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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 assessing 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 a screening tool that is sensitive and specific to very early Alzheimer’s disease to 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 neuropathological 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 (BA 35) and the anterolateral entorhinal cortex (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 usually start 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 reliably predict 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. As such, 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 data-driven and consists in longitudinal neuropsychological assessments of population-based cohorts of either healthy older individuals or older participants with SCD or MCI (for a review, Bastin & Salmon, 2014). These individuals are tested repeatedly with a neuropsychological test battery. Over time, some of them transition towards AD while others do not. Critically, retrospective analyses of baseline neuropsychological scores allow for the identification of cognitive functions that were impaired in the prodromal or preclinical phase in future demented patients compared with individuals who remained cognitively healthy. This approach is also useful to picture the chronological sequence of these cognitive impairments. Another approach 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 cognitive difficulties characterize the earliest stages of Alzheimer’s disease.

The current paper is embedded in this theory-driven 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), 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 describe potential functions associated with the transentorhinal cortex, which have been explored in the context of AD and its early stages. We selected articles that emphasized tasks in which performance is associated with the integrity of perirhinal and entorhinal cortices in MCI or AD and articles suggesting that some tasks are sensitive to cognitive impairment in the early stages of AD. Supplementary Table 1 summarizes the results of studies reporting an association between performance in various domains and measures of brain regions encompassing the transentorhinal cortex. We identified three functions that have been considered in the literature: context-free memory, conjunctive binding in short-term and long-term memory, and discrimination of objects in various cognitive domains. After having reviewed these results, we will propose a unifying view pointing to entity-level representation as one specific function of the transentorhinal cortex that should be considered as the best candidate for a cognitive marker of Alzheimer’s disease. We will conclude this paper by outlining critical directions for future research to provide clinical tools for the early diagnosis of AD.

1. **Potential functions of the transenthorinal cortex sensitive to early AD**
	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 familiarity-based recognition memory for objects or faces and to semantic memory (i.e., memory for general knowledge about the world).

*Familiarity-based recognition memory*

Didic et al.’s (2011) proposal was notably built on a series of findings regarding recognition memory for objects investigated in the AD continuum with the DMS48 (Delayed Matching to Sample 48) task. This is a task where individuals study incidentally pictures of concrete and abstract objects and then have to recognize them among two alternatives following a 3-minute retention interval. 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 functional 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 failed the DMS48 (indicated by a performance situated 1.5 SD below the mean) 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). Among the possible methodological explanations for these discrepant results, the way familiarity is assessed should be considered if one aims at testing the hypothesis that impaired familiarity is an early marker of AD. In traditional dual-process paradigms, familiarity is opposed to recollection and its contribution is often estimated by default (i.e., when recollection is not preferred, Yonelinas (2002)). However, the tasks usually encourage the use of recollection, so that the actual contribution of familiarity is hidden. Some test formats favor a greater reliance on familiarity, such as forced-choice tests compared to yes/no tests (Bastin & Van der Linden, 2003; Migo et al., 2009). Forced-choice recognition memory was found to be preserved in MCI and impaired in mild AD, additionally correlating with the volume of the perirhinal cortex (Westerberg et al., 2006, 2013). In contrast, poor forced-choice recognition memory discriminated between MCI patients who subsequently developed AD and MCI patients who remained stable (Bastin et al., 2021). Nevertheless, as the likelihood of recollection is not discarded in forced-choice tasks, one should use alternative tasks that isolate the contribution of familiarity (Anderson et al., 2021).

One such task consists in frequency ratings of recent exposures to materials (e.g., words or pictures of objects shown one, three, four, seven, nine, or 11 times), which rely on a graded feeling of familiarity (Hintzman & Curran, 1994). fMRI studies showed that the activity of the perirhinal cortex tracks actual as well as reported frequency of exposure (Duke et al., 2017; Yang et al., 2022). Patients with MCI showed reduced accuracy in their frequency judgments (Anderson et al., 2021; Sanger & Anderson, 2022). Another method to isolate familiarity in recognition memory tasks consists in imposing a short response deadline when participants identify studied pictures among unstudied pictures. With this method, it was shown that preservation versus impairment of familiarity in MCI depends on the nature of the materials. When studied and novel stimuli do not share overlapping features, fast familiarity decisions were as accurate in MCI patients as in healthy controls (Besson et al., 2015). In contrast, they were impaired when similar objects had to be discriminated against each other (Besson et al., 2020). In the latter study, during the test phase, studied pictures were slightly modified in terms of size and orientation with unstudied pictures being close exemplars from the same categories as studied pictures. Performance in this task correlated specifically with the volume of the anterolateral entorhinal cortex in a sample of MCI patients (Besson et al., 2020).

*Semantic memory*

Another form of context-free memory proposed to be affected by damage to the transentorhinal cortex is semantic memory (Didic et al., 2011). Semantic memory is impaired in MCI patients across a large variety of tasks (for a meta-analysis, see 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). Performance on these tasks predict future dementia in MCI (Chang et al., 2022; Marra et al., 2021) and has been related to the integrity of the transenthorinal cortex, 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 the perirhinal cortex, in mild MCI (Wright et al., 2022).

However, the fact that semantic memory scores correlate with other brain regions than the transenthorinal cortex suggests that this function is not a pure transentorhinal-related cognitive marker. In fact, the above-mentioned studies in early AD did not explicitly point to the aspects of semantic memory that would be sensitive to early cognitive changes due to AD. In section 3, we report work that focused on a candidate mechanism involved in semantic memory tasks that would be more specifically reliant on the transentorhinal cortex, namely fine-grained discrimination between concepts.

* 1. Conjunctive binding in short-term memory and long-term memory

Binding corresponds to the creation and storage of associations between pieces of information. A common distinction relates to the difference between relational and conjunctive binding (Cohen et al., 1999; Ecker et al., 2013). Relational binding refers to the association of different items together or linking an item with contextual information such as location. Conjunctive binding corresponds to the integration of various types of features within a unified representation such as colored shapes. Whereas relational binding is associated with the hippocampus, affected in several conditions such as healthy aging, amnesia, or epilepsy; conjunctive binding in short-term and long-term memory has been suggested as a potential early cognitive marker in AD (Anderson, 2019; Parra, 2013).

*Conjunctive binding in short-term memory*

Conjunctive binding in short-term memory (or conjunctive short-term binding) refers to the ability to maintain briefly in memory conjunctions between features forming unified representations. A recent meta-analysis by Cecchini et al. (2022) reported a large impairment in conjunctive short-term binding in individuals at all stages of the AD continuum (from subjective cognitive decline to dementia). Most of the studies used a change detection task in which participants are briefly presented with a display containing two or three colored shapes that they must study. Then a new display appears showing colored shapes that are either identical to the studied pairings or recombined (i.e., the shape of one color is now associated with another shape). Participants have to tell whether the associations in this display are the same as in the previous display. With this task, it was shown that, 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 impaired in in preclinical forms of familial AD, such as asymptomatic carriers of PSEN1 mutations (Parra, Abrahams, Logie, Méndez, et al., 2010; Parra et al., 2015), in individuals with SCD and in MCI (Cecchini et al., 2020; Koppara et al., 2015; Parra et al., 2019) and in demented patients with AD (Parra, Abrahams, Logie, & Della Sala, 2010). Compared to patients with Parkinson disease and depressed older participants, conjunctive short-term binding was only impaired in AD (Kozlova et al., 2020; Parra, Abrahams, Logie, & Della Sala, 2010). In addition, failure on a conjunctive short-term binding task was associated with 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 performance in the change detection task with conjunctive bindings is not supported by the hippocampus (Jonin et al., 2019; Martinez et al., 2019). One study in MCI reported a correlation between short-term memory performance for conjunctive binding and the volume of the parahippocampal gyrus encompassing the transentorhinal cortex (Valdes Hernandez et al., 2020). However, the association was no longer significant after controlling for demographic data. Moreover, short-term memory for single features, but not bindings, was found to correlate with tau burden in the entorhinal cortex in familial AD (Norton et al., 2020). Neuroimaging reports more often point to a role of more posterior regions, such as the ventral visual stream areas and temporoparietal cortex (Martinez et al., 2019; Parra et al., 2014; Shafritz et al., 2002) in conjunctive short-term binding.

Note also that the demands of the task matter. Contrary to change detection which is age-invariant, performance in a task requiring to reconstruct object-color pairings from short-term memory was diminished in healthy older individuals because it recruited cognitive control processes (Bastin & Besson, 2021). Additionally, age-related differences were also observed in a short-term memory task that measured the precision of memory for object colors via reproduction of the studied color of objects (Korkki et al., 2020). To our knowledge, short-term binding performance with these reconstruction or memory precision tasks has not been assessed in patients in the early stage of AD, but a few studies used a free recall task after study of colored shape arrays. These studies also reported impaired conjunctive short-term binding in MCI (Cecchini et al., 2020) and AD (Cecchini et al., 2020; Parra, Abrahams, Fabi, et al., 2009). Additionally, performance was 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). The meta-analysis by Cecchini et al. (2022) did not show any difference in the effect size of the impairment of AD patients in change detection tasks by comparison to free recall tasks. There are no studies relating binding performance in recall tasks with cerebral changes in patients. It might be that all tasks in which the precise feature conjunctions must be reconstructed would not be sensitive to transentorhinal pathology because, for instance, precision of memory representations has been shown to involve the angular gyrus (Richter et al., 2016).

*Conjunctive binding in long-term memory*

Long-term memory for conjunctive associations in early AD has been tested with a variety of materials (e.g., object-color associations, compound words, objects with overlapping features). A few studies reported an association between performance in these conjunctive long-term memory tasks and structure or functioning of medial temporal lobe regions. This includes the transentorhinal cortex in patients from the AD continuum or in older individuals at risk for cognitive impairment (i.e., indexed by low MoCA performance).

Mild AD and MCI patients showed poor memory for entities that needed to be created at encoding by unitizing features into a unique item (object-color unitization, Bastin et al., 2014; novel compound words, Delhaye, Mechanic-Hamilton, et al., 2019). Performance in these tasks correlated with metabolism of ventral visual stream regions encompassing the perirhinal cortex (Bastin et al., 2014) and volume of the perirhinal cortex (Delhaye, Mechanic-Hamilton, et al., 2019). To assess memory discrimination for objects with overlapping perceptual features, two studies compared 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 and cognitively healthy older participants (Yeung et al., 2017, 2013). 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 failure at discriminating between old and new similar objects (Yeung et al., 2013). In a subsequent study (Yeung et al., 2017), the viewing pattern of abstract objects, each composed of two different parts was examined for repeated objects, novel objects made of two parts belonging to repeated objects, recombined in a new configuration, and completely novel objects. The proportion of fixations directed to the critical region of an object, i.e., the junctions of the two parts of the object, that allowed to detect whether it was a known or an unknown configuration, was significantly and selectively predicted by the volume of the anterolateral entorhinal cortex.

Additionally, individuals at risk for cognitive impairment as well as patients with MCI have a reduced ability to select a studied item over a highly similar (both conceptually and perceptually) lure object (Fidalgo et al., 2016; Gellersen et al., 2023; Stark et al., 2013) in recognition memory tasks. Studies in mixed samples from the Alzheimer continuum showed that 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 (Kivisaari et al., 2013) and with the presence of tau pathology in an anterior temporal network encompassing the transenthorinal cortex (Maass et al., 2019). Interestingly, as for short-term binding, the task demands were also considered as memory performance in at-risk individuals and in healthy older participants was mediated by executive function scores when the test was in a yes/no format, but not when it was in a forced-choice format (Gellersen et al., 2021, 2023).

In these tasks, mnemonic discrimination is thought to require a conjunctive representation of objects features that is sufficiently fine-grained to support interference from resembling objects (Cowell et al., 2019). Interestingly, memory performance in such tests is partly mediated by perceptual discrimination abilities for materials with overlapping features and/or from a viewpoint-invariant perspective (Gellersen et al., 2021, 2023). This may indicate that impoverished fine-grained visual representations compromise any cognitive process, whether mnemonic or perceptual, that relies on them as proposed by the representational-hierarchical hypothesis (Barense et al., 2005; Graham et al., 2010; Saksida & Bussey, 2010). A small number of studies tested discrimination of objects based on conceptual or perceptual features in populations with AD or MCI with tasks in the perceptual or language domains, as will be presented in the next section.

* 1. Discrimination of objects

A few studies tested early AD patients with tasks in the domain of perceptual discrimination and language that required forming a distinct and unique representation of specific objects.

*Discrimination based on conceptual features*

In the language domain, several studies report a category-specific naming deficit in AD, whereby the naming of living 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 living things correlated with a thinner medial perirhinal cortex (Kivisaari et al., 2012). In a semantic memory task consisting in judging whether a picture and a word represent the same concept, a larger number of errors for items that shared many semantic features (e.g., horse-donkey) was related to a smaller volume of BA 35 in mild AD patients (Frick et al., under review).

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 thought to be more easily confusable because living concepts share many common features and few distinctive features, contrary to non-living entities (Tyler & Moss, 2001).

*Discrimination based on perceptual features*

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 in healthy young individuals (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). Similarly, patients with MCI or mild AD have greater difficulty identifying objects when they are presented in an overlapping line-drawn display (Alegret et al., 2009) or as a scrambled fragmented puzzle (Delhaye, Bahri, et al., 2019). This difficulty was related to a decreased volume of the perirhinal cortex (Delhaye, Bahri, et al., 2019). More recently, however, Gellersen et al. (2023) reported perceptual discrimination decrements in older individuals with cognitive impairment independently of the degree of feature ambiguity in the stimuli. Furthermore, an association was found between this deficit and reduced cortical thickness of the entorhinal cortex. All these studies suggest that early pathology of the transentorhinal cortex may impair perceptual processing of objects with overlapping features.

1. **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 tasks sensitive to early AD and/or to changes in the structure or function of the transentorhinal cortex, it is always necessary to create, store and retrieve an *entity*-level representation, even if they pertain to various cognitive domains. 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 relying on projection from the perirhinal cortex to the hippocampus, and slower, finely detailed processing of objects relying on projection from the perirhinal cortex to the entorhinal cortex to the hippocampus (Burke et al., 2018). The transentorhinal cortex stores orthogonal representations of entities before they are integrated with context in the hippocampus (Burke et al., 2018). Representations of entities allow us to make fine-grained discrimination between very similar stimuli (e.g., living items, very similar objects) based on 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).

Recent fMRI studies support the idea that the transentorhinal cortex (more precisely, the perirhinal cortex) is central for such entity representation by coding, in a conjunctive and integrative fashion, the joint representation of perceptual-conceptual features of an object. Individually, these features are processed in distinct regions of the brain, such as the temporal pole/parahippocampal cortex for conceptual features, or the lateral occipital cortex for perceptual features (Martin et al., 2018). Similarly, recent studies showed that this preferential involvement of the transentorhinal region in the representation of objects is independent of the type of process or operation performed, be it of episodic or perceptual nature (Gardette et al., 2022; Ross et al., 2018).

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 requires recognition of unique entities. Familiarity-based discrimination between objects with overlapping features was notably related to perirhinal or anterolateral entorhinal integrity (fast recognition of viewpoint-invariant objects, Besson et al., 2020; DMS48, Gour et al., 2011; forced-choice recognition memory with similar silhouettes, Westerberg et al., 2013). Of note, the involvement of the transentorhinal cortex was mainly observed with the forced-choice test format or speeded response paradigm, rather than yes/no tasks. In contrast, other recognition memory tasks of equal difficulty 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 (Besson et al., 2015). Similarly, in semantic memory, only tasks where it is necessary to distinguish between closely overlapping features would require the transentorhinal cortex and be deficient in early AD (Clarke & Tyler, 2015). Equally difficult tasks that do not require fine-grained conceptual discrimination should be preserved. For instance, conceptual verbal fluency tasks consisting in citing exemplars from living categories, such as animals or vegetables (Wright et al., 2022), and naming of living entities (Kivisaari et al., 2012) appeared sensitive to transentorhinal damage, likely because concepts representing living things share many common features and differ from close concepts only on a few features. Conjunctive binding creates entities by fusing features into a unified representation in such a way that changing one feature alters the identity of the stimulus. In long-term memory, discrimination between studied and new stimuli based on their unique conjunction of features appears to involve the transentorhinal cortex (Delhaye, Mechanic-Hamilton, et al., 2019; Kivisaari et al., 2013; Yeung et al., 2017). This was sometimes contrasted with relational binding in long-term memory, assessed for instance with object-location associative tasks, which instead depends on the hippocampus (Davachi, 2006). A similar distinction may exist in short-term memory, but despite behavioral evidence for impaired conjunctive short-term binding in all stages of AD (Cecchini et al., 2022), the link with the transentorhinal cortex remains elusive. Finally, in line with the representation-hierarchical view (Barense et al., 2005; Graham et al., 2010; Saksida & Bussey, 2010), tasks beyond the memory domain that also require disambiguation of objects or concepts based on their feature configuration should suffer from transentorhinal damage, notably perceptual discrimination between items with overlapping features (Delhaye, Bahri, et al., 2019).

1. **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 a particular cognitive domain? 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. Within the transentorhinal cortex, some theories propose a functional dissociation between the entorhinal and perirhinal cortices, notably with a role of the anterolateral entorhinal cortex in integrating spatial information into the object representations supported by the perirhinal cortex (Yeung et al., 2019). However, most recent imaging studies in preclinical and prodromal AD do not reach sufficient spatial precision to infer any functional dissociations between anterolateral entorhinal and perirhinal cortices. This question should thus be further investigated in future studies.

In addition, beyond the transentorhinal cortex, the use of representations will likely engage distinct connected cerebral networks as a function of the domain. Some of the reviewed studies suggested the involvement of additional brain regions (Supplementary Table 1). For instance, performance in semantic tasks was also related to the volume or gray matter density of anterior and lateral temporal and inferior prefrontal regions (Joubert et al., 2010; Venneri et al., 2008; Wright et al., 2022), which are key structures in the cerebral network of semantic memory (Jefferies, 2013; Lambon Ralph & Patterson, 2008). For perceptual integration of objects, faces and other conjunctive stimuli, fMRI studies suggest a contribution of regions from the posterior ventral visual stream (O'Neil et al., 2009; Parra et al., 2014; Staresina & Davachi, 2010). It might be that some networks involve brain regions that are affected in other pathologies than AD. For example, 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 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. This tool should include a control condition of equal difficulty for a population of non-risk older adults to probe the specificity of the impairment to entity-level discrimination. This control task could involve representations relying on brain structures that are spared in the early course of AD, such as representations of complex associations or scenes that rely on the hippocampus (Yonelinas, 2013) or representation of basic perceptual features that depend on posterior occipitotemporal areas (Patterson et al., 2007). Considering the topographical progression of neurodegeneration (Braak & Del Tredici, 2018), one predicts that the first cognitive deficit will concern representations of entities when the pathology is restricted to the transentorhinal cortex, followed by deficit in tasks relying on representations of complex associations such as scenes when the pathology invades the hippocampus (Bastin et al., 2019). Tasks requiring representations of stimuli based on low-level features should remain intact until the dementia stage.

Finally, test format matters. Tasks that require reconstructive processes (e.g., reconstruction of pairings, yes-no recognition memory tasks) recruit executive functions and prefrontal areas more than tasks with no such demands (Bastin & Besson, 2021; Gellersen et al., 2021, 2023). As prefrontal dysfunction is observed in several age-related conditions, from healthy aging to neurological disorders (Maillet & Rajah, 2013), tasks that minimize the contribution of executive functions should be more specific to early cognitive changes due to the transentorhinal pathology. Ideal tasks would involve forced-choice decisions, graded judgments such as frequency ratings, or indirect measures of performance such as eye-movement patterns specific to conditions of interest.

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, the goal of having a test that detects early signs of cognitive decline due to AD is within reach.

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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. Both contributed equally to the revision.

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