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Targeting the function of the transentorhinal cortex to identify early cognitive markers of Alzheimer's disease

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Abstract

Initial neuropathology of early Alzheimer's disease accumulates in the transentorhinal cortex. We review empirical data suggesting that tasks that assess cognitive functions supported by the transenthorinal cortex are impaired as early as the preclinical stages of Alzheimer's disease. These tasks span across various domains, including episodic memory, semantic memory, language, and perception. We propose that all tasks sensitive to Alzheimer-related transentorhinal neuropathology commonly rely on representations of entities supporting the processing and discrimination of items having perceptually and conceptually overlapping features. In the future, we suggest that a screening tool that is sensitive and specific to very early Alzheimer's disease should probe memory and perceptual discrimination of highly similar entities.

Keywords: neuropsychology, transentorhinal cortex, Alzheimer's disease, Mild Cognitive Impairment, cognitive markers.

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1. Introduction

The quest for early cognitive markers of Alzheimer's disease (AD) is driven by the fact that brain pathological hallmarks of the disease (i.e., amyloid plaques, neurofibrillary tangles, neuronal and synaptic loss) start decades before the emergence of clinical symptoms such as episodic memory decline in the typical form (Jack et al., 2018). Neurofibrillary tangles and synaptic loss are better predictors of cognitive decline than amyloid burden (Terry et al., 1991; Timmers et al., 2019). They follow a typical pattern of topographical progression, with initial cortical accumulation in the transenthorinal cortex (Braak & Braak, 1995; Braak & Del Tredici, 2018). The transentorhinal cortex corresponds to the medial portion of the perirhinal cortex and the anterolateral entorhinal cortex (BA 35) (Taylor & Probst, 2008). When neuropathology is limited to the transentorhinal cortex, individuals are mostly asymptomatic, which does not preclude sub-clinical cognitive changes. Overt memory deficits starts usually when the pathology invades the hippocampus. The preclinical stage (i.e., asymptomatic stage, including cases of Subjective Cognitive Decline or SCD) and the predementia stage (that includes cases of Mild Cognitive Impairment or MCI) are now considered the critical time windows for interventions, including disease-modifying therapies and cognitive rehabilitation programs.

Nevertheless, the presence of brain pathology cannot predict reliably when an individual will become demented, notably because cognitive reserve built from lifestyle protective factors can delay symptoms onset (Stern, 2012). In contrast, the presence of subtle cognitive decline in the preclinical and predementia stages is a more robust predictor of future cognitive and functional outcomes (Elman et al., 2020), as they signal the emergence of clinical

consequences of neuropathology despite cognitive reserve. So, the identification of the most sensitive and specific cognitive markers of AD is a key for early diagnosis.

Two approaches have been classically used in the investigation of early cognitive markers of AD. One approach is bottom-up-like, and consists in longitudinal neuropsychological assessments of population-based cohorts of either healthy older individuals or older adults with SCD or MCI (for a review, Bastin & Salmon, 2014). These individuals are tested repeatedly with a more or less extensive neuropsychological battery. Over time, some of them transition towards AD while others do not. Critically, retrospective analyses of baseline neuropsychological scores allow to identify the cognitive functions that were impaired in the prodromal or preclinical phase in the future demented patients in comparison to individuals who remained cognitive healthy. This approach is also useful to picture the chronological sequence of these cognitive impairments. Another approach is top-down-like because it is essentially theory-driven. The starting point of this approach is the relation between the topography of Alzheimer-related neuropathology and cognitive theories concerning the function of the affected brain regions. This allows researchers to predict what should be the cognitive difficulties characterizing the earliest stages of Alzheimer's disease. The current paper is embedded in this top-down approach, with the objective to provide a state-of-the-art proposal of the most promising cognitive markers of AD. More specifically, we consider here that the earliest cognitive changes in AD should concern the cognitive functions depending on the transentorhinal cortex. As part of the medial temporal lobe, the transentorhinal cortex is usually associated with episodic memory (Squire et al., 2004), (Squire et al., 2004), although recent findings shed lights on other functions supported by this brain region (Clarke & Tyler, 2015; Graham et al., 2010).

Accordingly, in the present paper, we will briefly describe potential functions associated with the transentorhinal cortex, which have been explored in the context of AD and its early stages.

We identified three functions that have been considered in the literature: context-free memory, binding in short-term memory, and discrimination of objects in various cognitive domains. After having reviewed these functions, we will propose a unifying view pointing to entity-level representation as one specific function of the transentorhinal that should be considered as the best candidate for a cognitive marker of Alzheimer's disease given the recent advances in the field. We will conclude this paper by outlining critical directions for future research to provide clinical tools for early diagnosis of AD.

2. Potential functions of the transenthorinal cortex sensitive to early AD

2.1. Context-free memory

Based on non-human animal data and neuropsychological evidence in humans, Didic et al. (2011) posited that the transentorhinal cortex supports context-free memory, whereas context-rich memory (i.e., memory for events situated in time and space) relies on the hippocampus. Context-free memory refers to recognition memory for objects or faces which relies on familiarity-based decisions and to semantic memory (i.e., memory of general knowledge about the world). Recognition memory for objects was notably investigated in the AD continuum with the DMS48 (Delayed Matching to Sample 48), which is a task where individuals must pick studied pictures among two alternatives. Decisions can rely on familiarity, without a need for memory of context. In MCI and early AD, performance on the DMS48 correlated with resting-state functioning connectivity within a network centered on the transentorhinal cortex (Gour et al., 2011) and with synaptic density measured with SV2A-PET in a parahippocampal area including the transentorhinal cortex (Bastin et al., 2020). Patients with MCI who fail the DMS48 had a memory profile close to the typical profile of AD patients (Barbeau et al., 2004) as well as a hypometabolic and atrophic cerebral pattern typical of prodromal AD (Barbeau et al., 2008; Didic et al., 2010; Guedj et al., 2006)

compared with MCI individuals who successfully perform on the task. Moreover, longitudinal studies in MCI indicated that impaired performance on the DMS48 could predict accelerated cognitive decline (De Anna et al., 2014) and conversion to AD with a sensitivity and specificity of 81.8% (Didic et al., 2010, 2013). However, context-free memory assessed through familiarity-based recognition memory may not always be a reliable cognitive marker of AD. Indeed, studies assessing familiarity in the preclinical and prodromal phases of AD provided conflicting findings, and there are as many studies showing impaired familiarity in these populations as studies reporting preserved familiarity (for reviews, Koen & Yonelinas, 2014; Schoemaker et al., 2014; Simon & Bastin, 2015).

As for semantic memory, it is impaired in MCI patients across a large variety of tasks (for a meta-analysis, Joubert et al., 2021). Semantic memory tasks (like category fluency which consists in citing as many exemplars from a category as possible) are sensitive to early cognitive decline in the prodromal and preclinical stages of AD (Papp et al., 2017), predict future dementia in MCI (Chang et al., 2022; Marra et al., 2021) and have been related to the integrity of the transenthorinal cortex and of other regions such as the hippocampus and anterior temporal lobes (Barbeau et al., 2012; Joubert et al., 2010; Venneri et al., 2008, 2019). Recently, it was shown that the loss of the semantic advantage in fluency tasks, indexed as the discrepancy between category and phonological verbal fluency performance, was associated with reduced grey matter density in the anterior medial temporal lobes, including perirhinal cortex, in mild MCI (Wright et al., 2022).

Although context-free memory appears sensitive to early cognitive changes due to AD, the presence of some divergent findings for familiarity-based recognition memory and the fact that semantic memory scores correlate with other brain regions than the transenthorinal cortex suggest that these functions are not pure transentorhinal-related cognitive marker, at least as

they are typically measured. We will return to this issue in the section proposing a unifying view by specifying that there are different forms of familiarity and semantic memory.

2.2. Binding in short-term memory

Binding in short-term memory refers to the ability to maintain in memory for a few seconds associations between pieces of information. A common distinction relates to the difference between relational binding (i.e., the association of different items together or linking an item with contextual information such as location) and conjunctive binding (i.e., the integration of various types of features within a representation such as colored shapes (Cohen et al., 1999; Ecker et al., 2013)). Whereas relational binding is associated with the hippocampus and is affected in several conditions such as healthy aging, amnesia, or epilepsy, conjunctive binding in short-term memory has been put forward as a potential early cognitive marker in AD (Parra, 2013).

Whereas conjunctive short-term binding is preserved in healthy aging (Bastin, 2018; Parra, Abrahams, Fabi, et al., 2009; Parra, Abrahams, Logie, et al., 2009), it is specifically impaired in AD contrary to other types of dementia, such as frontotemporal dementia, vascular dementia, Lewy body dementia and dementia associated with Parkinson's disease (Cecchini et al., 2017; Della Sala et al., 2012). Moreover, conjunctive short-term binding is deficient in preclinical forms of familial AD, such as asymptomatic carriers of PSEN1 mutations (Parra et al., 2015) as well as in individuals with SCD and in MCI (Koppara et al., 2015). In addition, failure on a conjunctive short-term binging task predicts the presence of amyloid in the brain of participants in a mixed sample of cognitively healthy individuals, MCI, and AD patients (Cecchini et al., 2021).

While these data suggest sensitivity of conjunctive short-term binding to preclinical and prodromal stages of AD, the link with the transentorhinal cortex is less obvious. Some

research has identified that this type of binding is not supported by the hippocampus (Jonin et al., 2019; Martinez et al., 2019), but would be underlid by medial temporal lobe areas encompassing the transentorhinal cortex (Valdes Hernandez et al., 2020) or more posterior regions, such as the ventral visual stream areas and temporoparietal cortex (Parra et al., 2014).

2.3. Discrimination of objects

The umbrella term "discrimination of objects" encompasses a series of tasks that span across various cognitive domains (e.g., episodic memory, semantic memory, perceptual discrimination, or language) tested in the context of early AD. The common element across these tasks is the importance of forming a distinct representation of specific objects.

In the language domain, several studies pointed to a category-specific naming deficit in AD, whereby the naming of livings entities, such as animals, tends to be impaired to a greater extent than the naming of non-living entities, such as tools (Laws et al., 2007). In a sample of cognitively healthy older participants, MCI patients and patients with AD, this naming impairment for livings things correlated with a thinner transenthorinal cortex (Kivisaari et al., 2012). Other studies, including notably patients with neurological diseases such as herpes simplex viral encephalitis that affects the anterior part of the medial temporal lobe, confirmed the strong relationship between processing of living entities and the transentorhinal cortex (for a review, Clarke & Tyler, 2015). Living entities are known to be more easily confusable because living concepts share many common features and few distinctive features, contrary to non-living entities (Tyler & Moss, 2001).

In episodic memory tasks in mixed samples from the Alzheimer continuum, false recognitions of objects that were highly similar to studied items (e.g., resembling objects, or a living entity from the same subordinate category) were associated with a reduced volume of the transenthorinal cortex (Fidalgo et al., 2016; Kivisaari et al., 2013) and with the presence of tau

pathology in an anterior temporal network encompassing the transenthorinal cortex (Maass et al., 2019). Two studies examined novelty detection by comparing fixation time for repeated versus novel objects in a continuous stream of stimuli while recording eye movements in older participants at risk for cognitive decline versus cognitively healthy older participants (Yeung et al., 2013, 2017). Whereas cognitively healthy older adults looked longer at novel objects than at repeated objects, at-risk individuals' visual fixation behavior indicated that they treated novel similar objects like repeated stimuli, suggesting a failing at discriminating between old and new similar objects (Yeung et al., 2013). In a subsequent study (Yeung et al., 2017), the viewing pattern of different parts of objects was examined for repeated objects, novel objects made of two parts belonging to repeated objects and recombined in a new configuration, and completely novel objects. The proportion of fixations directed to the critical region of an object that allowed to detect whether it was a known or an unknown configuration was significantly and selectively predicted by the volume of the transentorhinal cortex.

In a semantic memory task consisting in judging whether a picture and a word represent the same concept, a larger number of errors for living items that shared many semantic features (e.g., horse-donkey) was related to a smaller volume of the transentorhinal cortex in mild AD patients (Frick et al., unpublished data).

Perceptual discrimination of objects has been studied in early stages of AD with oddity tasks (i.e., to select the stimulus that is different from others in a set) or matching tasks (i.e., to decide whether two stimuli are identical or not). Such tasks recruit the transenthorinal cortex (Devlin & Price, 2007; O'Neil et al., 2009). It was shown that perceptual discrimination of highly similar objects (but not dissimilar objects) is impaired in MCI (Gaynor et al., 2019; Newsome et al., 2012) and in individuals at risk for AD because of a familial history of AD cases (Mason et al., 2017).

In all these tasks, independently of the domain tested, it is necessary to discriminate between objects at a fine-grained level to distinguish among stimuli having many common semantic or perceptual features, such as the highly confusable living entities or objects sharing many perceptual features. The involvement of the transenthorhinal cortex in these various tasks points to the notion that its function is not limited to memory, which is an important claim in current representational views of cognitive functioning (Bastin et al., 2019; Bussey & Saksida, 2007; Graham et al., 2010; Ranganath & Ritchey, 2012).

3. A unifying view of the function of the transentorhinal cortex: Representation of entities

Despite some promising findings reviewed above, it is still premature to propose the ultimate task that could be integrated in a neuropsychological test battery for an efficient early detection of future dementia due to AD. A priori, the above findings could be taken as a disparate panel of tasks that seem sensitive to early cognitive changes due to AD pathology. However, we claim here that all these tasks share a common element that could be the key to identify the best cognitive marker of AD. This common element also defines the specific function of the transentorhinal cortex, which is of interest for the theoretical modeling of memory functioning beyond the clinical diagnosis of AD.

In all the above-described tasks, even if they pertain to various cognitive domains, it is always necessary to create, store and retrieve an *entity*-level representation. An entity is defined as an exemplar of a category which is distinguished from other similar exemplars by its unique configuration of perceptual-conceptual traits. Entities rely on two complementary circuits in the medial temporal lobe: coarse, gist-like, rapid processing of object information relies on projection from the perirhinal cortex to the hippocampus, and slower, finely detailed processing of objects relies on projection from the perirhinal cortex to the entorhinal cortex to

the hippocampus (Burke et al., 2018). As the apex of a hierarchy of processing in the ventral visual stream, the transentorhinal cortex stores orthogonal representations of entities, allowing us to make fine-grained discrimination between very similar stimuli (e.g., living items, very similar objects), distinguishing them through the unique conjunctive integration of their features (Bastin et al., 2019; Bussey & Saksida, 2007; Ferko et al., 2022; Graham et al., 2010; Ranganath & Ritchey, 2012) before it is integrated with context in the hippocampus (Burke et al., 2018). The formation of such integrated representations is impaired in mild AD, in relation with an alteration in the volume of the transentorhinal region (Delhaye et al., 2019). This entity-level representation can be used in many different tasks but will always require an intact transentorhinal cortex. In the case of episodic memory, and more particularly context-free memory, the transentorhinal cortex should be needed for a particular type of familiarity that require to recognize unique entities. Familiarity for entities can be assessed in a visual recognition memory task in which participants first study a series of pictures of objects, and then have to identify studied pictures among unstudied pictures (Besson et al., 2020). To specifically probe familiarity for entities, the task has two particularities. First, recognition decisions are made rapidly, therefore the process of recollection, which takes longer, cannot intervene. Second, studied pictures are slightly modified in terms of size and orientation (to avoid perceptual familiarity) and unstudied pictures are close exemplars from the same categories as studied pictures (to avoid conceptual familiarity). Performance in this familiarity for entities task correlated specifically with the volume of the transentorhinal cortex in a sample of MCI patients (Besson et al., 2020). In contrast, other recognition memory tasks in which familiarity for entities is not required should not depend on the transentorhinal cortex and should not be impaired in early AD. This would be the case of any recognition memory task in which decisions can rely on familiarity assessment of low-level perceptual (color, shape) or conceptual (superordinate category) features. Similarly, in semantic memory tasks,

only those where it is necessary to distinguish between closely overlapping features would require the transentorhinal cortex and be deficient in early AD (Clarke & Tyler, 2015).

4. Future perspectives

We suggest that the best cognitive marker of early AD needs to measure the ability to represent entities that relies specifically on the transentorhinal cortex. Should the task pertain to particular cognitive domains? A priori any domain, such as episodic memory, semantic memory, perception, language, or novelty detection, could be probed as long as representations of entities are used. Nevertheless, beyond the transentorhinal cortex, the use of representations will engage distinct connected cerebral networks as a function of the domain. It might be that some networks involve brain regions that are affected in other pathologies than AD (e.g., anterior temporal areas recruited by semantic tasks are disrupted in frontotemporal lobar degeneration). Therefore, we propose that a tool mixing tasks from various domains, all probing representations of entities, would be an ideal candidate screening tool. Indeed, even if there is individual variation in performance across domains as a function of affected brain networks, the principal component common to all domains would be representation and discrimination of entities that should be consistently disturbed by transentorhinal damage. Once this tool is created, it will have to be validated to meet three conditions. First, if it is sensitive to early AD-related transentorhinal neuropathology, the task must be able to predict future progression to AD in preclinical and prodromal stages. Second, to provide additional and unique value compared to traditional neuropsychological tasks, it must be more sensitive and specific to early AD than other tasks. Third, to provide a screening tool dedicated to diagnosis of early AD specifically, it must provide good differential diagnosis between AD and other age-related pathologies.

Thanks to the recent advances in cognitive neuroscience, this endeavor is well-engaged, and the path is no so long before the quest reaches its target.

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Conflict of interest

The authors report no conflict of interest.

Authors' contribution

CB wrote the first draft of the manuscript. ED completed the manuscript.

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