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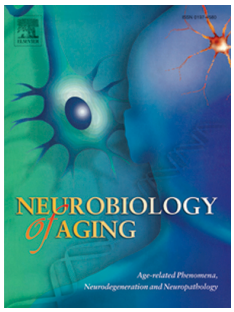

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Emma Delhaye, Mohamed Ali Bahri, Eric Salmon, Christine Bastin

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Impaired perceptual integration and memory for unitized representations are associated with perirhinal cortex atrophy in Alzheimer's disease

Emma Delhaye[1,2], Mohamed Ali Bahri[1], Eric Salmon[1,2,3], Christine Bastin[1,2]

[1]GIGA-CRC In-Vivo Imaging, ULiege, Belgium

[2] PsyNCog, Faculty of Psychology, ULiege, Belgium

[3]Memory clinic, CHU Liege, ULiege, Belgium

Corresponding author: Emma Delhaye

Bât. B30, GIGA-CRC In-Vivo imaging, Allée du 6 Août 8, 4000 Liège 1, Belgium

e-mail: emma.delhaye@uliege.be

Phone: +32 499 61 55 34

Abstract

Unitization, the capacity to encode associations as one integrated entity, can enhance associative memory in populations with an associative memory deficit by promoting familiarity-based associative recognition. Patients with Alzheimer's Disease (AD) are typically impaired in associative memory compared with healthy controls, but do not benefit from unitization strategies. Using fragmented pictures of objects, this study aimed at assessing which of the cognitive processes that compose unitization is actually affected in AD: the retrieval of unitized representations itself, or some earlier stages of processing, such as the integration process at a perceptual or conceptual stage of representation. We also intended to relate patients' object unitization capacity to the integrity of their perirhinal cortex (PrC), as the PrC is thought to underlie unitization and is also one of the first affected regions in AD. We evaluated perceptual integration capacity and subsequent memory for those items that have supposedly been unitized in 23 mild AD patients and 20 controls. We systematically manipulated the level of perceptual integration during encoding by presenting object pictures that were either left intact, separated into two fragments, or separated into four fragments. Subjects were instructed to unitize the fragments into a single representation. Success of integration was assessed by a question requiring the identification of the object. Participants also underwent a structural MRI exam, and measures of PrC, posterior cingulate cortex volume and thickness, and hippocampal volume, were extracted. The results showed that patients' perceptual integration performance decreased with the increased fragmentation level, and that their memory for unitized representations was impaired whatever the demands in terms of perceptual integration at encoding. Both perceptual integration and memory for unitized representations were related to the integrity of the PrC, and memory for unitized representations was also related ~~to a lesser extent~~ to the volume of the hippocampus. We argue that, globally, ~~T~~this supports representational theories of memory that hold that the role of the PrC is not only perceptual nor only mnemonic but instead underlies complex object representation.

Keywords: unitization, Alzheimer's Disease, perirhinal cortex

1. Introduction

Episodic memory relies on the capacity to bind together different pieces of information, such as several items or an item and its context, to form complex memories. While the encoding of arbitrary associations has typically been attributed to the hippocampal function, giving rise to subsequent recollection-based recognition memory, the encoding of simple items is instead thought to be supported by the perirhinal cortex (PrC), which would promote subsequent familiarity-based recognition memory (Bowles et al., 2007; Brown & Aggleton, 2001; Montaldi & Mayes, 2010; Ranganath & Ritchey, 2012). Unitization, which designates the ability to create a perceptually or conceptually integrated and unique representation of an association (Graf & Schacter, 1989) would similarly rely on the PrC (Diana, Yonelinas, & Ranganath, 2010; Haskins, Yonelinas, Quamme, & Ranganath, 2008; Staresina, 2006; Staresina & Davachi, 2008, 2010). Moreover, unitized associations would allow familiarity to support associative recognition (Parks & Yonelinas, 2009, 2015, Yonelinas, 1999, 2002; Yonelinas, Aly, Wang, & Koen, 2010). Consistently, unitization was shown to attenuate the age-related associative deficit in older adults by promoting associative familiarity (Ahmad, Fernandes, & Hockley, 2015; Bastin et al., 2013; D'Angelo et al., 2016; Troyer, D'Souza, Vandermorris, & Murphy, 2011; Zheng et al., 2015). It also proved its worth in the case of amnestic patients with impaired recollection but preserved familiarity (Giovanello, Keane, & Verfaellie, 2006; Quamme, Yonelinas, & Norman, 2007; see also Ryan, Moses, Barense, & Rosenbaum, 2013).

Typical probable Alzheimer's Disease (AD) is characterized by gradually progressive deficits starting with severe impairments in episodic memory (McKhann et al., 2011). Further exploring these deficits, numerous studies showed that both patients with mild cognitive impairment (MCI), thought to be at high risk of developing AD, as well as AD patients, demonstrate altered memory for arbitrary associations (MCI: Algarabel et al., 2012; Atienza et al., 2011; Chen & Chang, 2016; Fowler, Saling, Conway, Semple, & Louis, 2002; Hanseeuw et al., 2011; Oedekoven, Jansen, Keidel, Kircher, & Leube, 2015; Pike et al., 2012; Troyer et al., 2008, 2012; Wolk, Dunfee, Dickerson, Aizenstein, & DeKosky, 2011. AD: Algarabel et al., 2012; Gallo, Sullivan, Daffner, Schacter, & Budson, 2004; Hanaki et al., 2011; Huijbers, Bergmann, Olde Rikkert, & Kessels, 2011; Kessels, Feijen, & Postma, 2005; Lee, Rahman, Hodges, Sahakian, & Graham, 2003; Lindeboom, Schmand, Tulner, Walstra, & Jonker, 2002; Lowndes et al., 2008; Sperling et al., 2003; Wolk et al., 2011). Interestingly, in MCI patients, this impairment has been related to the integrity of the gray

matter in medial temporal regions such as the hippocampus (Chen & Chang, 2016), and to the volume of the entorhinal cortex (Atienza et al., 2011) and hippocampus (Atienza et al., 2011; Hanseeuw et al., 2011; Troyer et al., 2012). One study also showed left anterior hippocampal hypoactivation in response to associative encoding (Hanseeuw et al., 2011), while others revealed, in some MCI patients, hippocampal hyperactivation during encoding of novel pairs of items (Celone et al., 2006; Dickerson et al., 2005; Hämäläinen et al., 2007). In AD patients, studies show a decrease in hippocampal activity when encoding new items pairs (for a review, see Sperling, 2007)

Very few studies have assessed memory for unitized associations in patients with Alzheimer's disease. Bastin et al. (2014) assessed relational (i.e., arbitrary associations) versus conjunctive (i.e., unitized associations) memory in AD patients and found evidence of deficits in both kinds of associative memory. They also showed that poor conjunctive memory was related to hypometabolism in an anterior temporal-posterior occipital brain network encompassing the perirhinal cortex, while relational memory was associated to metabolism in regions of the default mode network. Delhaye et al. (unpublished results) also showed impaired associative memory in AD patients for semantically-related word pairs, such materials being thought to promote bottom-up unitization (Tibon, Gronau, Scheuplein, Mecklinger, & Levy, 2014). Moreover, several studies in working memory suggested that AD patients are impaired at remembering conjunction of visual features (e.g., Della Sala, Parra, Fabi, Luzzi, & Abrahams, 2012; Parra et al., 2008, 2010).

Although more studies are needed to determine whether AD patients could benefit from unitization under specific conditions, the current evidence speaks for an impaired unitization in patients. The existing studies do not allow to disentangle which of the cognitive processes that compose unitization is actually affected. Indeed, the difficulties could lay in the retrieval of unitized associations itself, but another possibility could be that the difficulties stem from earlier stages of processing, such as a failure in the encoding of the integrated representation into episodic memory or, more probably, a deficiency of the integration process itself at a perceptual or conceptual stage of representation. The latter deficit would actually be compatible with findings that MCI and AD patients display impairments of visuoperceptual processing (Alegret et al., 2009; Alegret et al., 2010), particularly prominent for complex object discrimination when objects display highly overlapping features, inducing high interference (Newsome, Duarte, & Barense, 2012). This complex perceptual discrimination function is thought to be sustained by the PrC through its support of very fine-

grained representations (representational-hierarchical view, Bartko, Winters, Cowell, Saksida, & Bussey, 2007; Bussey & Saksida, 2002; Bussey, Saksida, & Murray, 2005; Cowell, Bussey, & Saksida, 2006), and damage to the PrC would thereby compromise complex object representations that are necessary for both memory and perception. In the same vein, Kivisaari, Tyler, Monsch, and Taylor (2012) showed that the volume of the PrC in MCI and AD patients predicted their naming performance for living things, thought to be more similar to one another because they share many features, relative to non-living things that have more distinctive features. Moreover, a recent study showed that intra-item configural processing (i.e., the attention to the spatial arrangement of an object's features) was predicted by the anterolateral entorhinal cortex volume, which is closely adjacent to the PrC (Yeung et al., 2017).

In this context, the current study focused on integration processes that would be prerequisites for successful unitization and aimed at assessing AD patients' capacity to actively form a perceptually fused and complex object representation and evaluating their subsequent memory for these unitized representations. In order to manipulate the level of perceptual integration during encoding, we adapted a paradigm developed by Staresina and Davachi (2010). Concretely, we systematically increased the demands on unitization by presenting object pictures that were either left intact, separated into two fragments, or separated into four fragments, and subjects were instructed to unitize the fragments into a single representation. The actual creation of an integrated representation was evaluated by requiring judgements about objects size, assuming that participants needed to access the complete representation of the objects to identify it and answer the size question. Subsequent memory was assessed by a recognition memory task. Participants also underwent a structural MRI exam and measures of PrC, posterior cingulate cortex (PCC) volume and thickness and hippocampal volume were extracted. We expected that if patients were unable to benefit from unitization due to poor perceptual processing/integration capacities, their performance should already be impaired on the encoding task. In contrast, if unitization deficits were due to impaired encoding or retrieval capacities, AD patients should display altered performance in the recognition memory task only. In both cases, we expected the deficit (if any) to be related to the PrC structural measures specifically, and not to other regions' atrophy.

2. Methods

2.1 Participants

Twenty healthy older adults and 23 patients diagnosed with probable mild AD (MMSE>21) took part in the study. Demographic data are presented in Table 1. All participants were community-dwelling and had normal or corrected-to-normal vision. Healthy older volunteers were recruited from the greater Liège area. None of them reported neurological or psychiatric past disorder, nor did they show any sign of cognitive decline, as confirmed by their score superior to 131 out of 144 on the Mattis Dementia Rating Scale (Mattis, 1973). They were free of medication that could affect cognitive functioning, and reported being in good health. AD patients were recruited from the Liège Memory Clinic and voluntarily participated in the study. AD diagnosis was made according to the diagnostic guidelines provided by the National Institute on Aging-Alzheimer's Association workgroups with positive biomarkers of neurodegeneration on structural MRI and FDG-PET (McKhann et al, 2011).

2.2 Neuropsychological evaluation

All participants underwent a neuropsychological test battery assessing their cognitive functioning in domains such as memory (working and episodic memory), executive function, attention, processing speed, and visual organisation. The following tests were used to assess these domains: (1) memory: forward/backward digit span from the Wechsler Memory Scale-III (WMS-3), the Logical Memory (LM) subtest from the WMS-3, the Doors subtest (part A and B) from the Doors and People test (Baddeley, Emslie, & Nimmo-Smith, 1994); (2) executive function: the Stroop task (Golden & Freshwater, 1978, with the interference score computed according to Bruyer, Van der Linden, Rectem, & Galvez, 1995); (3) attention and processing speed: the Digit Symbol Substitution subtest from the WAIS-3; (4) visual organisation: the Hooper Visual Organisation test (Hooper, 1983). Additionally, the Mattis Dementia Rating Scale was used to describe participants' global cognitive fitness. Unfortunately, one control and 3 patients did not undergo the whole neuropsychological battery because it occurred in a separate session which they could not attend to. Neuropsychological performance is presented in Table 1.

	Controls *Mean (SD)*	AD *Mean (SD)*	*p value*
Demographic data			
Age	71.3 (4.75)	76 (9.24)	.04
Education	14.1 (3.84)	11.05 (4.29)	.02
Gender (F/M)	12/8	7/16	
Mattis Dementia Rating Scale	140.53 (3.63)	120.47 (9.66)	< .001

Memory			
WAIS-3 Digit Span forward length	6.00 (1.15)	5.15 (0.81)	.01
WAIS-3 Digit Span backward length	4.32 (1.67)	3.45 (0.60)	.07
WMS-3 LM immediate recall	21.85 (7.07)	7.57 (5.00)	< .001
WMS-3 LM delayed recall	22.5 (7.86)	3.71 (5.04)	< .001
Doors – part A	10.95 (0.91)	7.55 (2.09)	< .001
Doors – part B	6.74 (2.51)	3.65 (1.60)	< .001
Executive function			
Stroop RT– color naming	71.00 (11.97)	102.95 (44.21)	.01
Stroop – interference score	0.29 (0.09)	0.23 (0.47)	.53
Attention & processing speed			
WAIS-3 Digit Symbol Substitution	56.53 (15.75)	33.05 (10.62)	< .001
Visual Organisation			
Hooper (corrected score)	23.3 (2.70)	14.65 (5.12)	< .001

Table 1- Demographics and neuropsychological profile.

2.3 Materials

The stimuli consisted in 180 coloured object pictures from the POPORO database (Kovalenko, Chaumon, & Busch, 2012). Ninety of these pictures were presented as study items during the encoding phase and the remaining 90 were used as lures during a subsequent recognition memory test. Targets and lures were matched in terms of semantic categories to ensure that memory discrimination is based on perceptual and not conceptual information. Following Staresina and Davachi (2010), the critical manipulation of the experiment was the visual presentation of the target at encoding: either in "zero-fragment" (F0 trials), where the pictures were presented in their visually intact form as one single piece, in two-fragments (F2 trials), where the images were split into two parts, or in four-fragments (F4 trials), where the images were split into four parts. F2 objects were split along the horizontal axis if the object's height exceeded its width and along the vertical axis if its width exceeded its height, and the resulting parts were shifted up-down or left-right, respectively. The four parts in F4 objects were shifted both up-down and left-right. Examples are displayed in Figure 1. The 90 study items were divided into three sets of 30 targets per fragmentation level. The material was counterbalanced so that, across participants, every object was shown in every fragmentation level and was used both as a study item and as a lure for the subsequent recognition memory test.

[insert figure 1 about here]

2.4 Procedure

Participants were tested individually on a laptop computer. During encoding, each trial consisted of the presentation of an object picture. To ensure that participants correctly identified the presented objects, they were instructed to decide whether or not the object could fit into a shoebox, with a possibility to answer "I don't know" if they could not identify the object. Those trials, as well as trials for which incorrect or no response was given, were excluded from all further analyses. The size judgment was chosen rather than an object naming question since AD patients tend to exhibit language impairments (Hodges & Patterson, 1995), as shown by evidence from object naming tasks (Hodges, Salmon, & Butters, 1991). The stimulus remained on the screen for a maximum duration of 6 seconds, and disappeared from the screen as soon as a response was made. After a 1 minute retention interval filled with mental calculation, participants were given a surprise and self-paced recognition memory test consisting of all 90 previously presented pictures (this time, all the pictures were presented in their visually intact form) mixed with 90 novel object lures. Subjects had to indicate whether the object was old (presented during the encoding phase) or new (not presented during the encoding phase). All responses were given orally and encoded by the experimenter.

2.5 MRI acquisition

MRI was performed at the end of the session in all participants. Subjects were equipped with ear plugs and their heads were stabilized with foam pads to minimize head motion. A high-resolution T1-weighted anatomical image was acquired on a 3-Tesla head-only scanner (Siemens, Allegra, Erlangen, Germany) operated with the standard transmit-receive quadrature head coil, using the three-dimensional modified driven equilibrium Fourier transform sequence [3D MDEFT (Deichmann, Schwarzbauer, & Turner, 2004)] with the following parameters: TR/TE/TI = 7.92/2.4/910 ms, FA = 15°, FoV = 256 x 240 x 176 mm^3, 1 mm isotropic spatial resolution.

2.6 MRI data analysis and automatic segmentation

All preprocessing and analyses were carried out using the FreeSurfer software (v5.3.0; http://surfer.nmr.mgh.harvard.edu/). Each subject's MR image was automatically segmented and labelled using the Desikan-Killiani atlas (Desikan et al. 2006) via the processing pipline of FreeSurfer. We obtained volumetric and cortical thickness values for our region of interest (Brodmann's area 35 (BA35), which we will refer to in the results and discussion sections as PrC) (see Augustinack et al., 2013, for more information about the

neuroanatomical boundaries used to define the BA35 perirhinal area as well as about the validation of the segmentation method). In order to assess the specificity of our results in relation with this region, rather than with global cortical atrophy, we also extracted values estimating the volume of the hippocampus and the volume and cortical thickness of the PCC, which are regions that were shown to be affected early in the course of AD (Yushkevich, Pluta, et al., 2015). The FreeSurfer segmented brain regions were subjected to visual inspection and no manual adjustments ~~was required~~ were performed. Examples of the BA35 automatic segmentation by FreeSurfer in healthy older participants and in AD patients are displayed in Figure 2.

[insert figure 2 about here]

2.7 Correction for head size and age

Extracted volumes were corrected for head size and age-induced brain shrinkage using a regression-based method similar to the one used by Yeung et al. (2017). Estimated total intracranial volume (eTIV) was derived from FreeSurfer results. By regressing each region's volume with the eTIV on the one hand, and the age on the other hand, two regression slopes (β) were obtained (representing the effect of eTIV change and age-related change on the volume). Then, volumes were adjusted both for–participant's eTIV and age using the formula:

$$Volume_{adjusted} = Volume_{raw} + \beta_{eTIV}(eTIV_{participant} - eTIV_{mean}) + \beta_{age}(age_{participant} - age_{mean})$$

The corrections were separately computed for each hemisphere. Volumes were subsequently summed across the two hemispheres, giving a single volume for each region and each participant.

Similarly, our measures of thickness were corrected for age-induced brain shrinkage only, using the same regression-based method, by regressing thickness with age. Each participant's regions' thickness was adjusted by each participant's age, using the following formula (with β representing the regression slope for the effect of age on thickness):

$$Thickness_{adjusted} = Thickness_{raw} + \beta(age_{participant} - age_{mean})$$

3. Results

3.1 Behavioural results

We performed a 2 (group: controls, AD) x 3 (fragmentation level: F0, F2, F4) repeated measures ANCOVA on the proportion of correctly identified items at encoding [i.e., (number of items associated with a correct size judgment) / (total number of target items)], with age and education as continuous predictors since groups were not matched for age nor education. The results showed a significant main effect of group with better identification performance in controls than in patients ($F(1,38)= 9.18$, $p < .01$, $\eta^2_p = .19$), but no main effect of fragmentation level ($F(2,76)= 0.03$, $p = .97$, $\eta^2_p = .01$). There was a significant group x level of fragmentation interaction ($F(2,76)= 5.62$, $p < .01$, $\eta^2_p = .13$), with no difference in identification performance between controls and AD patients for F0 trials (Bonferroni, $p = .45$), but a lower performance in AD patients than controls for F2 ($p < .01$, Cohen's d= 5.41) and F4 ($p < .001$, Cohen's d= 1.4) trials (see Figure 3).

[insert figure 3 about here]

A 2 (group: controls, AD) x 3 (fragmentation level: F0, F2, F4) repeated measures ANCOVA was then performed on the proportion of hits in the recognition memory test, after excluding all items that were not correctly identified at encoding. It showed a main effect of group with higher hit rate in controls than in patients ($F(1,38)= 22.04$, $p < .001$, $\eta^2_p = .37$), but no main effect of fragmentation level ($F(2,76)= 0.87$, $p = .42$, $\eta^2_p = .02$). There was no group x fragmentation level interaction ($F(2,76)= 2.21$, $p = .12$, $\eta^2_p = .05$).

A group x fragmentation level ANCOVA was calculated on the false alarms rate, with the fragmentation level variable indicating here the level of fragmentation of the target to which the distractor was matched. The only significant effect was the main effect of group ($F(1,38)= 9.73$, $p < .01$, $\eta^2_p=.2$), with a higher false alarm rate in patients compared with controls. All other Fs were ≤ 1.

We computed a discrimination index *d'* (corrected according to Snodgrass & Corwin, 1988) for each level of fragmentation using the distribution of the targets and their matched distractors. A group x fragmentation level ANCOVA on *d'* scores showed a significant main effect of group ($F(1,38)= 43.2$, $p< .001$, $\eta^2_p=.53$), with patients displaying a poorer discrimination performance compared with controls. All other effects were non-significant (all $Fs < 1$). See Figure 4.

[insert figure 4 about here]

3.2 Volumetric Imaging results

Standard independent samples t tests revealed a PrC atrophy in patients compared with controls, both in the measure of PrC volume (controls: M=4004.74mm^3, SD= 928.31, patients: M=3272.28mm^3, SD= 928.74; t(36)= -2.35, p=.02) and of PrC cortical thickness (controls: M=3.02mm, SD=0.48, patients: M=2.57mm, SD=0.45; t(36)= -2.97, p=.005). T tests also revealed hippocampal atrophy in patients compared with controls (controls: M=7270.77 mm³, SD=919.26, patients: M=5922.06 mm³, SD=1261.93; t(36)= -3.73, p<.001). It did not show any evidence of PCC atrophy in patients, neither in volume (controls: M=5059.61 mm³, SD=888.79, patients: M=4930.1 mm³, SD=849.06; t(36)= -0.46, p=.65) nor in cortical thickness (controls: M=2.43 mm, SD=0.18, patients: M=2.37 mm, SD=0.17; t(36)= -1.14, p=.26).

Because of some multicollinearity between measures, forward stepwise regression analyses were used to assess the influence of PrC, hippocampus and PCC's integrity on perceptual integration performance at encoding and/or on memory discrimination performance for unitized representations. The analyses were run in patients and in controls separately with each variable (proportion of correct identifications at encoding in F0, F2, F4 and discrimination performance in F0, F2 and F4) as the dependent variable, and the volume of the hippocampus and cortical thickness of the PrC and PCC as independent variables. We chose to use cortical thickness measures whenever possible because it showed good predictability for cognitive performance in AD (Dickerson et al., 2008; Dickerson, & Wolk, 2012). Because neuroimaging data were corrected for the effect of age, the same regression-based correction was used here on behavioural data to adjust for the effect of age as well.

For encoding scores, in AD patients, using brain regions integrity measures as predictors revealed that only the PrC cortical thickness was significantly related to perceptual integration performance in F0 (β = .61; F(1,19)= 10.83; p= .004; R^2= .38), F2 (β = .42; F(1,19)= 8.79; p= .008; R^2= .33) and F4 (β = .71; F(1,19)= 19.1; p< .001; R^2= .51). In controls, only the volume of the hippocampus was significantly related to perceptual integration performance in F0 (β = .42; F(1,17)= 4.92; p= .04; R^2= .23) and F2 (β = .45; F(1,17)= 6.77; p= .02; R^2= .3), while the PrC cortical thickness was significantly related to integration performance in F4 (β = .43; F(1,17)= 6.02; p= .03; R^2= .27).

For memory discrimination, in patients, only the PrC cortical thickness was significantly associated with performance in F0 (β = .54; F(1,19)= 13.78; p= .002; R^2= .43) and F2 (β = .51; F(1,19)= 7.38; p= .01; R^2= .29) and only the volume of the hippocampus was

significantly related to performance in F4 (β = .51; $F(1,19)$= 6.32; p= .02; R^2= .26). In controls, none of the regions entered in the regression was significantly related to performance in F0 nor in F4, but the hippocampus was significantly associated with performance in F2 (β = .65; $F(1,17)$= 11.6; p= .004; R^2= .42).

To ensure that the observed association between regions integrity on the one hand and perceptual integration and memory discrimination on the other hand was not simply driven by global cognitive decline, we checked whether the pattern of regressions remained after controlling for variance explained by the Dementia Rating Scale scores that we used to assess cognitive decline. To do so, we entered the score on the DRS as a covariate in the stepwise regression analyses alongside our measures of regional atrophy. Even when the DRS was included as covariate in the model, the pattern of results remained identical both in patients and in controls.

4. Discussion

Alzheimer's disease patients do not benefit from unitization strategies supporting encoding of new associations into memory. The current study explored whether AD impairs some prerequisite operations to unitization. More specifically, this study tested mild AD patients' capacity to (1) form an integrated and complex perceptual representation from separate pieces of visual information and (2) recognize these perceptually unitized representations, in order to determine which of the component cognitive process that allow unitization is affected: the actual retrieval of unitized object representations, or rather the initial stage of perceptual integration even before the encoding step in memory. Perceptual integration was assessed by the ability to provide a size judgment when pictures of objects were presented at three levels of fragmentation (Staresina & Davachi, 2010). Retrieval of unitized representations was evaluated by recognition accuracy for objects likely to have been correctly integrated (because they received a correct judgment at encoding). We expected the measures of these cognitive processes to be related to the atrophy of the perirhinal cortex, which is thought to support, on one hand, the creation of complex perceptual representations (Bartko et al., 2007; Bussey et al., 2005; Bussey & Saksida, 2002, 2005, 2007; Bussey, Saksida, & Murray, 2003; Cowell et al., 2006; Cowell, Bussey, & Saksida, 2010; Murray, Bussey, & Saksida, 2007), and on the other hand, memory for unitized associations (Haskins et al., 2008). We also included the structural integrity of the hippocampus and posterior cingulate cortex as predictors in the model to ensure that any relation between measures of

cognitive processes and integrity of the PrC would be specific rather than reflecting ~~global~~ more extensive AD-related brain atrophy.

The main findings were that AD patients demonstrated increasingly impaired perceptual integration performance with the increase in the demands on perceptual integration processes. Indeed, AD patients' size judgments were as good as those provided by controls when objects were intact, but were poorer as soon as the objects were fragmented. Critically, this impairment was strongly related to the atrophy of the PrC structure specifically. Moreover, patients also presented a global discrimination memory impairment, for single objects as well as, to a similar extent, for the object representations that were correctly perceptually integrated at the encoding stage. Discrimination memory impairment for single objects and unitized representations were also strongly associated with the measures of PrC (F0 and F2 conditions) and~~, to a certain extent~~ of hippocampal structural integrity (F4 condition).

Unitization of associations has been shown to be an efficient way to improve associative memory performance in populations with memory decline (aging, Ahmad et al., 2015; Bastin et al., 2013; D'Angelo et al., 2016; Troyer et al., 2011; Zheng et al., 2015; amnesia, Giovanello et al., 2006; Quamme et al., 2007; Ryan et al., 2013). In Alzheimer's disease, though, previous studies that assessed memory for unitized associations revealed that unitization does not facilitate memory performance (Bastin et al., 2014; Delhaye et al., unpublished results; Parra et al., 2008, 2010), as associative memory remained severely impaired, even more so than memory for arbitrary associations (Bastin et al., 2014). The current study sheds some light on the possible origins of AD patients' failure to benefit from unitization, at least in tasks that involve perceptual unitization. First, when presented with picture fragments, patients often failed to identify the objects, indicating a difficulty to mentally fuse the fragments into a perceptual representation of the object. Second, even when perceptual integration was successful, patients' memory for unitized representations was shown to be equivalent to their memory for single items, and both were impaired. So, the current results suggest that AD patients' previously observed associative deficit might not be attenuated by perceptual unitization because several steps seem to be altered. Indeed, both the creation of a perceptually integrated representation and the retrieval of this unitized representation, similar to single item retrieval, are impaired, these two abilities being moreover related to PrC -and, for retrieval of unitized representations specifically, to hippocampal- ~~(and to a lesser extent for memory discrimination only, hippocampal)~~ atrophy.

In the current study, perceptual integration of object fragments was assessed indirectly with a question requesting to estimate whether the object could fit into a shoe box. Such orienting task has been used previously in order to ensure deep encoding of items (Kirwan, Wixted, & Squire, 2008; Ranganath et al., 2004). One could argue that AD patients' poor performance in the encoding task would merely reflect estimation difficulties (Levinoff et al., 2006). If this was the case, one should have seen poor size judgments in all three conditions. Yet, AD patients performed poorly only when objects were fragmented, suggesting that the need to mentally fuse the fragments was responsible for their decreased performance in the orienting task. Still, in this study, perceptual integration of objects fragments was most probably supported by, and reflects the result of, a series of sub-processes that were not assessed here, such as mental rotation, visuo-spatial construction or visual imagery. The latter was indeed proposed to play a critical role in unitization through its role in fusing or integrating multiple items (Ryan et al., 2013). So, it is possible that patients' impaired performance in perceptual integration stemmed from impairment in one (or several) of these underlying sub-processes, which could themselves be related to other specific -potentially atrophied- brain regions.

Yet, the significant and strong correlation between size judgement performance of AD patients and PrC atrophy for fragmented pictures specifically suggests a role for the PrC in the processes necessary to build an integrated and complex representation in order to identify the objects. Because the correlation strength tracks the level of fragmentation, the data are consistent with studies suggesting that PrC is necessary for forming complex and fine-grained objects representations at the perceptual level. Importantly, here, the PrC was the only region found to be significantly related to performance, emphasizing its specificity for this cognitive process (but see limitations mentioned below). Newsome et al. (2012) indeed showed that MCI patients failed to discriminate between perceptually similar complex objects in a discrimination task, while their performance was improved when the degree of interference between objects was reduced. Kivisaari et al. (2012) also associated MCI and AD patients' PrC volume to their naming performance for living things that are highly similar due to the great number of features that they share relative to non-living things that are more distinctive from each other. Finally, Yeung et al. (2017) provided evidence for an association between the anterolateral entorhinal cortex volume and configural processing, that is, the processing of the arrangements between an object's features, in older participants with varying levels of brain atrophy and of cognitive decline.

Even when perceptual integration was successful, as indexed by correct size judgments, AD patients had impaired memory for objects and this deficit correlated also with PrC (F0 and F2 conditions) and~~, to a lesser extent~~ hippocampal (F4)~~,~~ atrophy. Results from F0 and F2 are consistent with studies that have related the PrC to recognition of single items and of unitized associations (for reviews, see e.g.: Mayes, Montaldi, & Migo, 2007; Ranganath & Ritchey, 2012; Yonelinas et al., 2010) and more specifically to familiarity-based recognition memory for these types of information, as opposed to arbitrary associations that would be recognized using recollection, which is thought to be hippocampus-dependent (Yonelinas, 2002). In MCI, PrC structural integrity has been associated with familiarity-based memory performance (Westerberg et al., 2013; Wolk et al., 2011). Therefore, it may be that the impaired ability of AD patients to recognise previously studied objects in F0 and F2 reflects deficient familiarity, while the impaired recognition of F4 objects related to hippocampal atrophy could represent impaired recollection, which could suggest that F4 objects might have not been recognized as unitized representations. There has been some conflicting results regarding the fate of familiarity in AD and its prodromal stage. Several studies reported impaired familiarity (Algarabel et al., 2012; Ally, Gold, & Budson, 2009; Besson et al., 2015; Gallo et al., 2004; Hudon, Belleville, & Gauthier, 2009 (in AD patients); Pitarque et al., 2016; Westerberg et al., 2013 (in AD patients); Wolk et al., 2011; Wolk, Mancuso, Kliot, Arnold, & Dickerson, 2013; Wolk, Signoff, & DeKosky, 2008), while others showed intact familiarity in the patients (Belleville, Ménard, & Lepage, 2011; Genon et al., 2013, 2014; Hudon et al., 2009 (in MCI patients); Troyer et al., 2012; Wang, Yonelinas, & Ranganath, 2013; Westerberg et al., 2013 (in MCI patients)). Various reasons have been proposed to explain this variability in findings, including methodological differences (Koen & Yonelinas, 2014; Schoemaker et al., 2014). The current findings open the possibility that familiarity could be impaired in AD only when some kinds of representations are needed. Although speculative, a hypothesis could be that the fact that PrC atrophy is related to both perceptual integration and recognition memory is actually due to a common factor, that is, the nature of the representation it processes/underlies.

This finding indeed dovetails with the current views that consider that the role of PrC is not restricted to object visual perception nor to object recognition memory, but supports both processes as soon as a complex representation of an object is needed (Barense, Gaffan, & Graham, 2007; Bussey & Saksida, 2007; Cowell, Bussey, & Saksida, 2010; Graham, Barense, & Lee, 2010; Ranganath, 2010; Ranganath & Ritchey, 2012). So, in line with

current theories about the PrC, the common factor could be the capacity to represent an object as one unique and integrated entity, allowing to avoid any confusion with similar objects sharing many features. Indeed, the role of the PrC has been considered as key in binding together objects' properties in order to form and maintain complex and fine-grained representations, thereby allowing the disambiguation or discrimination of perceptually as well as semantically confusable objects from other similar objects (Bussey & Saksida, 2005; Bussey & Saksida, 2007; Clarke & Tyler, 2015). In accordance with this idea, a study by Kivisaari and colleagues (2013) showed that participants with PrC damage such as ours were more prone to commit false positive responses to confusable distractor objects (sharing many features and with few distinctive features) in a recognition memory task, compared with less confusable ones. This was associated to the integrity of the anterior MTL, comprising the PrC. The authors suggested that object recognition memory performance is driven primarily by the characteristics of distractors and not target stimuli. Similarly, a study by Yeung, Ryan, Cowell, and Barense (2013) assessed recognition memory in older adults at risk for MCI while manipulating the level of interference of the distractors (i.e., the degree of feature overlap with the previously studied item) and showed increased false recognitions for high-interference distractors but not for low-interference ones. In the current recognition memory task, target objects and lures were matched in terms of semantic category in such a way that all distractors could be considered as somewhat confusable so that it may have been necessary to discriminate between targets and semantically similar items calling on complex and fine-grained representations –even though perceptual similarity was not controlled for. Potentially impaired capacity of elaborating these complex, fine-grained representations could thus account for both the perceptual integration deficit shown at encoding and the memory discrimination impairment pattern observed in this study.

Delineation of the PrC has differed in the literature depending on authors and there is no unanimous segmentation protocol (Yushkevich, Amaral, et al., 2015). Still, one important limitation of this study must be pointed out and has to do with the automatic method of segmentation implemented. Indeed, some variability in the extent of the PrC segmentation can be observed throughout our sample, with some brain segmentations being confined to the collateral sulcus, but others sometimes extending medially to the parahippocampal gyrus, thereby overlapping with the ErC territory. Thus, results involving the PrC in this study should be taken with caution as our PrC measure could be imprecise and may rather reflect a blend of PrC and lateral ErC. Still, whether our measure represents PrC's volume exclusively

or a blend of PrC and lateral ErC, both structures are thought to be involved in the process of unitization (through features integration and spatial arrangements integration, respectively). Thus, the current result of impaired perceptual integration in AD –whether it is feature integration or spatial arrangement integration, both necessary for building an integrated and complex object representation- stays highly coherent given these regions' functions as well as in explaining why AD patients tend to fail to benefit from unitization in episodic memory.

In conclusion, the current study suggests that patients with Alzheimer's disease cannot benefit from perceptual unitization because of a failure to create complex representations of objects that would allow to identify and perceptually discriminate these objects, as well as to discriminate them among resembling distractors in a recognition memory task. This deficit appears related to atrophy of the perirhinal cortex, supporting current views attributing a role to the perirhinal cortex in both perception and memory.

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Figure captions

Figure 1 – Illustration of the experimental manipulation with instances of object stimuli presented in zero, two and four fragments

Figure 2 – Illustration of the FreeSurfer automatic segmentation for the BA35 area (in blue) in 3 AD patients (P1 to P3) and 3 healthy older adults (P4 to P6). Images are shown in subject space with subjects' left on image right side.

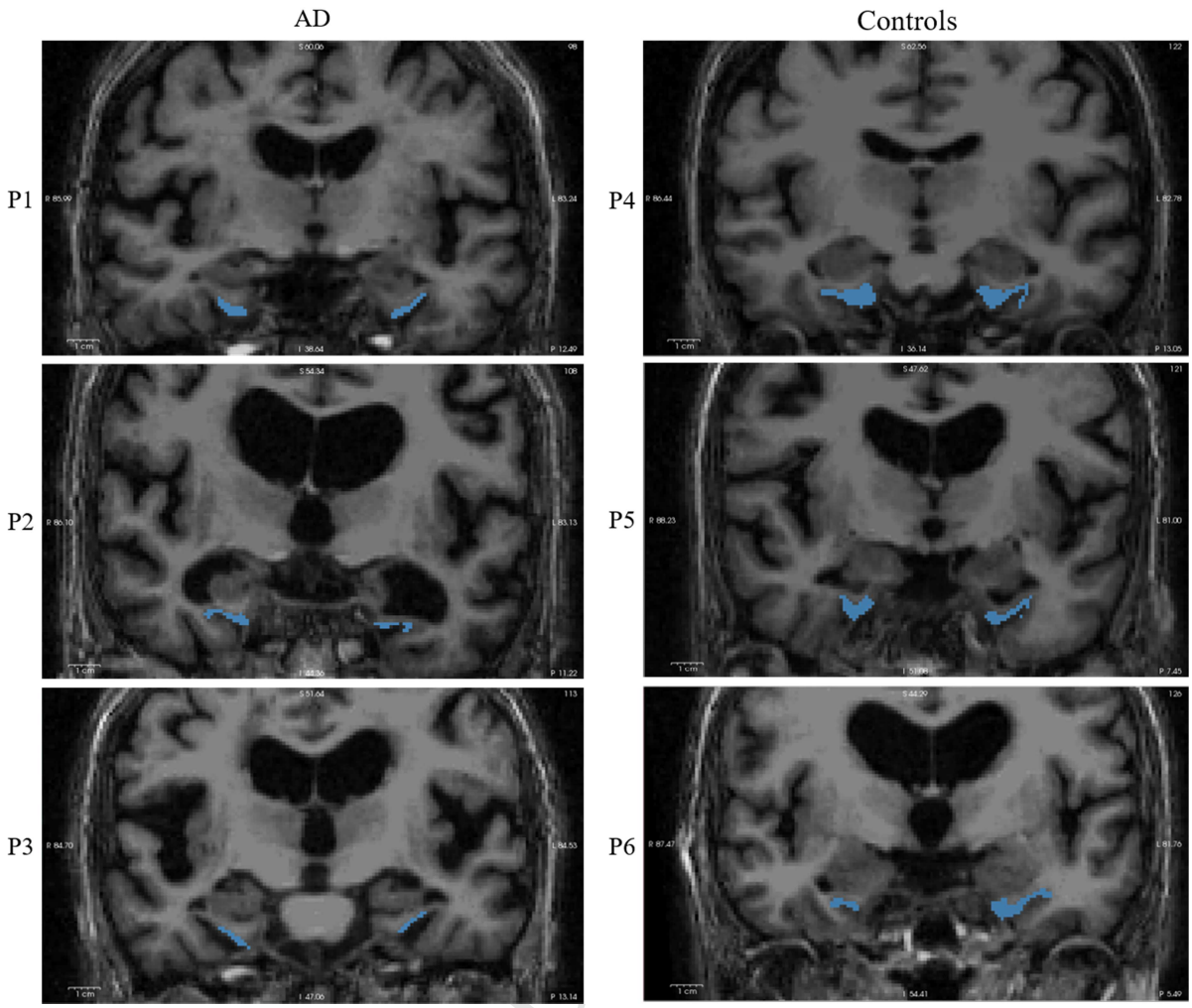
Figure 3- Boxplots of the p~~P~~roportion of correctly identified items across F0, F2 and F4 levels of fragmentation in the study phase. Each circle is a participant. Error bars represent the minimum and maximum points of the distribution, excluding outliers. ** $p < .01$; *** $p < .001$

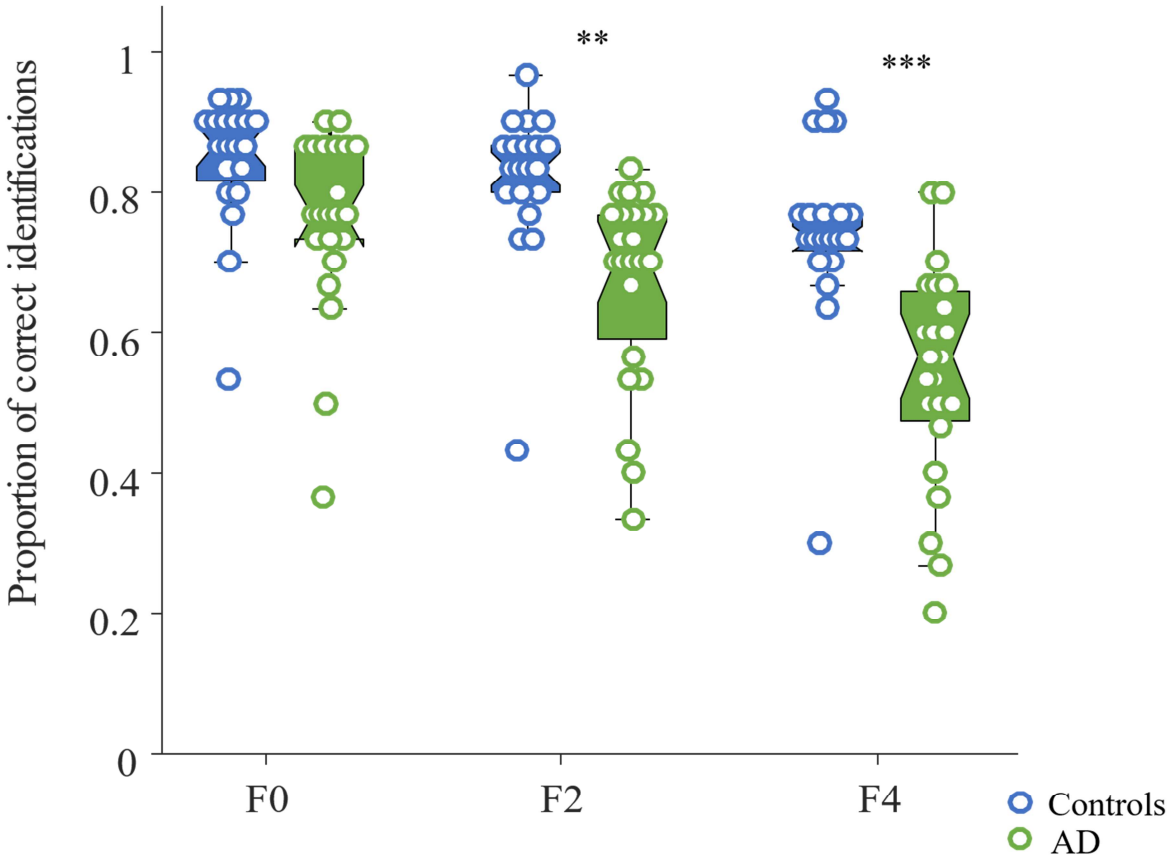
Figure 4 – Boxplots of the discrimination memory performance in the recognition memory test for F0, F2 and F4 trials. Each circle is a participant. Error bars represent the minimum and maximum points of the distribution, excluding outliers. *** $p < .001$

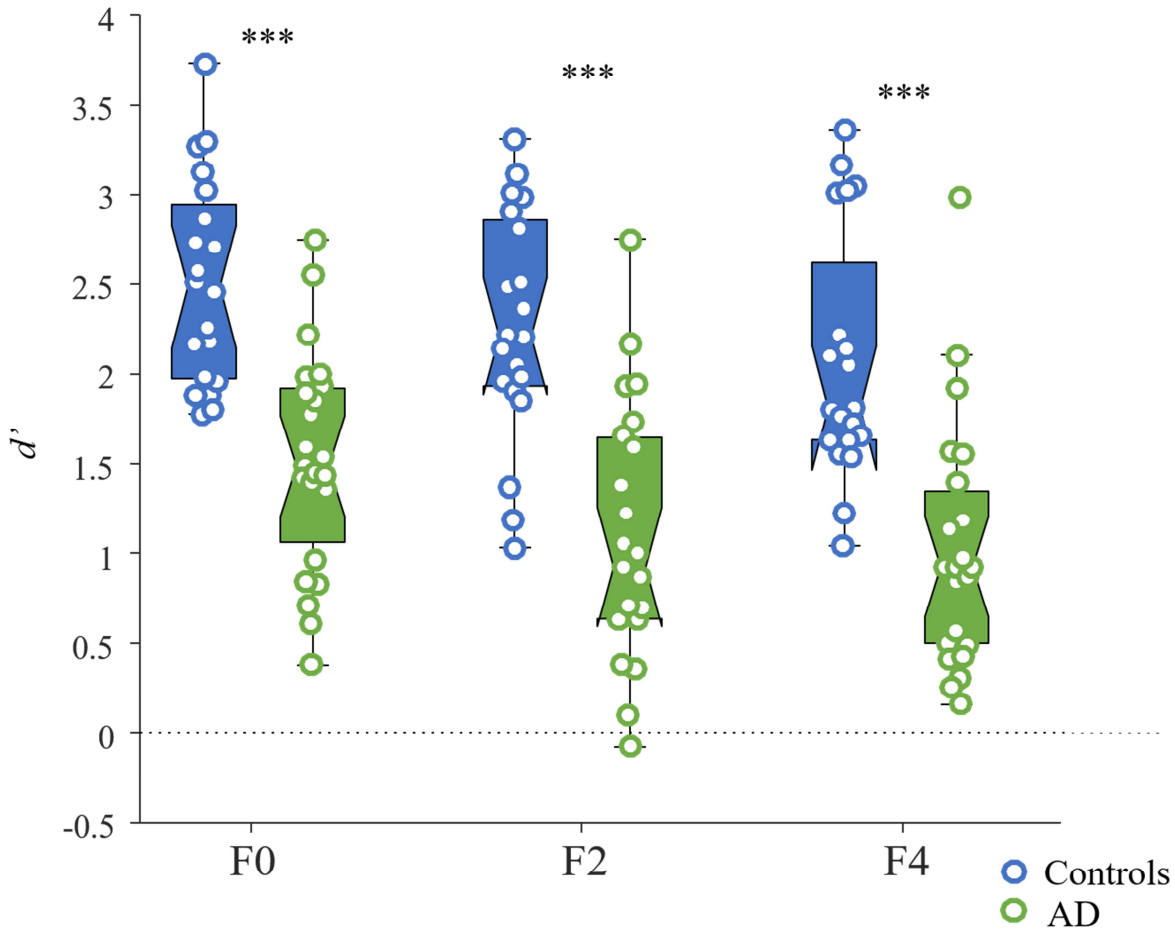
0-Fragment (F0)

2-Fragments (F2)

4-Fragments (F4)







Highlights:

- Mentally fusing object fragments is a prerequisite to identify and remember the object
- AD patients show impaired perceptual integration and memory for perceptually integrated items
- Both perceptual integration and memory for integrated items are related to atrophy of the perirhinal cortex
- The perirhinal cortex may support both perception and memory, probably through its role in complex object online representation.