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Perirhinal cortex is associated with fine-grained discrimination of conceptually confusable objects in Alzheimer's disease

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ABSTRACT

The perirhinal cortex (PrC) stands among the first brain areas to deteriorate in Alzheimer's disease (AD). This study tests to what extent the PrC is involved in representing and discriminating confusable objects based on the conjunction of their perceptual and conceptual features. To this aim, AD patients and control counterparts performed 3 tasks: a naming, a recognition memory, and a conceptual matching task, where we manipulated conceptual and perceptual confusability. A structural MRI of the antero-lateral parahippocampal subregions was obtained for each participant. We found that the sensitivity to conceptual confusability was associated with the left PrC volume in both AD patients and control participants for the recognition memory task, while it was specifically associated with the volume of the left PrC in AD patients for the conceptual matching task. This suggests that a decreased volume of the PrC is related to the ability to disambiguate conceptually confusable items. Therefore, testing recognition memory or conceptual matching of easily conceptually confusable items can provide a potential cognitive marker of PrC atrophy.

1. Introduction

It is well-established that the medial temporal lobe (MTL), comprising the hippocampus, entorhinal (ErC), perirhinal (PrC) and parahippocampal cortices, is critical for declarative long-term memory (Squire et al., 2004). In this system, the PrC, composed of Brodmann's areas (BA) 35 and 36, has received increasing interest in the last decades with a particular focus on its role in cognition (for a review, see Suzuki and Naya, 2014). The PrC plays a key role in memory-related behaviors such as the ability to recognize a previously experienced stimulus (Squire et al., 2007) and especially using familiarity, as opposed to recollection (e.g., Brown and Aggleton, 2001). For instance, a rare lesion-based human neuropsychological case, which had a surgical resection of a large portion of the PrC sparing the hippocampus, presents impaired familiarity with preserved recollection (Bowles et al., 2007). This line of evidence has also received strong support from a wide variety of neuroimaging studies (see Bastin et al., 2019, for review).

The MTL is widely connected with the neocortex, and the PrC receives much of its neocortical input from the ventral visual stream (Suzuki and Amaral, 1994), which is critical to build perceptual representations of objects (Lee et al., 2012). This has led some researchers to interpret the PrC as an extension of the representational hierarchy within the ventral visual stream for object identification (Murray and Bussey, 1999), making this cortex responsible for processing and storing representations of complex feature conjunctions (Bussey and Saksida, 2007). Based on this idea, Bussey et al. (2002) introduced the perceptual–mnemonic/feature conjunction model that emphasizes the conjunctive processing function of the PrC, required to perform fine-grained perceptual discrimination between highly similar objects composed of overlapping features. This model has been supported by multiple subsequent imaging and lesion studies, which have linked the PrC with fine-grained visual discrimination of perceptually ambiguous objects (e.g., Barense et al., 2007; Buckley and Gaffan, 2006; Bussey et al., 2005; Inhoff et al., 2019). In addition, some recent lesion and neuroimaging studies have suggested that this role of fine-grained object discrimination could be extended to the antero-lateral ErC (alErC) onto which the PrC projects directly, through the integration of the object with additional spatial features (Connor and Knierim, 2017; Ferko et al., 2022).

Nevertheless, not all inputs received by the PrC come from the ventral visual stream. Indeed, the PrC also receives multi-modal projections, such as from the insular cortex and area 13 of the

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orbitofrontal cortex (Suzuki and Amaral, 1994), and is also part of the anterior temporal lobe, that is considered by predominant semantic memory models as a semantic hub responsible for the amodal integration of conceptual information (Patterson et al., 2007; Ralph et al., 2016). As such, the left PrC has recently been identified as key for the integration of the meaning of object representations derived from visual information (Clarke and Tyler, 2015; Martin et al., 2018; Price et al., 2017; see Bastin et al., 2019) and is recruited when conceptually confusable objects must be differentiated (Bruffaerts et al., 2019; Clarke and Tyler, 2015; Kivisaari et al., 2012; Wright et al., 2015). Therefore, the cognitive role of the PrC is not only dealing with the conjunction of perceptual features but also with the conjunction of conceptual features (Martin et al., 2018), even though it is sometimes difficult to distinguish between a perceptual and conceptual feature (e.g., "has four legs"). This also implies that the PrC should not be confined to a role in mnemonic similarity tasks (Kent et al., 2016) developed under Yassa and Stark's model of pattern separation (Yassa and Stark, 2011). Indeed, under the assumption of a role in conceptual or perceptual disambiguation, its function is thus not restricted to memory, nor to discrimination between similar exemplars of the same concept but also to discrimination between exemplars representing different concepts or percepts, as long as they overlap. Taken together, these theories seem to point to the idea that the role of the PrC could be better understood by considering the type of representation it underlies (i.e., fine-grained representation of fully specified object concepts), rather than the type of process it supports (episodic memory vs. semantic memory vs. perception) (Sheldon et al., 2019; Bastin et al., 2019). However, as to what type of representation it precisely supports, the question remains elusive to date.

Critically, the study of the cognitive function of the PrC is particularly relevant in the frame of Alzheimer's disease (AD) research. AD-related neuropathology starts years before the onset of behavioral symptoms leading to AD diagnosis and occurs as an accumulation of tau neurofibrillary tangles propagates in the brain (see Sexton et al., 2022). More precisely, stage 1 of AD concerns the transentorhinal cortex, corresponding to BA35 within the PrC and to the alErC (see Braak and Braak, 1991, 1997). As such, one may predict that patients diagnosed with AD should display impairments when it comes to recruiting the cognitive functions supported by this region. It has recently been proposed that the very first impairment occurring early in the course of AD would thereby affect representations at the level of the entity by binding its perceptuo-conceptual features enabling it to differentiate it from similar but distinct entities (Bastin and Delhaye, 2023).

While studies exploring familiarity processing in patients with AD or with Mild Cognitive Impairment (MCI) at risk of AD led to inconsistent results (see Koen and Yonelinas, 2014; Schoemaker et al., 2014), some studies showed evidence for impairments in MCI patients to perform tasks requiring the fine perceptual discrimination of objects (Newsome et al., 2012; Yeung et al., 2013). Moreover, recent work showed that the volume of the alErC significantly and selectively predicts the processing of the spatial arrangement of conjunctive objects features in healthy aging (Yeung et al., 2017) as well as the ability to discriminate in memory between similar objects despite being differently presented at recognition using familiarity in amnestic MCI patients (Besson et al., 2020). In addition, studies have also reported a greater vulnerability to distinguish between distinctive features (e.g., "has stripes") than shared ones (e.g., "has four legs") early in the course of AD, causing close concepts to become gradually supported solely by shared features, and eventually merge these concepts together into a single unit (Laisney et al., 2011). This degradation was shown across a variety of tasks where distinctive features were manipulated such as in naming (Garrard et al., 2005), semantic priming (Laisney et al., 2011), or recognition memory (Flanagan et al., 2013). Finally, 2 studies have demonstrated an impaired capacity in AD patients to name (Kivisaari et al., 2012) and to discriminate in memory (Kivisaari et al., 2013) what the authors considered as "confusable" concepts, and this impairment was related to the atrophy of the left medial PrC.

Yet, these aforementioned studies considered "conceptual confusability" between object concepts as the distinction between belonging (confusable) or not (not confusable) to the same category-domain (living vs. non-living). In other words, in these studies, all living things were considered more "confusable" than non-living things. This is based on the idea put forward by some models of semantic memory that living things are inherently more confusable than non-living things due to their conceptual structure (see the Conceptual Structure Account; see Clarke and Tyler, 2015, for review). According to these models, concepts confusability could be precisely characterized by computing their feature-based statistics using feature-based matrices, where conceptual confusability would be defined by the number of conceptual features that they share, their tendency to co-occur, as well as the number of distinctive features that a particular concept has as compared to other concepts from the same category. Depending on these measures, a concept might be more or less confusable with other concepts. Yet, despite the fact that living concepts are thought to be inherently more confusable in nature because they share a greater number of features that tend to co-occur more often, and tend to have less distinctive features, there should still be more and less confusable concepts in both living and non-living domains. On this basis, Wright et al. (2015) developed a quantitative measure of the sensitivity to conceptual confusability, which relates performance to a quantitative distance between objects, based on their internal conceptual structure defined by their features. Thereby, this method goes beyond the approximative distinction between living vs. non-living used in previous studies (Kivisaari et al., 2012, 2013). Here we suggest that this method can then also be extended to perceptual distances between objects. Yet, to date, no study has ever used it to assess sensibility to perceptual confusability.

In this study, with the aim to better characterize the cognitive role of the MTL regions, and more specifically of the PrC region, we tested the hypothesis according to which this region is involved in conceptual and/or perceptual fine-grained discrimination, regardless of the type of memory involved, be it semantic or episodic, or the type of task. To do so, we sought to better quantify and characterize conceptual confusability among living and non-living things. We implemented several tasks assessing a variety of cognitive functions all requiring fine conceptual discrimination (naming task, subsequent recognition memory and conceptual matching task). Across these tasks, we manipulated conceptual similarity across the living and non-living things, using the quantification metrics of conceptual similarity developed by feature-based models. In addition, for the recognition memory task only, we accounted for the perceptual similarity between to-be-discriminated items (see Wright et al., 2015 and Naspi et al., 2021 for a similar method, and Section 2 for details). Our main hypothesis was that in both the recognition memory and conceptual matching tasks, the higher conceptual similarity would be related to the integrity of the left PrC in patients with AD but not in control participants. Indeed, we expected patients' variability in volumes and cognitive scores to come predominantly from a similar factor (the AD pathology within the transentorhinal region) while controls' variability—in the absence of such a common factor—to come from a more diverse set of factors not necessarily affecting simultaneously volumes and cognitive scores.

Table 1
Demographic information and comparison of the neuropsychological evaluation between AD patients and control participants (*t*-tests)

	AD patients mean (SD)	Control participants mean (SD)	*p*-value
Female/Male	10/14	11/12	
Age	74.79 (6.30)	72.26 (4.18)	0.113
Education	12.46 (3.09)	13.09 (3.34)	0.506
MoCA	21.00 (3.16)	27.43 (1.27)	< 0.001
Letter fluency	16.29 (7.36)	18.96 (4.47)	0.142
Category fluency	18.62 (6.83)	26.26 (5.32)	< 0.001
WAIS-3 digit symbol substitution	16.37 (14.50)	18.91 (18.72)	0.605
WAIS-3 vocabulary	31.85 (9.09)	37.21 (7.82)	0.056
WMS-3 Logical Memory immediate recall	7.96 (3.42)	13.13 (3.44)	< 0.001

Key: AD, Alzheimer's disease; MoCA, Montreal Cognitive Assessment; WAIS, Wechsler Adult Intelligence Scale; WMS, Wechsler Memory Scale.

2. Methods

2.1. Participants

A total of 24 patients diagnosed with mild probable AD (clinical criteria from McKhann et al., 2011) and 23 control participants took part in the study. They were matched in terms of age and education level. All participants were community-dwelling individuals; they were all French-speaking, had a normal or corrected-to-normal vision and reported no neurological or psychiatric history (except for the disease in the case of AD patients). They all underwent a short neuropsychological evaluation. Demographics and neuropsychological data are shown in Table 1. The study was approved by the Ethics Committee of the Medicine Faculty of the University of Liège. Participants signed an informed consent form prior to taking part in the experiment.

2.2. Materials

Two hundred seventy-six object concepts were selected from 16 categories of living and non-living things from existing feature norms (Centre for Speech, Language and the Brain property norms, Devereux et al., 2014) and were translated into French. Each selected concept was associated with a picture representing the object it defines. In a pilot test, an independent group of 10 young participants evaluated the exemplarity of the picture for the concept label on a scale from 1 (not representative at all) to 7 (very representative). Pictures received mean exemplarity judgments of 6.18 (range: 4.5–7). Concept pairs (e.g., target-distractor pairs in the memory task, or test pairs in the conceptual matching task) were characterized by an index of conceptual similarity as the cosine between their production frequency vectors within the feature norms database (McRae et al., 2005). We also extracted measures from the Conceptual Structure Account representing the interaction between feature sharedness and their correlational strength ('correlation × distinctiveness', C × D), which represents the extent to which concepts are distinctive (with more or less distinctive features, that more or less co-occur with one another) and thus, whether they will be more easily identified or will require additional differentiation processes.

In addition, perceptual distances between stimuli pairs in the episodic recognition task were computed using the HMax computational model of vision (available at http://cbcl.mit.edu/software-datasets/standardmodel), following Clarke et al.'s study (2015). HMax models different hierarchical stages of the ventral processing stream in different layers, progressing from early visual cortex (V1/V2) to the posterior inferior temporal cortex (IT). The C1 layers correspond to increasingly position- and scale-invariant early visual cortex (V1/V2) that maintain feature specificity, while C2 layers simulate the extrastriate visual area cells (V4/IT) that integrate visual features from previous layers to represent object shape. Measures based on these 2 layers have been validated in studies of visual object recognition that have distinguished the time courses and neural correlates of semantic versus visual processing (Clarke and Tyler, 2014; Clarke et al., 2015). Here, we captured the C1 and C2 responses of HMax IT (hence respectively capturing low- and mid-level visual object information (Riesenhuber and Poggio, 1999; Serre et al., 2007), on our images resized to 92 × 92, using the same setting (i.e., Serre et al., 2005) and precomputed S2 features from natural image fragments). Principal components analyses were then performed on each matrix, concatenating respectively C1 and C2 features across all stimuli, and only the respectively 12 and 6 best components were kept and concatenated in a single matrix of 18 visual features per stimuli. The perceptual distance between 2 stimuli was then computed as the euclidean distance between the 18-values vectors of each stimulus.

2.3. Procedure

Participants completed 3 tasks: a naming task, a recognition memory task, and a conceptual matching task. These tasks are described in the following.

2.3.1. Naming task

Ninety-six pictures of object concepts were presented one by one on a monitor for 3 seconds, preceded by a fixation cross (500 ms) and followed by a blank screen (500 ms). Half of the pictures represented living things and the other half represented non-living things. Participants were asked to name the object represented in the picture at a basic level within the 3 seconds presentation to avoid any ceiling effects, especially in control participants. Participants' verbal answers given within the 3 seconds presentation of the stimuli were collected by the experimenter using a dedicated answer sheet. The naming task served as the incidental encoding for the subsequent forced-choice recognition memory task that directly followed.

2.3.2. Recognition memory task

Sixty unique pictures (30 living and 30 non-living) from the naming task were randomly selected and matched with a distractor from the same subordinate categories (e.g., birds, mammals, etc.) (Fig. 1). Each target-distractor pair was associated with an index of their conceptual distance extracted from the feature-norms database (cosine), as well as with an index of their perceptual distance. There was no difference in conceptual distance between living and non-living pairs ($M_{\text{Living Pairs}}$ = 0.74 vs. $M_{\text{Non-Living Pairs}}$ = 0.72, t = 0.30, df = 58, p = 0.765) but this was not true for perceptual distance, with non-living pairs being more perceptually distant than living pairs ($M_{\text{Living Pairs}}$ = 3.75 vs. $M_{\text{Non-Living Pairs}}$ = 4.53, t = −3.24, df = 58, p = 0.002). Each trial began with a fixation cross (500 ms) followed by the target-distractor pairs. Each pair was presented on the monitor for 3 seconds and ended with a 500 ms blank screen. Within the 3 seconds presentation, participants were asked to indicate which of the 2 presented pictures was presented in the previous naming task using the right and left arrows of the keyboard.

2.3.3. Conceptual matching task

Trials for the conceptual matching task began with a fixation cross (500 ms) followed by a word-picture pair (120 trials in total)

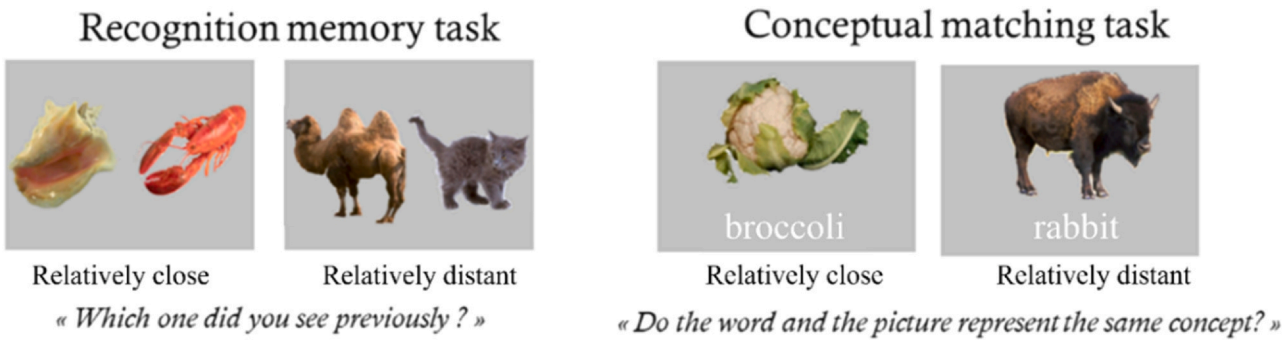

Fig. 1. Example of trials from the recognition memory task (left) and of the conceptual matching task (right) for living object concepts, illustrating concepts from higher versus lower conceptual distance values from the distribution of our sampled materials.

presented for 3 seconds and ended with a 500 ms blank screen. In half of the pairs, the picture matched the concept label (filler trials), while in the other half, the word and the picture did not correspond to the same concept, although the 2 concepts represented by the word and by the picture belonged to the same superordinate category. Cosine similarity was computed between each word-picture non-matching pair, half of the non-matching trials being livings, and the other half, non-livings. There was no difference in conceptual distance between living and non-living pairs ($M_{\text{Living Pairs}}$ = 0.34 vs. $M_{\text{Non-Living Pairs}}$ = 0.35, t = −0.25, df = 118 p = 0.892). Participants were instructed to determine whether the word referred to the same concept as the one represented in the picture or not (Fig. 1). Participants answered verbally, and their answers were encoded by the experimenter using the response keys “1” or “2”.

2.4. MRI acquisition

Images were acquired on a 3 T Siemens Prisma scanner with a 64-channel head coil. Two anatomical images were acquired: a T1-weighted structural Magnetic Resonance Imaging (MRI) (acquisition matrix = 240 x 256 x 224, voxel size = 1 x 1 x 1 mm^3) and a high-resolution T2-weighted structural MRI (acquisition matrix = 448 x 448 x 60, voxel size = 0.4 x 0.4 x 1.2 mm^3) with a partial field of view covering the entire MTL with an oblique coronal orientation perpendicular to the long axis of the hippocampus. The quality of each image was systemically visually checked, especially the T2-MRI that is highly sensitive to movement (after reminding the participant to stay still during the entire following 8 minutes of acquisition). When T2-MRI was acquired twice (N = 14), we chose the image with the best quality for further processing.

2.5. Volume segmentation

High-resolution T2-MRI was labeled using the Automatic Segmentation of Hippocampal Subfields software package using an atlas package available online (“ashs_atlas_upennpmc_20161128,” from the NITRC repository made available on Automatic Segmentation of Hippocampal Subfield (ASHS) website) (Yushkevich, Amaral, et al., 2015). This atlas package was generated from images manually segmented following classical documentation for the hippocampus segmentation (Adler et al., 2014; Duvernoy, 1988) and Ding and van Hoesen (2010) procedure for the entorhinal cortex (ErC) and PrC segmentation (the landmark used by this manual protocol for the anterior extent of the PrC—i.e., 2 mm anterior to the first slice of the hippocampal head—cuts off an anterior portion of the PrC (see also Yushkevich et al., 2015). The hippocampus, the ErC, BA35, and BA36 in the left and right hemispheres were thereby labeled in each participant. Each ASHS output was visually checked for quality control. For the ErC and PrC subregions, volumes were normalized by the extent of their segmentation in the slice direction (hippocampal axis), dividing their volume by the product of the number of slices and the slice thickness (Yushkevich et al., 2015). In addition, regional volumes were adjusted before analyses to account for the total estimated intracranial volume (ICV) for each participant using the formula $\text{Volume}_{\text{adjusted}} = \text{Volume}_{\text{raw}} - \beta_{\text{ICV}}(\text{ICV}_{\text{indiv}} - \text{ICV}_{\text{mean}})$, where β refers to the regression coefficient of the model on a given regional volume of interest while using ICV as a predictor, based on extensive prior work (e.g., Delhaye et al., 2019; Gellersen et al., 2023; Yeung et al., 2017).

2.6. Data analyses

The data were analysed with R version 4.1.2 (Team R Core, 2021). We analysed the accuracy on the 3 behavioral tasks on a trial-by-trial basis with binomial Generalized Linear Mixed Models (GLMMs) to account for the binary outcome (0, 1) of the dependent variable. These models fit with the package *lme4* (Bates et al., 2015). This model was run on the accuracy of the naming task with the group (AD, control) as a between-subjects factor, domain (living, non-living) as a within-subject factor, and C × D (to account for conceptual confusability) as a continuous factor (centered scale). Additionally, the participant’s ID and trial number were set as random factors. Another binomial GLMM was run for the recognition memory task with conceptual distance and perceptual distance based on the indices of perceptual and conceptual distance (both centered scale) as continuous factors. A third GLMM as that for the recognition memory task was run for the matching task with the same factors, with the exclusion of perceptual distance (because the pairs consisted of a word and a picture). Following these GLMMs, pairwise comparisons were used with Tukey’s adjustments when there were multiplicity issues using the *emmeans* package (Lenth et al., 2020) and the function *lstrends* from *lsmeans* package to deal with continuous factors; estimated marginal means (EMMs) from the models are reported. Plots of the results were obtained using the *ggplot2* package (Wickham, 2011) and error bars represent standard errors.

To investigate the recognition memory and matching tasks in relation to the integrity of the sub-hippocampal regions, we used a measure of the “accuracy sensitivity to conceptual/perceptual similarity”. To compute this measure, we adapted Wright et al. (2015)’s method by correlating each participant’s accuracy to the conceptual distance value on a trial-by-trial level using Pearson correlations and then transforming each Rho-value obtained for each participant by a Fisher transformation to give a Z-score. We also implemented the same method to compute a measure of “accuracy sensitivity to perceptual similarity” using the perceptual distance in the recognition memory task only. We then examined how these

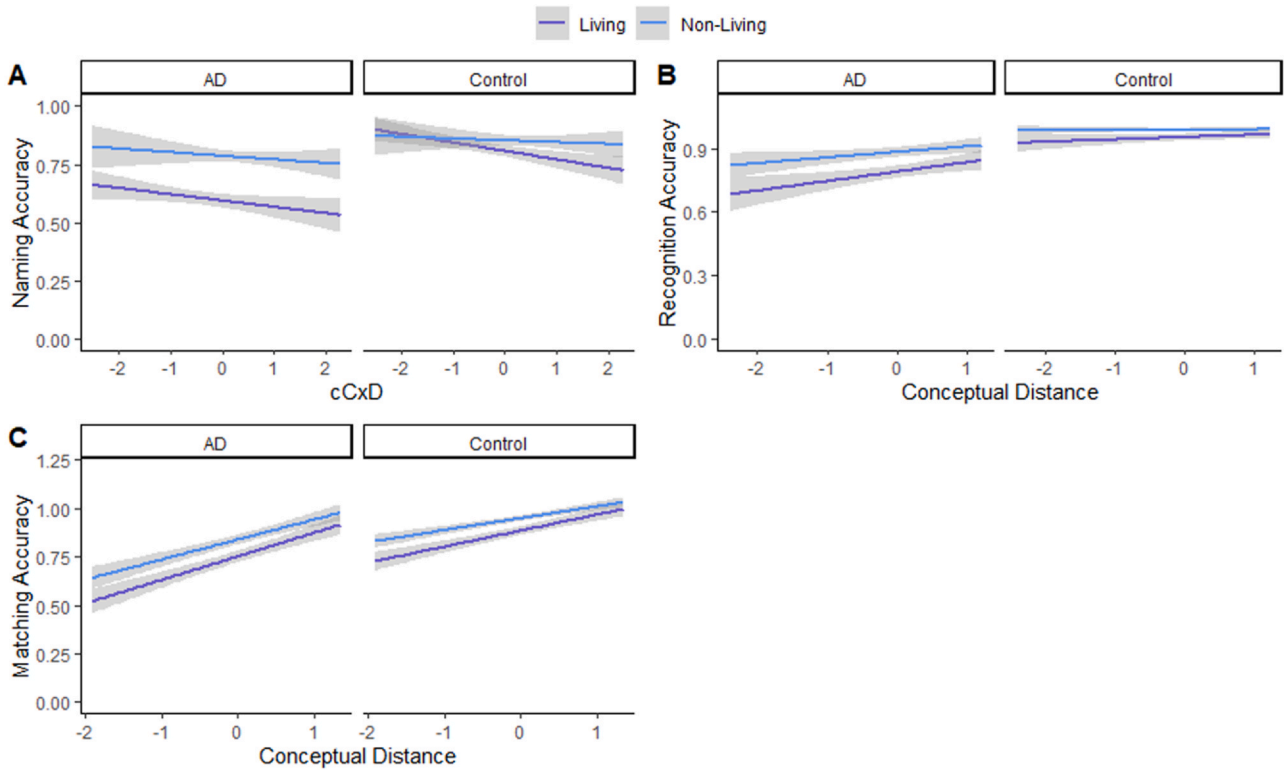

Fig. 2. Naming accuracy as a function of group, domain, and C × D (A), recognition memory accuracy (B), and conceptual matching accuracy (C) as a function of group, domain, and conceptual distance. Abbreviations: AD, Alzheimer's disease; C × D, correlation × distinctiveness.

scores were associated with 8 volumes of brain regions of interest: left and right ErC, left and right BA35, left and right BA36, and left and right hippocampus score (average of the volumes CA fields, dentate gyrus, and subiculum) separately for AD patients and control participants using multiple regressions. Importantly, these relations were controlled by the cognitive level as evidenced by the score at the MoCA, which was added as a control variable in our regression analyses.[1] Finally, we conducted these analyses separately between living and non-living stimuli for conceptual distance in AD patients only (we did not run these in control participants due to ceiling effects, nor for the perceptual distance, because of the observed significant difference between living and non-living stimuli in terms of this distance).

The data used for these analyses as well as the analytic codes are publicly available on the Open Science Framework repository: https://osf.io/r4gfy/.

3. Results

3.1. Naming task

Regarding the accuracy of the naming task, there were main effects of group, $\chi^2 = 22.46$, $df = 1$, $p < 0.001$, and domain, $\chi^2 = 8.45$, $df = 1$, $p = 0.004$, but not of C × D, $p = 0.290$. This indicated that, overall, control participants were more accurate than AD participants ($M_{control} = 0.91$ vs. $M_{AD} = 0.78$) and accuracy was higher for non-living stimuli than for living stimuli ($M_{living} = 0.80$ vs. $M_{non\text{-}living} = 0.90$). Interestingly, group and domain significantly interacted, $\chi^2 = 24.52$, $df = 1$, $p < 0.001$, revealing that whereas accuracy was similar between living and non-living stimuli for control participants ($M_{living} = 0.90$ vs. $M_{non\text{-}living} = 0.92$, $p = 0.250$), it was higher for non-living stimuli than for living stimuli in AD participants ($M_{living} = 0.64$ vs. $M_{non\text{-}living} = 0.87$, $p < 0.001$; Fig. 2). Control participants showed higher accuracy than AD participants for both living and non-living stimuli, $ps < 0.026$. Naming was not influenced by conceptual confusability.

3.2. Recognition memory task

Regarding accuracy on the recognition memory task, the analysis revealed the main effects of group, $\chi^2 = 37.35$, $df = 1$, $p < 0.001$, domain, $\chi^2 = 8.75$, $df = 1$, $p = 0.003$, and conceptual distance, $\chi^2 = 7.66$, $df = 1$, $p = 0.006$, but not of perceptual distance, $p = 0.751$. Overall, control participants were significantly more accurate than AD patients ($M_{control} = 0.99$ vs. $M_{AD} = 0.88$), accuracy for non-living stimuli was significantly higher than for living stimuli ($M_{living} = 0.94$ vs. $M_{non\text{-}living} = 0.97$) and the estimated marginal mean of linear trend for conceptual distance was positive (1.98) meaning that accuracy significantly increased as conceptual distance increased (Fig. 2). No interactions were significant, $ps > 0.168$.

Table 2 shows the results of the multiple regression assessing the relation between accuracy sensitivity to conceptual similarity and the volume of the different brain regions within the MTL. As indicated in Table 2, only the left BA36 was significantly associated with accuracy sensitivity to the conceptual similarity in both AD patients, $t = 2.20$, $p = 0.045$, and control participants, $t = 2.39$, $p = 0.038$. No other regions turned out to be significant in both populations, $ps > 0.088$.

[1] We also explored how the performance at the naming task could explain the relation between the brain volumes and conceptual and perceptual distance in the recognition and matching tasks. Yet, as these analyses did not reveal any significant effect of the naming performance, see Analytic Code "Supp_Analyses_NamingVar_AD.R" on https://osf.io/r4gfy/.

Table 2
Multiple regressions between accuracy sensitivity to conceptual and perceptual similarity and the volumes of the different brain regions of the MTL for the recognition memory task

	Conceptual similarity						Perceptual similarity					
	Control participants			AD patients			Control participants			AD patients		
Variables	β	*t*	*p*-value	β	*t*	*p*-value	B	*t*	*p*-value	β	*t*	*p*-value
Left BA35	−0.010	−0.574	0.579	−0.017	−1.506	0.154	−0.034	−1.818	0.099	−0.0003	−0.032	0.975
Right BA35	−0.008	−0.916	0.381	0.005	0.492	0.630	−0.006	−0.624	0.546	−0.007	−0.762	0.459
Left BA36	**0.008**	**2.392**	**0.038**	**0.006**	**2.204**	**0.045**	0.001	0.415	0.687	0.0002	0.082	0.936
Right BA36	−0.002	−0.586	0.571	−0.001	−0.404	0.693	0.003	1.218	0.251	0.003	1.140	0.272
Left ERC	0.008	0.743	0.474	−0.005	−0.379	0.7103	−0.0003	−0.025	0.980	0.013	1.366	0.194
Right ERC	−0.030	−1.888	0.088	0.008	0.738	0.473	0.010	0.603	0.560	0.005	0.560	0.585
Left Hippocampus Score	0.010	1.225	0.249	−0.008	−1.638	0.124	0.007	0.673	0.516	−0.002	−0.551	0.590
Right Hippocampus Score	−0.002	−0.313	0.761	0.006	1.257	0.229	−0.002	−0.363	0.724	0.002	0.408	0.689
MoCA	−0.0003	−0.019	0.985	0.002	0.146	0.886	0.024	1.172	0.268	−0.003	−0.306	0.764

Key: AD, Alzheimer's disease; BA, Brodmann areas; ERC, entorhinal cortex; MTL, medial temporal lobe; MoCA, Montreal Cognitive Assessment.

Table 3
Multiple regressions between accuracy sensitivity to conceptual similarity and the volume of the different brain regions of the MTL in the conceptual matching task

	Control participants			AD patients		
Variables	β	*t*	*p*-value	β	*t*	*p*-value
Left BA35	0.007	0.375	0.714	0.024	2.052	0.059
Right BA35	−0.016	−1.206	0.249	0.021	1.896	0.079
Left BA36	−0.0002	−0.041	0.968	**−0.007**	**−2.554**	**0.023**
Right BA36	0.005	1.292	0.219	−0.005	−1.435	0.173
Left ERC	−0.003	−0.210	0.837	−0.015	−1.297	0.215
Right ERC	0.018	1.024	0.324	−0.014	−1.301	0.214
Left Hippocampus Score	0.019	1.558	0.143	0.003	0.552	0.590
Right Hippocampus Score	−0.020	−2.102	0.056	0.002	0.498	0.626
MoCA	0.013	0.478	0.640	0.005	0.351	0.731

Key: AD, Alzheimer's disease; BA, Brodmann areas; ERC, entorhinal cortex; MTL, medial temporal lobe, MoCA, Montreal Cognitive Assessment

Regarding accuracy sensitivity to perceptual similarity, none of the regions of the MTL was associated with this measure for both AD patients and control participants, *ps* > 0.099 (Table 2).

3.3. Conceptual matching task

This analysis revealed a main effect of group, $\chi^2 = 29.84$, $df = 1$, $p < 0.001$, domain, $\chi^2 = 5.45$, $df = 1$, $p = 0.020$, and conceptual distance, $\chi^2 = 34.69$, $df = 1$, $p < 0.001$. Overall, control participants showed significantly higher accuracy than AD participants ($M_{control} = 0.97$ vs. $M_{AD} = 0.87$), accuracy for non-living stimuli was significantly higher than for living stimuli ($M_{living} = 0.90$ vs. $M_{non\text{-}living} = 0.96$) and the direction for conceptual distance was positive (estimated marginal mean of linear trend = 4.32), revealing that accuracy significantly increased as conceptual distance increased (Fig. 2). No interactions were significant, *ps* > 0.083.

Table 3 indicates the results of the multiple regression analyses regarding the relation between accuracy sensitivity to conceptual similarity and the volumes of the different brain regions within the MTL. For AD patients, the analysis yielded significant effects on the left BA36 (PrC), $t = -2.55$, $p = 0.023$, but not on other regions, *ps* > 0.059. For control participants, none of the brain volumes were significantly associated with this measure, *ps* > 0.056.

3.4. Living versus non-living items in the recognition and matching tasks

We applied the same regression analyses to investigate the relation between accuracy sensitivity to conceptual similarity and the brain volumes of the MTL and did so by considering living and non-living items separately for AD patients in both the recognition memory and conceptual matching tasks (Table 4). For the recognition task, these analyses revealed that the right PrC was significantly associated with the accuracy sensitivity measure for non-living items (right BA35: $t = 3.85$, $p = 0.006$; right BA36: $t = -2.65$, $p = 0.033$) but not other regions, *ps* > 0.063. For living items, no significant associations between the accuracy sensitivity measure and any brain regions were significant, *ps* > 0.082.

Regarding the conceptual matching task, no significant associations were found for living items, *ps* > 0.067, whereas for non-living items, both the left and right PrC and ErC were associated with the measure of accuracy sensitivity to conceptual similarity (right BA35: $t = 3.65$, $p = 0.003$; left BA35: $t = 2.30$, $p = 0.037$; right BA36: $t = -2.24$, $p = 0.042$; left BA36: $t = -2.38$, $p = 0.032$; right ERC: $t = -2.26$, $p = 0.040$; left ERC: $t = 2.17$, $p = 0.047$). The right and left hippocampus regions were not significantly associated with the accuracy sensitivity measure, *ps* > 0.319.

3.5. Comparison between mild and moderate AD patients

In light of the results obtained in the previous sections, we conducted exploratory analyses to examine the idea that the matching task might be particularly relevant to track PrC atrophy due to the AD neuropathology, for instance in individuals at risk to develop AD. We ran further analyses on conceptual confusability for the recognition memory and matching tasks by splitting the AD patients tested in our study into 2 groups based on the median of their scores at the MoCA. These low MoCA patients and high MoCA patients were matched in terms of age and education (for demographic information about these 2 groups, see Table S1 in the Supplementary Material). These analyses revealed that the only significant association was between the conceptual matching task

Table 4
Multiple regressions between accuracy sensitivity to conceptual similarity and the volumes of the different brain regions of the MTL for living and non-living stimuli in AD patients in the recognition memory task

	Recognition task						Matching task					
	Living			Non-living			Living			Non-living		
Variables	β	*t*	*p*-value	β	*t*	*p*-value	B	*t*	*p*-value	β	*t*	*p*-value
Left BA35	−0.020	−1.147	0.271	−0.027	−2.206	0.063	0.023	1.333	0.204	**0.026**	**2.299**	**0.037**
Right BA35	−0.009	−0.589	0.565	**0.051**	**3.849**	**0.006**	0.007	0.451	0.659	**0.040**	**3.650**	**0.003**
Left BA36	0.007	1.875	0.082	0.007	2.125	0.071	−0.008	−1.982	0.067	**−0.006**	**−2.377**	**0.032**
Right BA36	0.002	0.417	0.683	**−0.010**	**−2.650**	**0.033**	−0.003	−0.521	0.610	**−0.007**	**−2.243**	**0.042**
Left ERC	−0.005	−0.287	0.778	−0.06	−0.445	0.670	−0.008	−0.430	0.673	**−0.025**	**−2.173**	**0.047**
Right ERC	0.013	0.882	0.419	0.014	1.227	0.259	0.005	−0.314	0.758	**−0.024**	**−2.259**	**0.040**
Left Hippocampus Score	−0.007	−0.947	0.360	−0.007	−0.987	0.356	0.003	0.377	0.712	0.003	0.573	0.576
Right Hippocampus Score	0.008	1.090	0.294	−0.004	−0.519	0.620	−0.0001	−0.017	0.986	0.005	1.033	0.319
MoCA	−0.001	−0.056	0.956	0.021	1.440	0.1930	0.016	0.795	0.440	−0.008	−0.570	0.578

Key: AD, Alzheimer's disease; BA, Brodmann areas; ERC, entorhinal cortex; MTL, medial temporal lobe.

Table 5
Multiple regressions between accuracy sensitivity to conceptual similarity and the volume of the different brain regions of the MTL for AD patients with low scores at the MoCA (≤22; Low MoCA Group) and with high scores at the MoCA (> 22; High MoCA Group) in the recognition memory task and the conceptual matching task

	Recognition memory						Conceptual matching					
	Low MoCA patients			High MoCA patients			Low MoCA patients			High MoCA patients		
Variables	β	*t*	*p*-value	β	*t*	*p*-value	B	*t*	*p*-value	β	*t*	*p*-value
Left BA35	−0.042	−2.308	0.069	−0.042	−2.308	0.069	0.031	1.539	0.184	−0.003	−0.179	0.888
Right BA35	0.0002	0.012	0.991	0.0002	0.012	0.991	0.011	0.717	0.506	−0.063	−3.094	0.199
Left BA36	0.006	1.659	0.158	0.006	1.659	0.158	**−0.011**	**−2.597**	**0.048**	0.015	3.503	0.972
Right BA36	−0.001	−0.353	0.738	−0.001	−0.353	0.738	−0.004	−0.829	0.445	0.005	0.558	0.676
Left ERC	0.006	0.447	0.673	0.006	0.447	0.673	−0.025	−1.665	0.156	0.066	2.814	0.217
Right ERC	−0.003	−0.182	0.863	−0.003	−0.182	0.863	−0.033	−1.888	0.117	−0.010	−0.984	0.505
Left Hippocampus Score	−0.014	−1.686	0.153	−0.014	−1.686	0.153	−0.0001	−0.015	0.989	−0.059	−4.699	0.133
Right Hippocampus Score	0.019	1.733	0.144	0.019	1.733	0.144	0.015	1.204	0.282	0.014	1.489	0.376

Key: AD, Alzheimer's disease; BA, Brodmann areas; ERC, entorhinal cortex; MTL, medial temporal lobe.

and the volume of left BA36 of the AD patients with a low MoCA score ($t = -2.60$, $p = 0.048$). Other associations failed to reach significance, *ps* > 0.069 (Table 5).

4. Discussion

In the present study, we investigated fine-grained episodic and semantic discriminations of both perceptually (for episodic memory only) and conceptually confusable objects and their associations with the integrity of the brain structures of the MTL in AD patients and control counterparts, with the aim to improve our understanding of the role of the PrC region in cognition. More specifically, we used a quantitative measure to capture the structural conceptual and perceptual confusability of objects and their relation to performance to provide refined examinations of how volumes from the MTL structures are associated with finer-grained discrimination in AD (we called this score accuracy sensitivity to conceptual similarity).

First, behavioral results from the naming task showed that AD patients named less object concepts than control participants, but more particularly, that patients had difficulties for naming living stimuli as compared to non-living stimuli, regardless of their confusability, whereas no such difference was found for healthy volunteers. This result is in line with previous reports showing that AD patients experience word-finding difficulties and produce naming errors (e.g., "hippopotamus" for "rhinoceros") to a larger extent than healthy individuals and that these difficulties seem to be especially important for living stimuli (see Laws et al., 2007). Interestingly, when subsequently asked to recognize the previously seen objects on a forced-choice recognition memory task, although AD patients showed poorer recognition memory performance than control participants (e.g., Goldstein et al., 2019), both populations showed lower recognition accuracy for living stimuli than for non-living stimuli, and for both groups and across domains, accuracy was particularly lower when the pairs of items were relatively conceptually close (e.g., seashell and crayfish) than when the pairs showed items that are conceptually distant (e.g., cat and camel). These results are partially consistent with the previous findings showing that AD patients' recognition memory is poorer for living than for non-living stimuli (Kivisaari et al., 2013). Yet, contrary to this study, we found that poorer recognition of living stimuli as compared to non-living stimuli also holds for control participants and that poorer memory in case of high conceptual confusability occurred regardless of the domain. One possible explanation for this difference could be related to the fact that there were 96 stimuli in our naming (and encoding) task whereas, in Kivisaari et al. (2013), there were only 60 stimuli at encoding, therefore potentially making our encoding task costlier. Moreover, in our task, participants had to give their responses rapidly (3 seconds, see Methods), which measures rapid access to the concept, contrary to Kivisaari et al. (2013) who did not use such timing constraints in their design. In addition, this effect of conceptual confusability on memory in healthy subjects is relatively consistent with a study by Montefinese et al. (2015) showing that conceptual proximity between memory targets and lures, calculated using feature norms, induces an increase in false alarm rates, even in young subjects. However, controls' performance on this task is close to the ceiling, limiting the variability in the dataset and potentially hindering statistical effects, so we are cautious about any further interpretations. In addition, a similar pattern was observed for the conceptual matching task.

At the brain level, our analyses focused on the accuracy sensitivity to similarity score (i.e., correlating accuracy with the conceptual or perceptual distance at the trial level for each subject) adapted from

Wright et al. (2015). This method allows for finer conceptualization of conceptual confusability (see also Taylor et al., 2012) than considering objects' confusability as reflected by their domain, either living or non-living, hence using 2 discrete categories. Using this measure, we found that the left PrC (BA36) was associated with greater accuracy sensitivity to conceptual similarity in both AD patients and control participants in the recognition memory task, and in AD patients only in the conceptual matching task, with a trend of an association with left BA35 as well. Altogether, these results support the idea of a hemispheric specialization of the PrC, in accordance with previous findings on the importance of the left PrC in fine-grained disambiguation for highly confusable objects specifically, relative to less confusable ones (see Bruffaerts et al. 2019 for review; Bruffaerts et al., 2013; Clarke and Tyler, 2014; Duke et al., 2017).

In addition, when disentangling stimuli as livings vs non-livings (Table 4) and investigating the association between our measure of accuracy sensitivity to conceptual similarity and the different brain regions in AD patients, we observed strong relations between the volume of the perirhinal and entorhinal cortices, with some interesting lateralization differences depending on the task. For the recognition task, the right PrC (BA35 and BA36) was associated with the measure of accuracy sensitivity for non-living items while, for living items, only the left PrC (BA36) was marginally associated with this measure. In the matching task, on the other hand, both the left and right PrC (BA35 and BA36) and ErC were associated with accuracy sensitivity for non-living items whereas only the left PrC was marginally associated with performance for living items. The association between the ability to disambiguate non-living close concepts and the integrity of the right PrC might be explained by the coarse activation hypothesis (Jung-Beeman, 2005), which argues that semantic processing is coarser in the right than in the left hemisphere. Indeed, non-living stimuli are generally less complex than living stimuli in terms of their conceptual structure, and this might explain why distinguishing highly conceptually similar non-living concepts was more associated with the right PrC in AD patients. As for the left PrC, while it was also involved in the disambiguation of non-living items for the matching task (see also Liuzzi et al., 2019), it was specifically marginally associated with conceptual discrimination of more confusable items (i.e., living) in both tasks, fitting with the idea of a specific left-lateralized involvement of the PrC in fine-grained conceptual disambiguation (see Bruffaerts et al., 2019). Yet, more research is needed at this stage to unravel any potential lateralization of the PrC based on the type of items that have to be disambiguated and the type of task.

Interestingly, our results showed correlations in both patients and controls in the recognition memory task, while only in patients in the conceptual matching task. We did not have expectations as to observing correlations in our control group, with the reasoning that controls' variability in PrC integrity would come from a diverse set of factors not necessarily affecting simultaneously volumes and cognitive scores. These correlations in controls suggest that our measure of sensitivity to conceptual confusability in recognition memory is highly sensitive to variations in PrC volume, and not only to variations due to AD neuropathology, probably due to the episodic nature of the task, known to favor the use of familiarity (Bastin and Vander Linden, 2003), that is also highly reliant on the PrC. As for the matching task, the association between the PrC and accuracy sensitivity to conceptual similarity did not hold for control participants. We interpret this discrepancy in control participants in terms of the nature of the tasks. Indeed, the recognition memory task is tapping at the interface of episodic and semantic processes, leaving room for some variability, especially coming from episodic memory. Conversely, the matching task is purely semantic, where it is not expected that healthy controls would show variability as semantic memory, if anything, improves in aging (Lalla et al., 2022). In line with this idea, we observed that, when splitting the sample according to the MoCA scores, there were non-significant associations between the brain volumes and the accuracy sensitivity to conceptual similarity for the recognition memory task whereas in the matching task, the left PrC (BA36) was associated with this measure only for patients having lower scores at the MoCA. Therefore, it seems that the matching task might not be used as an early marker of PrC atrophy in the course of AD, although future studies using a sample of MCI patients would best allow to answer this question given the statistical limits of median split analyses (DeCoster et al., 2011), and the resulting small sample size for group comparisons and correlational analyses, that call for caution in their interpretation.

Concerning the recognition memory task, the absence of a relation between our measure of sensitivity to perceptual similarity and the PrC was surprising in the light of the extensive literature showing PrC involvement in fine-grained perceptual discrimination (e.g., Inhoff et al., 2019; but see Gellersen et al., 2023). A possible explanation for this result is that the HMax model we used captures visual features from low- and mid-level visual information, which might not finely reflect human perceived similarity. Previous studies have indeed shown that models based on objects' conceptual structure are better predictors of neural activity patterns associated with individual objects than the HMax model (Clarke et al., 2015), as the HMax model does not reflect abstract object information that is not directly related to the visual input, such as semantic domain (livings vs. non-livings) that has been used previously to characterize similarity in association with PrC integrity in healthy and pathological aging (Kivisaari et al., 2012, 2013).

Despite the important new findings evidenced in this study, it has nevertheless some limitations. First, it is now clear that brain volumes are not the most sensitive measure of the presence of AD in the brain, and more refined biomarkers exist to track the presence of AD neuropathology (Jack et al., 2018). Second, we used brain volumes as a proxy of brain function, although we reckon that functional alterations are not linearly linked with structural integrity changes (Jack et al., 2013). Illustrating these 2 limitations, it was convincingly shown that changes to the functional connectivity between MTL sub-regions related to tau pathology are associated with cognitive behavioral measures similar to ours in the absence of structural damage in cognitively unimpaired older adults (Berron et al., 2019). This limitation could thus explain why here, the brain volumes are not associated with cognitive performance for AD patients with higher scores at the MoCA as compared to those with lower scores (Table 5). Yet, our study aligns with a now extensive body of research using this correlational approach, all pointing to a clear association between regional volumes in the transentorhinal region and key cognitive functions such as conceptual and perceptual discriminations, not only in AD, but also in MCI (Delhaye et al., 2019) and in at-risk older adults without complaints (Gellersen et al.,

2023; Olsen et al., 2017; Yeung et al., 2017). In addition, the cross-sectional design employed might not be best to deal with the high variability of the neuro-cognitive profiles of AD patients, which could weaken the associations we investigated here (for a similar point albeit in healthy aging, see Armstrong et al., 2020). Future studies should use a longitudinal design to confirm cross-sectional findings that start to accumulate on the role of perirhinal shrinkage in the ability to disambiguate highly confusable objects across different tasks. Another limitation concerns the fact that our observed group differences for the associations between brain volumes and cognitive measures are based on significant and non-significant effects resulting from different statistical models. We acknowledge that conclusions could be stronger if the statistical design allows for the examination of group interactions in a single model, and if behavioral effects were characterized by significant group interactions, which was not the case.

To conclude, the present study reports that across different tasks, namely a recognition memory task and an item-matching task, the volume of the left PrC accounts for difficulties in the distinction between highly confusable objects, supporting existing evidence on the role of the left PrC in fine-grained conceptual disambiguation of confusable objects, here using refined measures to quantify conceptual confusability.

CRediT authorship contribution statement

Aurélien Frick: Data curation, Formal analysis, Visualization, Writing – original draft, Writing – review & editing. **Gabriel Besson**: Conceptualization, Methodology, Writing – review & editing. **Eric Salmon**: Resources, Supervision, Writing – review & editing. **Emma Delhaye**: Conceptualization, Funding acquisition, Investigation, Project administration, Writing – review & editing.

Disclosure statement

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Verification

We confirm that the work submitted has not been published previously and is not under consideration for publication elsewhere. All authors approved the final version of the manuscript.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neurobiolaging.2023.06.003.

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