypothesis that tau deposition in the anterior subhippocampal region during the earliest stages of AD will lead to dysfunction of neural networks implicated in context-free memory remains however to be confirmed, with a clear demonstration that context-free memory in patients with predementia AD is related to dysfunction of the anterior MTL network (see Table 2 for a list of testable hypotheses). In addition, longitudinal studies are needed in order to establish if this dysfunction predates context-rich memory related to dysfunction of the posterior MTL network. Studies that currently address this issue are mainly being conducted in patients with MCI, most of whom have already reached the limbic stage of AD [12]. Furthermore, several methodological issues have to be resolved. Standardized tasks assessing anterograde, strictly episodic, memory are not available in a clinical setting. Also, tasks assessing context-free and context-rich memory have to be matched for difficulty [64]. Moreover these comparisons have to take into account that some tasks assess retrograde memory (usually semantic tasks), while others assess anterograde memory. The hypothesis should be tested in longitudinal studies that focus on patients with preclinical AD with signs of amyloidosis and of neurodegeneration [119], a proportion of whom are likely to be at the transentorhinal stage of AD. However, this hypothesis only applies to the most frequent amnestic phenotype of AD with predominant MTL dysfunction thought to be associated with the $\varepsilon 4$ allele of apolipoprotein E, as well as other factors that remain to be identified [24, 120–123], while it does not apply to other "non-memory phenotypes" of AD where lesions first appear in neocortical regions and that appear to be independent from the $\varepsilon 4$ allele of apolipoprotein E [124–128].

Using neuropsychological tasks that are based on studies in animals and that are known to evaluate the function of neural networks involved in neuropathological processes should be considered for diagnostic purposes in neurodegenerative diseases. Such a translational approach, aiming at identifying a "cognitive biomarker", is most likely to contribute to early diagnosis. These cognitive markers could also be used as longitudinal markers to monitor disease progression during drug trials. In this context, it will be crucial to assess if tasks evaluating context-free memory may detect AD related pathology earlier than those evaluating context-rich memory.

Finally, the question as to the "episodic" nature of "episodic memory tasks" arises. That predementia AD is characterized by an impairment of episodic memory is predominantly based on the assumption that laboratory experiments of verbal and picture learning deal with episodic memory. As outlined in the introductory words, laboratory experiments deal with "what" the subject had to learn and two important features, "where" and "what" of episodic memory are missing in these tasks [4]. In fact, these so called episodic memory tasks may rather evaluate the anterograde aspects of context-free memory.

Table 2
Testable hypotheses suggested in this hypothesis article

1. Context-free memory is impaired before context-rich memory at the transentorhinal stage of AD
2. Context-free memory and context-rich memory are impaired at the hippocampal stage of AD
3. The onset of the hippocampal stage is concomitant with decreasing autonomy
4. The extent of context-free and context-rich memory impairment correlates with NFT burden and topography
5. The efficiency of drugs that target NFTs could be tested by assessing the extent of context-free and context-rich memory impairment in longitudinal studies

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