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RESEARCH ARTICLE

Associative memory for conceptually unitized word pairs in mild cognitive impairment is related to the volume of the perirhinal cortex

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Abstract
Unitization, that is, the encoding of an association as one integrated entity, has been shown to improve associative memory in populations presenting with associative memory deficit due to hippocampal dysfunction, such as amnesic patients with focal hippocampal lesions and healthy older adults. One reason for this benefit is that encoding of unitized associations would rely on the perirhinal cortex (PrC) and thus minimize the need for hippocampal recruitment. Mild cognitive impairment (MCI) is accompanied by a deficit in associative memory. However, unitization has never been studied to explore the potential benefit in associative memory in MCI, maybe because MCI is characterized by PrC pathology. However, the PrC may potentially still function sufficiently to allow for the successful adoption of unitization. In this study, we aimed at assessing whether unitization could attenuate MCI patients' associative memory deficit, and whether the ability to remember unitized associations would be modulated by the integrity of the PrC in MCI patients. Unitization was manipulated at a conceptual level, by encouraging participants to encode unrelated word pairs as new compound words. Participants also underwent a structural MRI exam, and measures of PrC were extracted (Brodmann Areas [BA] 35 and 36). Results showed that, contrary to healthy controls, MCI patients did not benefit from unitization. Moreover, their memory performance for unitized associations was related to the measure of PrC integrity (BA35), while it was not the case in controls. This finding thus suggests that unitization does not help to attenuate the associative deficit in MCI patients, and brings support to the literature linking unitization to the PrC function.

KEYWORDS
associative memory, episodic memory, mild cognitive impairment, perirhinal cortex, unitization

1 | INTRODUCTION

Mild cognitive impairment (MCI) has been proposed as an intermediate state between normal aging and dementia. By definition, MCI patients present with subjective and objective cognitive impairment in at least one domain (e.g., memory, language, etc.), within a context of globally normal cognition and daily functioning, thus they do not fulfill criteria for dementia (Petersen, 2004; Petersen et al., 2001). Nonetheless, they are at a greater risk for developing Alzheimer's Disease (AD) than healthy older adults without cognitive impairment (~12%/year vs. 1–2%/year, respectively) (Petersen, 2004). Indeed, a significant percentage of patients with MCI have underlying AD pathology (Petersen et al., 2006) and are best considered as being in the prodromal stage of AD. However, not all patients with MCI convert to clinical AD, and some even revert to a non-impaired cognitive status (Ganguli, Dodge, Shen, & DeKosky, 2004). Those who present with predominant memory impairment (amnestic MCI) are more likely to progress to AD than those with a non-amnestic presentation (Petersen & Negash, 2008).

David A. Wolk and Christine Bastin contributed equally.

The cognitive impairments that occur in MCI are accompanied by changes in brain structure and function. The first region affected by the hallmark neurofibrillary tangle (NFT) pathology of AD is the medial temporal lobe (MTL) (Braak & Braak, 1995), which comprises the hippocampus as well as the adjacent entorhinal (ErC), perirhinal (PrC; comprising Brodmann Area [BA] 35 and BA36 subregions) and parahippocampal cortices (PhC) (Squire, Stark, & Clark, 2004). The MTL, and particularly the hippocampal formation, has been closely linked to memory for associations (Diana, Yonelinas, & Ranganath, 2007; Eichenbaum, Sauvage, Fortin, Komorowski, & Lipton, 2012; Mayes, Montaldi, & Migo, 2007; Montaldi & Mayes, 2010; Ranganath, 2010; Ranganath & Ritchey, 2012). Indeed, a number of studies have found that MCI patients are specifically impaired in associative memory; that is, the binding of two or more arbitrary pieces of information together into an episodic memory (Algarabel et al., 2012; Atienza et al., 2011; Chen & Chang, 2016; Fowler, Saling, Conway, Semple, & Louis, 2002; Hampstead, Stringer, Stilla, Amaraneni, & Sathian, 2011; Hampstead, Towler, Stringer, & Sathian, 2018; Hanseeuw et al., 2011; Oedekoven, Jansen, Keidel, Kircher, & Leube, 2015; Pike et al., 2012; Troyer et al., 2012, 2008; van Geldorp et al., 2015; Wang, Li, Li, & Zhang, 2013; Wolk, Dunfee, Dickerson, Aizenstein, & DeKosky, 2011). Moreover, MCI patients' associative memory impairment has been shown to be related to both hippocampal and ErC volume (Atienza et al., 2011; Chen & Chang, 2016; Hanseeuw et al., 2011; Troyer et al., 2012). Some studies of associative encoding have described abnormal hippocampal hyperactivation in early-stage MCI patients (Celone et al., 2006; Dickerson et al., 2005; Hämäläinen et al., 2007) and others have shown hypoactivation in the hippocampus in later-stage MCI patients (Hampstead et al., 2011; Hanseeuw et al., 2011).

Unitization has been explored as a strategy to overcome associative memory deficits linked to hippocampal dysfunction. Unitization consists of encoding previously separate items as a single coherent component (Graf & Schacter, 1989; e.g., the color blue associated with the object “shirt” could be unitized as a blue shirt). Lesion and neuroimaging studies have indicated that unitization is critically supported by the PrC (Diana, Yonelinas, & Ranganath, 2010; Haskins, Yonelinas, Quamme, & Ranganath, 2008; Quamme, Yonelinas, & Norman, 2007; Staresina & Davachi, 2008, 2010), thereby minimizing the need for hippocampal recruitment during encoding and shifting encoding to non-hippocampal structures such as the PrC.

This encoding strategy has been shown to improve associative memory in populations displaying associative memory deficits, such as amnestic patients with focal hippocampal lesions (Diana et al., 2010; Giovanello, Keane, & Verfaellie, 2006; Quamme et al., 2007; Ryan, Moses, Barense, & Rosenbaum, 2013) and healthy older adults (Ahmad, Fernandes, & Hockley, 2015; Badham, Estes, & Maylor, 2012; Bastin et al., 2013; D'Angelo et al., 2016; D'Angelo, Noly-Gandon, Kacollja, Barense, & Ryan, 2017; Troyer, D'Souza, Vandermorris, & Murphy, 2011; Zheng et al., 2015). It might therefore also be a useful encoding strategy for patients with AD or MCI given their known associative memory impairment. However, NFT pathology in AD not only affects the hippocampus, but also the PrC. In fact, NFT pathology is reported to appear first in the transentorhinal cortex, which is part of the PrC and roughly corresponds to BA35 prior to involvement of the hippocampus (Braak & Braak, 1995). It is therefore possible that unitization may not be beneficial in this specific patient group in contrast to hippocampal lesion patients. Indeed, in AD, the few existing studies on this topic have failed to find any benefit from unitization to mitigate patients' associative memory deficit (Bastin et al., 2014). It is possible that the substantial NFT pathology in PrC prevents AD patients from efficiently recruiting the PrC to effectively perform unitization by hampering the formation of a complex integrated representation (Delhaye, Bahri, Salmon, & Bastin, 2019).

However, to our knowledge, no study has yet evaluated the benefit of unitization in associative memory in MCI patients. While PrC NFT pathology is expected to be present in prodromal AD (i.e., MCI level impairment) and atrophy has been observed in this region in studies of MCI using morphometric MRI (Krumm et al., 2016; Yushkevich et al., 2015), it may potentially still function sufficiently to allow for the successful adoption of unitization. Moreover, as MCI is a heterogeneous group, the unitization strategy may benefit a subset who do not have underlying AD pathology. Therefore, the goal of the present study was to assess, for the first time, whether unitization could attenuate MCI patients' associative memory deficit. Moreover, we wanted to directly relate the impact of unitization to PrC volumes to further support the link between this brain region and the unitization process. More specifically, we hypothesized that the ability to remember associations under unitization instructions would be modulated by the integrity of the perirhinal cortex in MCI patients. Unitization was manipulated at a conceptual level, by encouraging participants to encode unrelated word pairs as new compound words, using a task that has been shown to activate the perirhinal cortex (Haskins et al., 2008) and to significantly improve associative memory performance in amnesic patients (Quamme et al., 2007).

2 | METHODS

2.1 | Population

Behavioral data were acquired in 48 participants from a research study of aging and cognitive impairment conducted at the Penn Memory Center at the University of Pennsylvania. The subjects included were 29 cognitively normal controls (NC) recruited from the community and 19 patients with a diagnosis of MCI (established using Petersen's (2004) criteria). Patients were mainly amnestic MCI (aMCI) subjects, with the exception of four who were non-amnestic (single domain). Among the aMCI, there were seven patients with memory as single domain affected and eight patients with one or more non-memory domains affected in addition to memory (multiple domain aMCI). All subjects were recruited from the Penn Memory Center/Alzheimer's Disease Center (PMC/ADC). Cognitively healthy older adults and MCI patients were matched in terms of age and education. See Table 1 for detailed demographics. The study was performed in compliance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and the standards established by the University of Pennsylvania Institutional Review Board and the National Institutes of Health. All subjects provided informed consent for this study.

2.2 | Neuropsychological evaluation

In order to characterize their neuropsychological profile, all participants underwent psychometric testing assessing cognitive domains such as episodic memory (CERAD word list memory test, Morris et al., 1989; Benson figure delayed, Possin, Laluz, Alcantar, Miller, & Kramer, 2011), working memory (digit span forward and backward), language and verbal functioning (MINT, Gollan, Weissberger, Runnqvist, Montoya, & Cera, 2012; Ivanova, Salmon, & Gollan, 2013; category [Goodglass & Kaplan, 1983] and letter fluency), visuo-spatial abilities (Benson figure copy), and executive functioning (Trail Making Test, part B, Armitage, 1945). See Table 1 for details about the neuropsychological profile of NC and patients.

2.3 | Materials

Eighty word pairs and their associated describing sentences were randomly selected from the materials used in Quamme et al. (2007). The pairs were composed of four- to six-letter English nouns with medium-to high word frequency. For each pair, a compound definition was derived for the compound word encoding condition (CW; high-unitization condition), and a simple sentence frame in which the two words fit plausibly was derived for the noncompound word encoding condition (NCW; low-unitization condition). Two versions of the task were built so that each word pair would appear either in its CW version or in its NCW version. In all compound definitions, the pair was interpreted such that the second word was the primary noun, and the first word served as a modifier. The definitions contained only synonyms or associates of the study items. For instance, the compound WALNUT-PLAN was interpreted as a plan for growing walnuts, and the definition given was "A scheme for growing nuts". The sentence frames used in the NCW encoding condition were constructed with two blank spaces where the first item was intended to fit in the first space and the second item to fit into the second blank space. The sentences were constructed to give interpretations to the pairing of the nouns. For instance, the sentence frame of the pair WALNUT-PLAN was "He ate a __ while receiving the __." All sentence frames and compound definitions were presented below the pair on the screen.

TABLE 1 Demographics and neuropsychological profile for NC and MCI patients

	Controls Mean (SD)	MCI Mean (SD)	*p* value
Demographic data			
Age	74.93 (9.17)	74.68 (5.73)	.92
Education	15.62 (2.62)	16.21 (2.3)	.43
Gender (F/M)	(22/7)	(9/10)	
Global cognitive functioning			
MoCA (/30)	26.86 (2.56)	22.63 (3.51)	<.001
Memory			
Digit span forward—Length	6.48 (1.45)	6.26(1.41)	.61
Digit span backward-length	5.0(1.19)	4.21 (1.03)	<.05
Word list memory encoding (/30; CERAD)	23.17 (4.31)	16.79 (5.59)	<.001
Word list recall	7.83 (1.77)	5.21 (2.7)	<.001
Word list recognition (/20)	19.48 (0.78)	18.58 (1.74)	.07
Benson figure delayed copy	12.55 (2.91)	6.63 (4.96)	<.001
Language & verbal functioning			
MINT—Total score (/32)	30.03 (2.29)	28.21 (3.61)	.05
Category fluency	35.62 (7.45)	27.00 (7.13)	<.001
Letter fluency	28.69 (8.53)	26.05 (9.02)	.31
Executive function			
TMT—Part B (time in seconds)	114.9 (80.59)	140.53 (91.14)	.31
TMT—Part B (nb errors)	0.86 (1.77)	1.53 (1.93)	.22
Visuo-spatial abilities			
Benson figure copy—Total score	15.65 (0.81)	15.16 (1.21)	.10

2.4 | Procedure

Participants completed both conditions, separately from one another. The order of presentation of the conditions was counterbalanced across participants. The encoding was incidental, such that participants were not informed that their memory would be subsequently assessed. During the encoding phase, to ensure that participants processed the associations either in a unitized or in a non-unitized fashion depending on the condition, they were instructed to rate on a scale from one (not well at all) to four (very well), in the CW condition, how well the compound definition combined the meanings of the two nouns into a cohesive meaningful compound, and in the NCW condition, how well each word fit in the corresponding blank space to produce a meaningful sentence. Each study phase was composed of 40 word pairs. All the pairs were used in the subsequent associative recognition memory test: 20 of them were presented in an intact form and 20 of them were recombined by switching the second noun of the pair with the second noun from another pair. Participants were instructed to decide whether each pair had been previously presented or not. Both encoding and associative recognition phases were self-paced. The delay between the incidental encoding task and the associative recognition test was filled with a 3-min mental calculation exercise.

2.5 | MRI data acquisition

We obtained MRI data for 24 of the participants (16 NC and 8 MCI). MRI scans were acquired on a 3 T Siemens Prisma scanner at the Hospital of the University of Pennsylvania. The scans were acquired using a 64-channel array coil. The protocol includes a "routine" T1-weighted (MPRAGE) whole-brain scan and a "dedicated" T2-weighted (TSE) scan with partial brain coverage and an oblique coronal slice orientation (positioned orthogonally to the main axis of the hippocampus). The parameters of the T2-weighted scan are (TR/TE: 9240/80 ms, 180° flip angle, 14% phase oversampling, 0.4×0.4 mm^2 in plane resolution, 1.2 mm slice thickness, 60 interleaved slices with no gap, acquisition time 8:10 min). The parameters of the T1-weighted scan are (TR/TE/TI = 2400/2.24/1060 ms, 8° flip angle, $0.8 \times 0.0.8 \times 0.8$ mm^3 resolution, acquisition time 6:38 min).

2.6 | MRI data analyses and automatic segmentation

All preprocessing and analyses were carried out using the automated segmentation of hippocampal subfields (ASHS) toolbox (Yushkevich et al., 2015). ASHS automatically segments hippocampal subfields as well as subhippocampal regions (ErC, BA35, BA36, and PhC) using multi-atlas label fusion and learning-based error correction. For the current study, we only focused on BA35 and 36 as this region is thought to play an important role in unitization. ErC was used as a reference region that is thought to be affected early in AD but not involved in unitization. The volumes were normalized by the number of slices. All MRI scans and automated segmentations were visually assessed for quality. Automated segmentations were edited, if the segmentation showed considerable over- or under-segmentation on three or more slices. The edits were blinded for diagnosis and other demographics. Two subjects' scan did not pass the quality assessment and were excluded from the MRI data analyses, such that these analyses were run with 15 NC and 7 MCI (three single domain aMCI, two multiple domain aMCI and two single domain non-amnestic MCI). All seven MCI patients included in the correlation analysis with MRI volumes performed within 1.5 standard deviations from the group's mean and so were representative of the whole group.

2.7 | Statistical analyses

We computed *d′* scores (Macmillan & Creelman, 2005) in each condition (CW and NCW) of the behavioral task as indices of discrimination performance. The problem of minimum and maximum hit et FA rates (0 or 1) in the calculation of *d′* scores was corrected by adding 0.5 to each frequency (of hits and of FAs) and dividing by N + 1, where N is the number of old or new trials (Snodgrass & Corwin, 1988). Mixed analyses of variance (ANOVA) with conditions (CW, NCW) as within-subject factor and group (NC, MCI) as between-subject factor were conducted on the hit and false alarm (FA) rates as well as on the *d′*.

To further explore performance and potential differences within the patients group according to their exact diagnosis (amnestic single-domain vs. amnestic multiple-domain vs. non-amnestic single-domain), we calculated Z scores on *d′* in patients using *d′* mean and standard deviations of the control group (Wolk, Signoff, & DeKosky, 2008). Additionally, due to small sample size, we performed nonparametric Mann Whitney tests to compare Z scores in CW and in NCW between the three MCI subgroups.

Non-parametric Mann–Whitney tests were also used to compare the volumes of the regions between groups. Finally, we computed nonparametric Spearman rank correlations to assess the relationship between regional volumes and behavioral performance.

3 | RESULTS

3.1 | Behavioral results

The conditions by group ANOVA on the hit rates revealed a main effect of condition ($F[1,46] = 10.50$, $p < .01$, $\eta^2 = 0.18$), with higher hit rates for CW than NCW, and a main effect of group ($F[1,46] = 7.64$, $p < .01$, $\eta^2 = 0.14$), with higher hit rates in NC than in MCI. There was no condition x group interaction ($F[1,46] = 0.92$, $p = .34$, $\eta^2 = 0.02$).

A mixed ANOVA on the false alarm (FA) rates across groups and conditions showed a significant main effect of group, with greater FA rates in MCI than in NC ($F[1,46] = 4.79$, $p < .05$, $\eta^2 = 0.09$), but no main effect of condition ($F[1,46] = 0.89$, $p = .35$, $\eta^2 = 0.02$) and no interaction between group and condition ($F[1,46] = 0.12$, $p = .72$, $\eta^2 = 0.01$). Hits and FA distributions across groups and conditions are displayed in Figure 1.

A mixed ANOVA on *d′* scores across groups and conditions revealed a main effect of group ($F[1,46] = 16.48$, $p < .001$, $\eta^2 = 0.26$), with better performance in NC than in MCI, but no main effect of condition ($F[1,46] = 2.41$, $p = .13$, $\eta^2 = 0.05$), as confirmed by separate t-tests within each group (NC: $t(28) = 1.78$, $p = .09$; Cohen's $d = 0.33$; MCIs: $t(18) = 0.64$, $p = .53$; Cohen's $d = 0.15$) and no condition x group interaction ($F[1,46] = 0.45$, $p = .51$, $\eta^2 = 0.01$). The results indicate that MCI patients performed worse than controls in both conditions, as confirmed by separate t-tests (CW: $t(46) = 3.76$; $p < .001$; Cohen's d = 1.11; NCW: $t(46) = 3.63$; $p < .001$; Cohen's

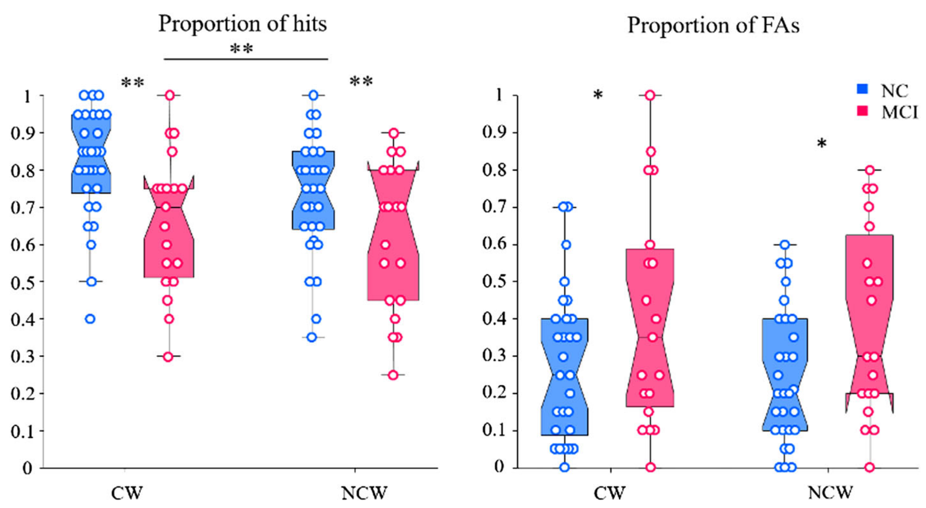

FIGURE 1 Boxplots of hit and FA rates across groups and conditions. Each circle represents a subject. *p < .05; **p < .01 [Color figure can be viewed at wileyonlinelibrary.com]

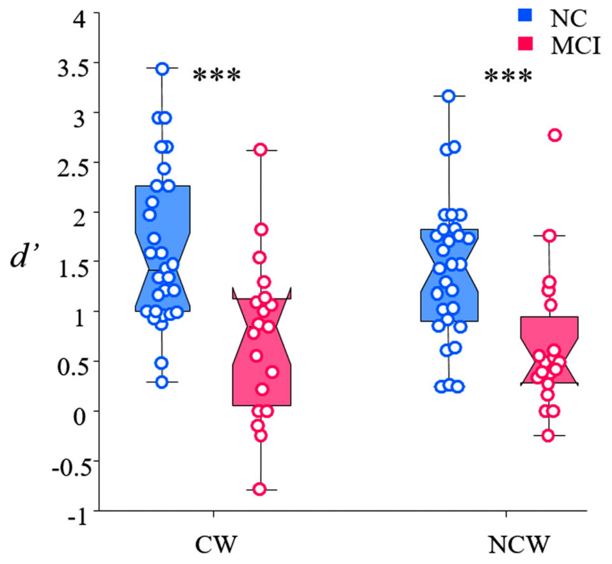

FIGURE 2 Boxplots of discrimination performance (d') across groups and conditions. Each circle represents a subject. ***p < .001 [Color figure can be viewed at wileyonlinelibrary.com]

d = 1.07). Plots of the discrimination performance for each group and condition are displayed in Figure 2.

In the CW condition, performance was 1.5 standard deviations below controls' mean in two patients with single-domain aMCI (29%) and five patients with multiple-domain aMCI (62%), but none with non-amnestic MCI. In the NCW condition, three single-domain aMCI (43%) and three multiple-domain aMCI (37%), but again no non-amnestic MCI, performed more than −1.5 standard deviations under controls' mean. Mann–Whitney tests showed that, in the CW condition, there was a trend for more severe impairment in multiple-domain aMCIs (mean z-score = −1.52, SD = 1.29) than in non-amnestic MCIs (mean z-score = −0.33, SD = 0.48) (W = 4.00, p = .05). There was no score difference between multiple-domain aMCIs and single-domain aMCIs (W = 17.00, p = .22), nor between single-domain aMCIs and non-amnestic MCIs (W = 23.00, p = .11). In the NCW condition, no differences were revealed between the three MCI subgroups (all ps > 0.1).

3.2 | Volumetric imaging results

The ErC and the PrC (BA35 and 36) are thought to be the first regions affected in prodromal AD; Mann–Whitney tests were used to compare volumes of these regions between NC and MCI. The analysis did not reveal significant differences in mean volumes between the groups for the ErC (right: W = 37, p = .54; left: W = 43, p = .97; mean: W = 56, p = .84), for BA35 (right: W = 28.5, p = .27; left: W = 32, p = .58; mean: W = 42, p = .49), or for BA36 (right: W = 40, p = .9; left: W = 28, p = .7; mean: W = 54, p = .94).

Spearman correlation analyses were used to assess whether the volume of the PrC was specifically associated with memory performance in the high level of unitization condition, in NC and participants with MCI, separately. Correlations were computed between d' scores in each condition and the mean volumes for each region (see Figure 3). In controls, no significant correlation was found, neither for the CW condition (with BA35: ρ = −0.06, p = .84; BA36: ρ = 0.14, p = .63) nor for the NCW condition (BA35: ρ = 0.11, p = .71; BA36: ρ = 0.26, p = .36). In MCI, in the CW condition, there was a significant positive correlation between performance and the volume of BA35 (ρ = 0.87, p < .05) and BA36 (ρ = 0.78, p < .05). The correlation between the volume of BA35 and performance in the NCW condition failed to reach significance (ρ = 0.71, p = .08), but there was a correlation between the volume of BA36 and performance for NCW (ρ = 0.77, p < .05). Of note, the correlation between BA35 and CW performance did not differ significantly from the correlation between BA35 and NCW condition, p = .27.

Spearman correlations were also computed to assess the relationship between performance in the two conditions and the mean volumes of the ErC, in NC and participants with MCI, separately. This was used as a control measure to ascertain that the previously evidenced correlations were specific to the PrC and not a result of more global MTL atrophy. In both groups, the correlations between the volume of the ErC and d' scores in the CW condition (controls: ρ = 0.07, p = .79; patients: ρ = 0.58, p = .17) and between the volume of the ErC and performance in the NCW condition (controls: ρ = −0.02, p = .94; patients: ρ = 0.51, p = .24) all failed to reach significance.

4 | DISCUSSION

The current study aimed at exploring whether unitization could help attenuate MCI patients' associative memory deficit, and whether their memory for unitized associations would be related to the integrity of the PrC. To assess this, MCI patients and cognitively normal controls participated in two conditions of an associative memory task: a high-unitization condition in which word pairs were integrated to form a new compound word with its own new definition, and a low-unitization condition in which word pairs were processed separately as two distinct entities, in separate frames within a sentence. We further evaluated whether their performance on these two conditions was related to the volumes of BA35, BA36, and the control region ErC.

Results showed that unitization did not help MCI patients to attenuate their associative memory deficit. Indeed, in the high-unitization condition, they remained as impaired compared to controls as they were in the low-unitization condition, if not more so. This result provides a first set of evidence relative to unitization in MCI and converges with existing findings in AD, according to which patients with AD displayed diminished capacity to improve their associative memory through unitization (Bastin et al., 2014). This result contrasts with findings highlighted in amnestic patients with focal hippocampal lesions, who do benefit from unitization in associative memory, contrary to our sample of patients with MCI. This may be explained by the divergent patterns of cerebral injury between these two populations, as discussed below. Further, in this study, as in most previous studies, the source of this impairment remains uncertain, whether it is in the creation of a unitized and integrated representation at the encoding stage or in the subsequent recognition stage. Only one study previously suggested that both the capacity to form a complex and integrated representation at an initial processing stage and the recognition of unitized associations were impaired in AD, but this was for perceptual unitization (Delhaye et al., 2019). Here, one possible explanation could be that some conceptual impairments, or

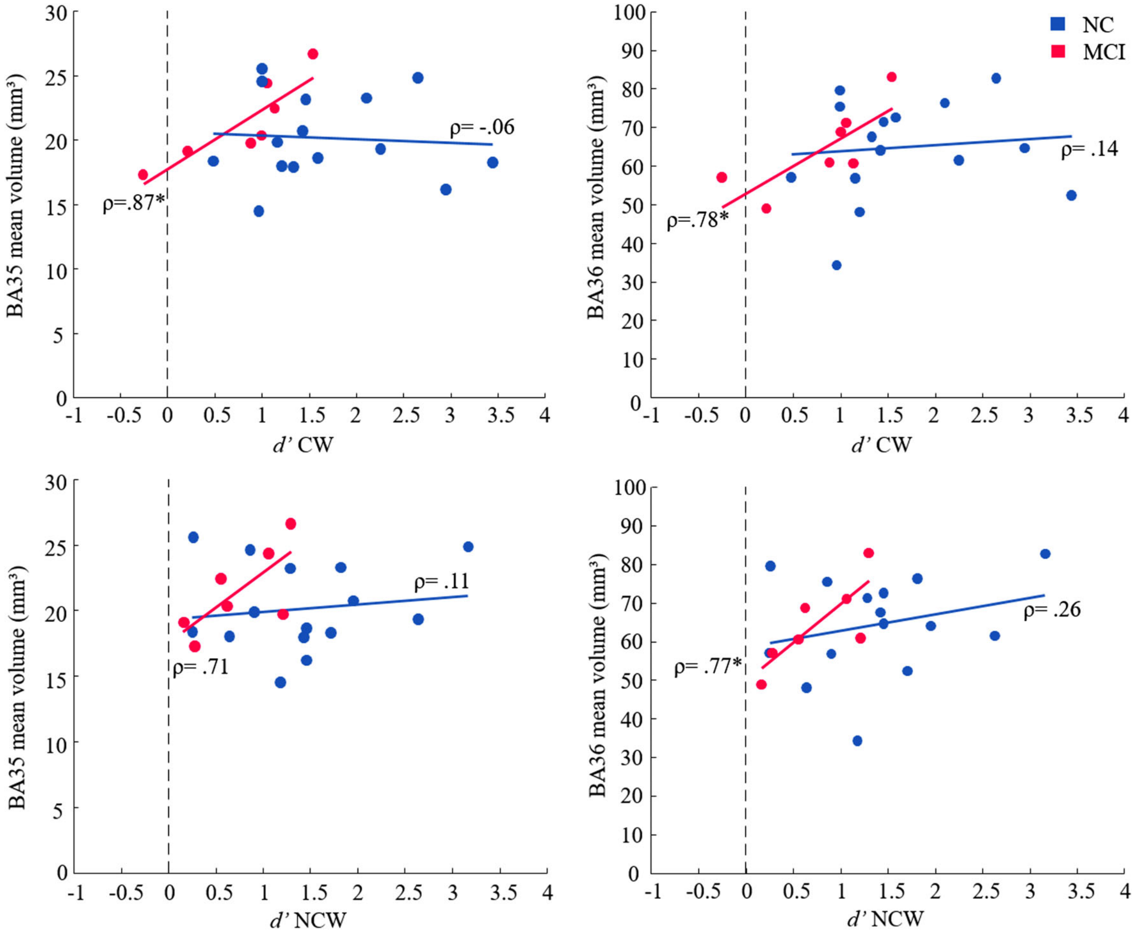

FIGURE 3 Correlations between discrimination performance (*d*') in CW and NCW conditions and BA35 and BA36 volumes in normal controls (NC) and MCI patients, respectively. **p* < .05 [Color figure can be viewed at wileyonlinelibrary.com]

subtle difficulties with semantic memory in MCI patients (Joubert et al., 2008), as suggested by their impaired conceptual fluency scores in this study, could have led patients to some difficulty properly combining the concepts in the high-unitization condition. This could have contributed to similarities between the high- and low-unitization conditions in the patients that, for instance, were not seen in amnesic patients with focal hippocampal lesions and no conceptual impairment. Still, some more light needs to be shed on the case of MCI, and on conceptual unitization.

Interestingly, MCI patients' performance under high-unitization instructions was related to the volume of BA35, a subregion within the perirhinal cortex that is the first region associated with the NFTs of AD, while no such correlation was demonstrated in healthy controls. Even though BA35 volume was not significantly reduced in MCI patients as a group, probably because of the heterogeneous composition of the clinical entity and limited power in the sample studied here, there was variability in BA35 volumes that was significantly associated with memory performance under unitization instructions. This provides evidence to suggest that in MCI patients, the greater the atrophy in BA35, the poorer the memory for unitized associations. Our results could thus join the existing literature suggesting that unitization is supported by the PrC (Diana et al., 2010; Haskins et al., 2008; Quamme et al., 2007; Staresina & Davachi, 2008, 2010), and suggest that PrC damage impairs memory for unitized associations. Possible PrC injury in our MCI population also explains the discrepancy between our result and those from hippocampal amnestic population (Giovanello et al., 2006; Quamme et al., 2007). Further, this result supports the idea developed by some authors which posits that the vulnerability of "object-based" memory, by definition including memory for unitized representations, could be a cognitive marker of early AD due to the early involvement of PrC (Bastin et al., 2014; Das, Mancuso, Olson, Arnold, & Wolk, 2016; Didic et al., 2011; Wolk, Mancuso, Kliot, Arnold, & Dickerson, 2013). Still, while the correlation results are intriguing, these findings should be taken as preliminary given the limited sample size and require replication in larger cohorts. Moreover, correlations between BA35 and performance in the low-unitization condition and between BA36 and performance in both the high- and the low-unitization conditions are also high. Additionally, the correlation between BA35 volume and high-unitization performance was not significantly higher than those for the low-unitization condition. So, one possibility could be that this relationship is not specific to unitized associations but rather represent a more global involvement of the perirhinal cortex in associative memory. This would be in line with theories that ascribe a role for the perirhinal cortex not only in memory for items or unitized associations, but more globally, in memory for associations between similar information (within domain) such as word pairs, as suggested by the Domain Dichotomy view (Mayes et al., 2007).

The current results also bring some indirect contribution to the debate about familiarity-based memory in MCI. Unitization has been shown to promote familiarity-based memory (i.e., associative familiarity) (Parks & Yonelinas, 2009, 2015; Yonelinas, 1999, 2002; Yonelinas, Aly, Wang, & Koen, 2010) and the PrC is critical for familiarity (Bowles et al., 2007; Bowles, O'Neil, Mirsattari, Poppenk, & Köhler, 2010; Brown & Aggleton, 2001; Diana et al., 2007; Montaldi & Mayes, 2010; Ranganath & Ritchey, 2012; Staresina, Fell, Do Lam, Axmacher, & Henson, 2012). In MCI, some studies suggest that familiarity is preserved, but others, including meta-analyses, report data showing impairment of familiarity in MCI (for a review, see Schoemaker, Gauthier, & Pruessner, 2014) and related this deficit to atrophy of the extrahippocampal regions (Wolk et al., 2011, 2013). Here, we used a task in which associative memory tended to be improved by encoding instructions that induce unitization. Such memory for unitized associations using this task has previously been shown to be supported by familiarity (Quamme et al., 2007). The current results, in which MCI patients were impaired at recognizing word pairs in the high unitization condition and this difficulty correlated to atrophy of the PrC, suggests that impaired familiarity may be the mediator of this correlation. This should be tested in future studies.

One noteworthy limitation of this study concerns the inclusion criteria for MCI patients. Patients were included based on clinical criteria, in the absence of pathophysiological biomarkers of AD. This means that an undetermined proportion of the MCI patients harbor AD pathology and some may have other etiologies that underlie their memory weakness. Even if, at a group-level, one cannot consider that the results speak for the early stage of AD, the correlational approach revealed that variability in PrC atrophy (potentially indicative of a likelihood of an AD etiology) was related to the extent to which patients were able to remember associations processed in a unitized fashion. Finally, the results from this study should be taken with caution given the small sample size for patients, especially in the MRI data analyses.

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