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Relationship of Contextual Cueing and Hippocampal Volume in Amnestic Mild Cognitive Impairment Patients and Cognitively Normal Older Adults

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Abstract

There is currently some debate as to whether hippocampus mediates contextual cueing. In the present study, we examined contextual cueing in patients diagnosed with mild cognitive impairment (MCI) and healthy older adults, with the main goal of investigating the role of hippocampus in this form of learning. Amnestic MCI (aMCI) patients and healthy controls completed the contextual cueing task, in which they were asked to search for a target (a horizontal T) in an array of distractors (rotated L's). Unbeknownst to them, the spatial arrangement of elements on some displays was repeated thus making the configuration a contextual cue to the location of the target. In contrast, the configuration for novel displays was generated randomly on each trial. The difference in response times between repeated and novel configurations served as a measure of contextual learning. aMCI patients, as a group, were able to learn spatial contextual cues as well as healthy older adults. However, better learning on this task was associated with higher hippocampal volume, particularly in right hemisphere. Furthermore, contextual cueing performance was significantly associated with hippocampal volume, even after controlling for age and MCI status. These findings support the role of the hippocampus in learning of spatial contexts, and also suggest that the contextual cueing paradigm can be useful in detecting neuropathological changes associated with the hippocampus. (*JINS*, 2015, *21*, 285–296)

Keywords: Spatial learning, Alzheimer's disease, Cognitive aging, MRI, CA1, Implicit

INTRODUCTION

With the increased focus on early and accurate detection of Alzheimer's disease (AD), there is burgeoning interest in cognitive neuroscience of mild cognitive impairment (MCI), and in studies that use analytic experimental, well-designed paradigms to disentangle the cognitive deficits in MCI. Such paradigms have advantages over more global assessments of cognition because they are aimed at specific aspects of cognition whose underlying brain networks are well understood. Implicit learning is a less studied, yet potentially important system that can offer insights into the neural effects of MCI.

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Implicit learning generally refers to a situation where a person learns about the structure of a stimulus environment without conscious effort to learn and without ability to describe what has been learned (Reber, 1993). It is said to occur when participants demonstrate knowledge of the regularity by the speed and/or accuracy of their responses, but reveal little awareness of what they have learned. Implicit learning has multiple forms, which call upon distinct neural systems and are differentially affected by neurodegenerative diseases, such as Alzheimer's disease, Huntington's disease, and Parkinson's disease (Eldridge, Masterman, & Knowlton, 2002; Ferraro, Balota, & Connor, 1993; Fleischman, 2007; Gabrieli, Stebbins, Singh, Willingham, & Goetz, 1997; Heindel, Salmon, Shults, Walicke, & Butters, 1989; Machado et al., 2009). The nature of implicit learning in the construct of MCI has been less studied, with mixed results.

Our earlier study, the first to examine implicit sequence learning and contextual cueing in MCI, has shown context learning deficits, while sequence learning remained relatively intact in MCI (Negash et al., 2007). Studies that used a more complex sequence structure, however, have shown sequence learning deficits in MCI (Nemeth et al., 2013). Results from priming studies have also been mixed (Gong et al., 2010; LaVoie & Faulkner, 2008; Perri, Carlesimo, Serra, & Caltagirone, 2005). Moreover, the neural mechanisms underlying implicit learning systems in MCI are even less understood (for reviews see Fleischman & Gabrieli, 1998; Howard & Howard, 2012).

The present study examined contextual cueing in the amnestic subtype of MCI, and the role of hippocampus in this form of learning. The contextual cueing paradigm is a visual search task developed by Chun and colleagues to examine learning of visuospatial contexts (Chun & Jiang, 1998). In this task, people are asked to search for a target (e.g., a horizontal T) in an array of distractors (rotated L's). Unbeknownst to participants, some displays contain repeated configurations that provide a contextual cue to the location of the target, while novel displays are generated randomly. Contextual learning is measured by the difference in performance between repeated and novel configurations. Furthermore, such learning has been shown to occur implicitly in that people do not develop explicit knowledge of the relationship between the spatial context and the target location (Chun & Phelps, 1999; Howard, Howard, Dennis, Yankovich, & Vaidya, 2004).

The contextual cueing paradigm is of particular interest in MCI and AD because, unlike other implicit learning forms, it has been argued to be sensitive to medial temporal lobe (MTL) function. For example, contextual cueing is impaired in amnesic patients with damage to the MTL system (Chun & Phelps, 1999; Manns & Squire, 2001; Preston & Gabrieli, 2008). MTL atrophy, particularly in the hippocampus, is established as one of the earliest changes accompanying amnestic MCI (Duara et al., 2008; Korf, Wahlund, Visser, & Scheltens, 2004; Whitwell et al., 2007). While this implicates the potential role of contextual cueing in detecting hippocampal change in aMCI, there have been only few studies that examined this learning system in MCI (Kessels, Meulenbroek, Fernandez, & Olde Rikkert, 2010; Negash et al., 2007), and none that have related learning directly to hippocampal volume. Establishing a relationship between hippocampal integrity and contextual cueing effect can provide important information in our understanding of the neural basis of contextual cueing. To this end, the present study examined the extent to which contextual cueing effect is modulated by hippocampal volume in patients diagnosed with amnestic MCI and healthy older adults.

METHOD

Participants

Participants were identified from the ongoing cohort in the University of Pennsylvania Alzheimer's Disease Center/Penn Memory Center (ADC/PMC). Informed consent was obtained from all participants, which was approved by the University of Pennsylvania Institutional Review Board. As part of their participation in the ADC/PMC, each patient undergoes an extensive evaluation, including medical history and physical examination, neurological history and examination, and psychometric testing, often including all elements of the National Alzheimer's Coordinating Center's (NACC) Uniform Data Set (Beekly et al., 2007; Morris et al., 2006; Weintraub et al., 2009). For the purposes of this study, each subject completed at least the following psychometric battery within 3 months of the experimental paradigm: Mini-Mental Status Exam [MMSE; (Folstein, Folstein, & McHugh, 1975)]; Digit Span subtest of the Wechsler Adult Intelligence Scale III (Wechsler, 1987); Category fluency (animals) (Spreen & Strauss, 1998); Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Word List Memory (WLM) test (Morris et al., 1989); Trail Making Test (TMT) A and B (Reitan, 1958); and a 15- or 30-item version of the Boston Naming Test [BNT; (Kaplan, Goodglass, & Weintraub, 1983)]. Clinical diagnosis was determined by review of the above data, in addition to relevant blood work and brain imaging, at a consensus conference attended by neurologists, neuropsychologists and/or psychiatrists.

The diagnosis of amnestic MCI was made in accordance with the criteria of Petersen et al. (1999), and included both single and multiple domain MCI (Petersen & Negash, 2008). Cognitively normal (CN) was defined as an absence of significant cognitive complaints, normal performance on age-adjusted cognitive measures, and consensus conference designation as "normal." Participants were excluded if they had a history of another significant neurological condition, such as clinical stroke, alcohol or drug abuse/dependence within 2 years of enrollment, or any significant medical/psychiatric condition that would impact compliance with the study protocol.

MRI Acquisition

Participants underwent structural MRI as part of their participation in the study. MRI scans were acquired on a 3 Tesla (T) Siemens Trio scanner at the Hospital of the University of Pennsylvania. An 8-channel array coil was used in all but one subject, who was scanned using a 32-channel head coil. A standard T1-weighted (MPRAGE) whole brain scan was acquired with the following parameters [8-channel: repetition time/echo time/inversion time (TR/TE/TI) = 1600/3.87/950 ms, 15° flip angle, $1.0 \times 1.0 \times 1.0\ mm^3$ resolution, acquisition time 5:13; 32-channel: TR/TE/TI = 1900/2.89/900 ms, 9° flip angle, $1.0 \times 1.0 \times 1.0\ mm^3$ resolution, acquisition time 4:26 min]. In addition, a "dedicated" T2-weighted (turbo spin echo) scan with partial field of view and an oblique coronal slice orientation perpendicular to the long axis of the hippocampus, adapted from (Mueller et al., 2007), was acquired in all but one subject. The parameters for the T2-weighted MRI were: 8-channel: TR/TE: 5310/68 ms, echo train length 15, 18.3 ms echo spacing, 150° flip angle,

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0% phase oversampling, $0.4 \times 0.4\ mm^2$ in plane resolution, 2 mm slice thickness, 30 interleaved slices with 0.6 mm gap, acquisition time 7:12 min; 32-channel: TR/TE: 7200/76 ms, echo train length 15, 15.2 ms echo spacing, 150° flip angle, 75% phase oversampling, $0.4 \times 0.4\ mm^2$ in plane resolution, 2 mm slice thickness, 30 interleaved slices with no gap, acquisition time 6:29 min.

Image Processing

Participants' hippocampi were segmented from T1-weighted MRI using the open-source, publicly available AHEAD software package (https://www.nitrc.org/projects/ahead/). The method uses a multi-atlas label fusion strategy, first described in (Wang et al., 2011) and further refined in (Wang & Yushkevich, 2013). It begins by computing one-to-one spatial correspondences of a target image with several manually labeled atlas images using deformable registration. Segmentation labels from the atlas images are mapped into the target image space and combined into a single consensus segmentation using label fusion (Artaechevarria, Munoz-Barrutia, & Ortiz-de-Solorzano, 2009). This segmentation is then refined using a learning-based error correction technique that further improves labeling accuracy. This method has been evaluated in the ADNI dataset, yielding a Dice overlap of ~0.9 for hippocampus.

Hippocampal subfields and MTL cortical regions were segmented in T2-weighted MRI using the recently developed automatic segmentation method called ASHS (Yushkevich et al., 2014). This method uses a similar multi-atlas label fusion technique as AHEAD, describe above. An open source implementation is available at http://www.nitrc.org/projects/ashs/.

Given the potential role of caudate in implicit learning, the caudate nucleus was labeled in each participant using Hammers atlas (Hammers et al., 2003). To do so, each participant's T1-MRI was registered to a template brain containing these labels using Advanced Normalization Tools (ANTs) (Avants, Epstein, Grossman, & Gee, 2008), and the caudate labels were transferred to the native MRI to compute the volumes.

Contextual Cueing Task

Upon completion of informed consent, participants were asked to perform the contextual cueing task. In this task, participants were instructed to locate and identify a target item among 11 distractors. Items were presented on a computer screen in white on a gray background, as shown in Figure 1. The target was a horizontal *T* with the tail pointing either left or right by 90°, and the distractors were *L*s randomly rotated by 0°, 90°, 180°, or 270°. Each element subtended approximately 1.1° of visual angle at a viewing distance of 56 cm. Arrays were generated by randomly placing the 12 items into cells of an invisible grid (6 rows × 8 columns) grid. Every element was randomly repositioned by ±2 pixels along each axis to avoid colinearity. Targets never appeared in the four center cells or at the extreme corners of the display grid.

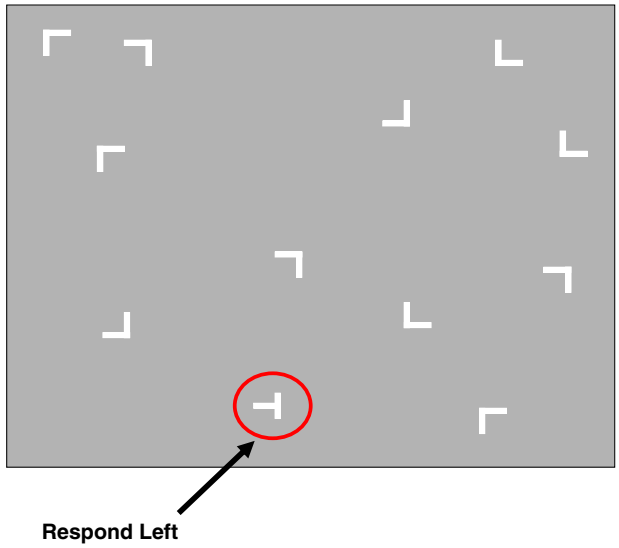

Figure 1. Schematic for the contextual cueing task. Participants locate the rotated target T (indicated by arrow) amongst L distractors, and indicate its orientation (in this case, rotated to the left).

On each trial, a white fixation dot appeared for 1 s, followed by an array that remained on the screen for up to 10 s until a response was made. Participants were instructed to locate the "T" and respond to its orientation as quickly and accurately as possible using keys on a keyboard ("z" for targets facing left and "/" for right facing right). Auditory feedback of a high-pitch tone indicated a correct response, and a low-pitch tone indicated incorrect response or no response within the 10-s time-out period.

Following 24 practice trials, participants completed 20 blocks of 24 trials each. Twelve of these trials contained unique configurations of distractors (Novel) that were generated randomly. The remaining 12 contained configurations of distractors that repeated across the blocks, appearing once in each block (Repeated). In repeated arrays, the locations of the distractors predicted the location of the target, but not its orientation (left *vs*. right). Therefore, this regularity could be used to predict the target location but not the correct response. Remaining arrays for each block also had a fixed set of target locations, but with novel configurations of distractors across the experiment. The order of repeated and novel arrays was randomized within each block. Each participant received a different set of repeated and novel arrays. Participants were encouraged to take short breaks between blocks. Several previous studies, including our own, have shown this task to be implicit in that participants are not able to describe what they had learned in verbal reports, or distinguish between novel and repeated trials on the recognition test (Chun & Phelps, 1999; Greene, Gross, Elsinger, & Rao, 2007; Negash et al., 2007). The present study, however, is limited in addressing this issue directly, as we did not assess explicit awareness.

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Statistical Analysis

The mean reaction time (RT) for correct trials was calculated separately for each configuration type (novel or repeated) for each block for each participant. The 20 blocks were grouped into five epochs, each containing four blocks. For each participant, a mean response time (RT) was determined separately for correct responses to new and repeated configurations on each block. The mean RTs were then averaged across blocks to obtain a single RT for each individual and configuration type (new or repeated) on each epoch. A similar data reduction was performed on accuracy. As is typical with these tasks, accuracy levels were high, particularly for the control group [mean (*SD*): Control = 0.96 (0.19); MCI: 0.89 (0.30)], and comparisons involving accuracy did not reach significance (p-values > .1), likely due to very high level of accuracy and ceiling effects (data not shown).

To examine the role of hippocampal volume in contextual learning, linear regression was conducted, in which a measure of contextual learning was entered as the dependent variable and hippocampal volume as the independent variable. The model also adjusted for intracranial volume. All analyses were performed using SPSS 20.0 (IBM, Armonk, NY), with two tailed tests and a type I error of 0.05.

RESULTS

There were 22 MCI patients and 37 healthy controls. Participant characteristics are shown in Table 1. The groups did not differ in age or years of education. Psychometric testing revealed a pattern characteristic of amnestic MCI, where the MCI group performed significantly worse than controls on measures of global cognition (MMSE), memory (CERAD Word List Learning, immediate and delayed recall), language (Boston Naming, Category Fluency), and attention (Trail Making Tests, Digit Span).

Contextual Learning

Figure 2 shows the mean response times of novel and repeated configurations across the five epochs for MCI and control groups. As the figure indicates, both aMCI and Control groups exhibited non-specific skill learning in that response times decreased across epochs; the main effect of Epoch was significant [$F(4,228) = 63.05$; $p < .0001$]. The figure also indicates that aMCI patients were slower overall compared to controls, main effect of Group was significant [$F(1,57) = 7.79$; $p = .007$], consistent with several studies showing processing speed deficits in MCI patients (Facal, Juncos-Rabadan, Pereiro, & Lojo-Seoane, 2014; Lopez et al., 2006; Wenger, Negash, Petersen, & Petersen, 2010). The Group × Epoch interaction did not reach significance ($p > .10$), indicating no group differences in overall skill learning.

Importantly, both groups showed similar amounts of contextual learning; the Group × Configuration interaction was not significant [$F(1,57) = 0.541$; $p = 0.46$]. Separate analyses of variance (ANOVAs) on each group showed a main effect of Configuration for both MCI, [$F(1,21) = 62.08$; $p < .0001$] and control groups, [$F(1,36) = 99.57$; $p < .0001$], suggesting that each group showed contextual cueing.

In addition, given that this task is susceptible to noise, especially at the beginning of training, we carried out further analysis in which we grouped the 20 blocks into two (first 10 blocks and last 10 blocks). We then examined learning on the last 10 blocks, where both groups clearly displayed contextual cueing effects, as can be observed in Figure 2 (i.e., learning is present by the third epoch). Both groups showed significant contextual cueing, and group differences were not observed; the Group × Configuration (Novel *vs*. Repeated) ANOVA on

Table 1. Participant characteristics

	Control ($n = 37$)	a-MCI ($n = 22$)	Statistic t or χ^2	p Value
Age	73.5 (6.7)	73.6 (5.8)	0.01	*0.98*
Education (years)	16.0 (2.7)	17.8 (5.4)	1.4	*0.10*
Gender (F/M)	21/16	13/10	0.031	*0.86*
APOE status (ε4+/ε4–)[a]	7/22	7/8	1.8	*0.18*
MMSE	29.4 (0.16)	27.01 (1.9)	–5.1	*<.0001*
Trails A	33.0 (9.8)	48.9 (34.3)	2.1	0.024
Trails B	73.3 (22.1)	137.0 (78.8)	3.6	0.0006
Boston Naming	28.6 (1.7)	26.5 (3.1)	–2.8	0.004
Category Fluency (Animals)	20.4 (5.1)	15.8 (4.8)	–3.4	0.0006
Digit Span Forward	7.1 (0.9)	6.5 (1.1)	–1.8	0.033
Digit Span Backward	4.9 (1.3)	4.3 (0.8)	–2.0	0.024
CERAD 10-Item Word List Immediate Recall (sum of Trials 1–3)	22.6 (3.5)	16.9 (3.9)	–5.4	<.0001
CERAD 10-Item Word List Delayed Recall	7.7 (1.7)	3.2 (1.9)	–8.8	<.0001

[a]APOE data were not available for all participants.

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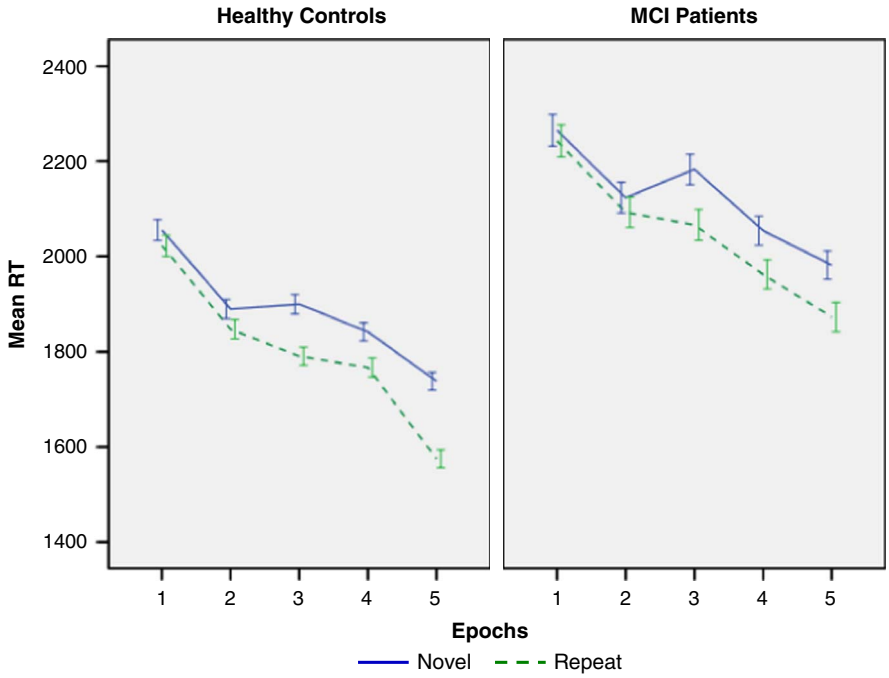

Figure 2. Mean reaction times (RTs) across epochs for Novel (solid lines) and Repeated trials (dotted lines) for mild cognitive impairment (MCI) and healthy control groups. Error bars represent one standard error.

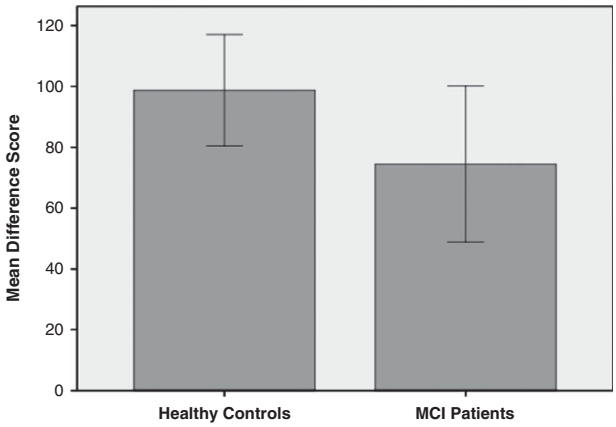

Figure 3. Mean difference scores for mild cognitive impairment (MCI) and healthy control groups. Error bars represent one standard error.

the last 10 blocks revealed a main effect of Configuration [$F(1,57) = 31.42$; $p < .0001$] while the Group × Configuration interaction was not significant [$F(1,57) = .616$; $p = .44$]. Subsequent separate ANOVAs on each group showed main effects of Configuration for both aMCI [$F(1,21) = 8.42$; $p = .009$] and Control [$F(1,36) = 29.09$; $p < .0001$] groups, indicating that both groups showed contextual cueing.

We also calculated a *difference score* on the last 10 blocks, that is, mean RT on novel configurations minus mean RT on repeated configurations. Thus, a positive difference score indicated contextual learning. Figure 3 shows the mean difference score for aMCI and Control groups. As the figure indicates, the absolute difference scores were relatively larger for controls (mean: 98.76, *SD*: 111.4) compared to the MCI (mean: 74.51, *SD*: 120.5), but the group comparison did not reach significance, $t(57) = 0.78$, $p = .436$.

Hippocampal Volume

Hippocampal data were available for 46 participants (27 controls, 19 aMCI). As expected, mean hippocampal volumes (average of left and right) were significantly smaller in aMCI patients compared to controls (MCI = 1764.5 mm^3 [*SD* = 71.3], Controls, 2090.2 mm^3 [*SD* = 57.5]; $t(44) = 3.6$; $p = .001$). Of particular interest, we examined whether performance on contextual cueing was associated with hippocampal volume, since that would provide evidence for its dependence on hippocampal function and perhaps AD-related change. In a linear regression model that adjusted for intracranial volume (ICV), contextual cueing (difference score on last 10 blocks) significantly correlated with mean hippocampal volume (estimate = 0.14, SE = 0.056; $p = .0172$), in that higher hippocampal volume was associated with greater learning. Based on literature suggesting right-lateralized involvement of hippocampus in visuospatial tasks (Burgess, Maguire, & O'Keefe, 2002; Manelis & Reder, 2012; Smith & Milner, 1981), we also repeated this analysis for left and right hippocampus separately. Figures 4a and b show the scatterplots for contextual cueing versus raw left and right hippocampal volumes, respectively. In regression models that adjusted for ICV, we observed a significant linear relationship between contextual cueing level and right hippocampal volume

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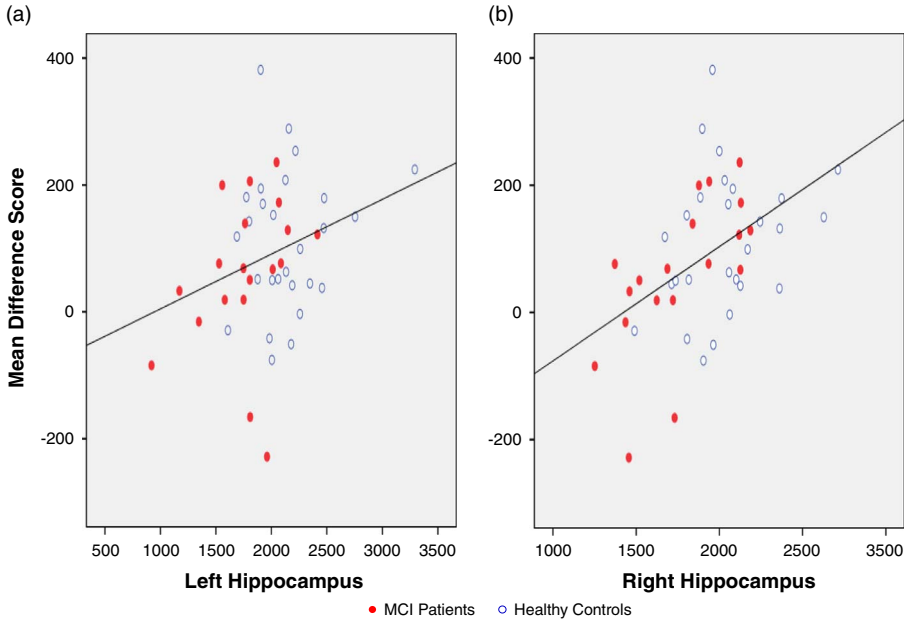

Figure 4. Scatterplots of mean difference scores versus left hippocampal (a) and right hippocampal (b) volumes, with regression line superimposed, for mild cognitive impairment (MCI) (solid circle) and control (open circle) participants.

(estimate = 0.191, SE = 0.056; $p = 0.0015$), but not left, (estimate = 0.078, SE = 0.049; $p = 0.12$).

Even though the initial ANOVA reported earlier had not revealed significant group differences in contextual cueing, MCI patients had displayed numerically (but not significantly) smaller learning effects than the controls, as well as the expected significantly smaller hippocampi. Therefore, to reduce the possibility that the contextual cueing by hippocampal volume relationship described above is driven by group effects, we also added MCI status as a covariate. The right hippocampus retained significance even after adding MCI diagnosis into the model, (estimate = 0.188, SE = 0.062; $p = 0.0045$), whereas MCI status was not significant (estimate = 1.703, SE = 17.54; $p = 0.92$). Consistent with a lack of group effect, a univariate model with MCI status was not significant, (estimate = 12.126, SE = 15.45; $p = 0.44$).

We also examined the extent to which contextual cueing within the MCI group alone is related to their hippocampal volume. In an analysis where MCI patients were dichotomized into large and small hippocampal volumes based on median split, individuals with larger hippocampi (mean: 149.72 ms; *SD*: 58.2; $n = 9$) showed significantly higher contextual cueing compared to those with smaller hippocampi (mean: −22.72 ms; *SD*: 103.6; $n = 10$), $t(17) = 4.39$; $p = .0004$. These findings, then, provide further support for the notion that contextual cueing deficit (or lack thereof) in MCI patients is linked to their hippocampal volumes.

Similarly, we examined the potential predicting role of age in contextual cueing in this cohort (Age range: 61–84 years). The univariate model with age as covariate was not significant, (estimate = − 1.787; SE = 2.352; $p = .45$), indicating that contextual cueing is not affected by age in this sample. Indeed, the relationship of right hippocampal volume with contextual cueing remained significant after adding age as a covariate to the model with ICV, (estimate = 0.176, *SE* = 0.059; $p = .0051$). Furthermore, in a model that included all the above covariates (age, ICV, and MCI status), right hippocampal volume continued to be a significant predictor of contextual cueing, (estimate = 0.169, SE = 0.067; $p = 0.015$). The right hippocampus remained significant even after a Bonferroni correction of $p = 0.025$, for multiple comparisons involving left and right hippocampi. Thus, these findings suggest that it is hippocampal volume, and not MCI diagnosis or age, which best predicts contextual cueing effect.

Hippocampal Subfields and other MTL Regions

While the hippocampus is often presented as a single structure, it is in fact a complex, heterogeneous region composed of several histologically distinct regions, which include the hippocampus proper (consisting of cornu ammonis subfields, CA1, CA2, CA3), dentate gyrus (DG), and subiculum (SUB) (Amaral & Lavenex, 2007). These subfields likely make unique contributions to memory processes and appear to be differentially vulnerable to AD pathology; for instance, the neurofibrillary tangle (NFT) pathology in AD tends to most prominently involve the CA1 subfield of the hippocampus proper (Bobinski et al., 1998; West, Coleman, Flood, & Troncoso, 1994). Thus, we further examined the differential role of hippocampal subfields in contextual cueing using T2-weighted images. More importantly, there is currently some debate over the involvement of hippocampus in contextual cueing, with some studies suggesting that it is the extrahippocampal MTL region, rather than hippocampus

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Table 2. Associations between Contextual Cueing and MTL Subregions

Variables[a]	Estimate (SE)[b]	*p* Value
CA1	0.70 (0.21)	**0.0021**
CA2	0.009 (0.07)	0.184
CA3	–0.01 (0.03)	0.637
DG	0.33 (0.14)	**0.023**
SUB	0.17 (0.06)	**0.014**
ERC	0.002 (0.005)	0.720
BA35	0.002 (0.005)	0.697
BA36	–0.008 (0.018)	0.653

Note. All the variables represent regions on the right hemisphere.
[a]Linear regression models adjusted for intracranial volume (ICV).
[b]The estimates are unstandardized beta weights.
CA = cornu ammonis; DG = dentate gyrus; SUB = subiculum; ERC = entorhinal cortex; BA = Brodmann area.

per se, that is critical to contextual cueing (Manns & Squire, 2001; Preston & Gabrieli, 2008). As anterior extrahippocampal MTL regions are also significantly affected in prodromal AD, particularly the entorhinal cortex (ERC) and perirhinal cortex (PRC, which includes Brodmann areas 35 and 36: BA35/BA36), we wanted to examine the relationship of contextual cuing to these regions. This is a particularly important issue to assess given that hippocampal atrophy may serve, to some extent, as a surrogate for the atrophy in these extrahippocampal regions.

In a linear regression model, each of the regions (CA1, CA2, CA3, DG, SUB, ERC, BA35, and BA36) was entered as an independent variable, adjusted for ICV, and contextual cueing (difference score on last 10 blocks) was entered as a dependent variable. As Table 2 indicates, there were significant associations between contextual cueing and hippocampal subfields in the right hemisphere, particularly, CA1, dentate gyrus, and subiculum. Parahippocampal regions (ERC/PRC), on the other hand, did not show significance. These findings provide further support for the distinct role of hippocampus in contextual cueing; the involvement of CA1 and dentate gyrus is also consistent with literature from animal model studies postulating that these regions are involved in pattern separation and higher-order representation of stimuli embedded in contexts and places (Chen, Olsen, Preston, Glover, & Wagner, 2011; Lee & Solivan, 2010; Tsien, Huerta, & Tonegawa, 1996)

Finally, we examined the potential role of the caudate nucleus in contextual cueing as this region has been implicated in several implicit learning forms (Knowlton, Mangels, & Squire, 1996; Lieberman, 2000; Stillman et al., 2013). In an analysis that controlled for ICV, we observed no significant relationship between contextual cueing and the caudate nucleus, either for the left, (estimate = 0.027, SE = 0.021; $p = 0.19$) or right (estimate = .025, SE = 0.016; $p = 0.13$), hemisphere. These findings, then, provide further support for the notion that contextual cueing performance is dependent on hippocampal, but not caudate, integrity.

DISCUSSION

The present study investigated contextual cueing in aMCI, with the main goal of examining the potential role of hippocampal volume in this form of learning. Several findings emerged. First, behavioral results did not reveal a statistically significant difference in contextual cueing between aMCI and healthy control groups, with both groups showing the cueing effect. Second, and more importantly, the contextual cueing effect was found to have a significant and linear relationship with right hippocampal volume, but not extrahippocampal MTL structures or caudate nucleus. Third, we confirmed the presence of a contextual cuing effect in an older adult population and a lack of modulation with age. Indeed, the current results specifically link the integrity of contextual cuing to hippocampal volume beyond the influence of both group status and age effects. We will discuss these findings in turn.

The lack of a statistically significant difference in contextual cuing between the groups is in contrast to our previous study in which we reported contextual cueing deficits in MCI compared to cognitively normal older adults (Negash et al., 2007). Several factors may have contributed to the conflicting findings, including heterogeneity of MCI and the individual variability exhibited by the contextual cueing task.

As discussed in more detail below, MCI is a heterogeneous diagnostic construct and only a subset of such individuals truly have underlying AD pathology (Albert et al., 2011). Likewise, cognitively normal adults are also heterogeneous in that a significant fraction of patients harbor "preclinical AD" related brain changes (Sperling et al., 2011). As such, difference in results between cohorts may reflect the relative enrichment of preclinical and prodromal AD in these populations. It is certainly possible that participants in the current cohort were in a milder stage of impairment and potentially more heterogeneous with regard to etiology than our prior study. In light of this etiologic uncertainty, to the extent that experimental paradigms can be specific to the underlying pathology, such as hippocampal atrophy, they can prove useful in early detection of AD-related changes.

The observed cross-experiment differences may also have been due to variability in the contextual cueing task itself. Several studies now report wide variations in contextual cueing performance, where participants within a reasonably homogenous group show different levels of cueing effects (Bennett, Barnes, Howard, & Howard, 2009; Lleras & Von Muhlenen, 2004; Vaidya, Huger, Howard, & Howard, 2007). As Figure 4 shows, we have also observed individual differences in the present study, where some participants within a given group (MCI or control) displayed learning effects while others did not. Furthermore, there were also participants who showed a negative or 'reverse' effect such that they responded faster to novel versus repeated configurations. The phenomenon of 'reverse learning' is puzzling and has also been observed by other studies (Bennett et al., 2009; Lleras & Von Muhlenen, 2004). It is unclear exactly what participants are learning about the regularity in this

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context, and more work is needed to understand the nature of learning in contextual cueing. In the present study, truncating negative scores to zero did not substantially impact the results. Nonetheless, relatively large variability of contextual cuing does reflect a limitation of the experimental paradigm.

Despite the lack of clear group difference in contextual cueing, we observed that contextual cueing was significantly associated with hippocampal volume, with lower hippocampal volume being associated with less learning. Furthermore, consistent with the lateralization of hippocampal involvement in visuospatial learning, we observed a significant association of contextual cueing for the right, but not left, hippocampus. We also examined the contributions of age and MCI status to the contextual cueing effect, and observed that right hippocampal volume was significantly associated with contextual cueing even after adjusting for these covariates. To the best of our knowledge, this is the first study highlighting the potential role of hippocampal volume, even more than MCI status or age, in predicting contextual cueing performance in MCI patients and healthy controls. Finally, we explored potential unique contributions of hippocampal subfields and extrahippocampal regions, and observed a distinct role for the hippocampus proper, with CA1, dentate gyrus, and subiculum, but not extrahippocampal MTL regions, displaying significant associations with contextual cueing. It is important to note, however, that because hippocampal subfield measures are highly correlated with each other, it is difficult to disentangle the role of specific subfields in this contextual cueing performance (e.g., CA1 *vs*. DG).

Whether hippocampus is involved in contextual cueing has been investigated in several patient and neuroimaging studies, with mixed results. Chun and Phelps conducted the first study using the contextual cueing paradigm in amnesic patients with damage to the medial temporal lobe system, including the hippocampus, and showed cueing deficits in patients compared to age- and education-matched controls (Chun & Phelps, 1999). This pattern was also replicated in a study using midazolam, a drug that induces temporary anterograde amnesia (Park, Quinlan, Thornton, & Reder, 2004). Manns and Squire, on the other hand, have compared amnesic patients with damage specific to hippocampal region and those with extensive damage to the MTL region, including extrahippocampal cortical regions, and found that patients with damage confined to the hippocampal region displayed contextual cueing, whereas those with more extensive MTL damage did not, and have, thus, argued that contextual cueing is not dependent on hippocampus (Manns & Squire, 2001). Results from functional neuroimaging studies have also been mixed. Some studies report that facilitated performance to repeated configurations is associated with increased hippocampal activation (Greene et al., 2007), with some evidence pointing to increased activation in the right hippocampus for repetition facilitation (Manelis & Reder, 2012). Others argue that hippocampal activation occurs only when there is explicit recognition of repeated contexts (Preston & Gabrieli, 2008; Westerberg, Miller, Reber, Cohen, & Paller, 2011). The present study provides support for the notion that the integrity of the hippocampus proper modulates contextual cueing performance; in patients diagnosed with MCI and healthy controls, lower hippocampal volume correlated with reduced cueing effect, suggesting that the observed effects in MCI may be mediated by associated hippocampal disease.

It is important to note the apparent paradoxical result in that we observed no group differences in contextual cueing despite group differences in hippocampal volume and associations between hippocampal volume and contextual cueing. We should first note that the absolute difference between groups was larger when the analysis was restricted to participants who underwent MRI scanning; 111.69 (SD = 110.4) and 58.96 (SD = 121.2), for control and MCI groups, respectively, which is more consonant with the hippocampal findings. Nonetheless, this group difference in contextual cueing still did not reach significance (p = .13).

Furthermore, it is possible that the higher variance of the experimental task might limit the power to observe a group difference relative to average hippocampal volume measurements despite the correlation of these measures. As stated above, there is relatively wide variation in contextual cueing performance within reasonably homogenous groups, a limitation of the method. Finally, the lack of group effect for contextual cueing despite the relationship with hippocampal volume may have been due, in part, to the heterogeneity of the MCI patients, and even controls. While a significant proportion of MCI patients likely have an underlying prodromal AD, many do not and either have other neurodegenerative (e.g., FTD, DLB) or non-neurodegenerative (vascular disease, more robust age-associated impairment) causes of their mild memory difficulties. Indeed, as the scatterplot in Figure 4 indicates, there is considerable overlap between the hippocampal volume of MCI and controls, consistent with the notion that several the MCI group likely do not have underlying AD given the much lower risk of progression in those with more normal hippocampal volumes, which has been extensively reported in the literature (e.g., Heister, Brewer, Magda, Blennow, & McEvoy, 2011; Jack et al., 1999). Furthermore, as several studies have shown, a substantial proportion of neuronal loss (30–50%) is required before volumetric changes are evident (Price et al., 2001; Rossler, Zarski, Bohl, & Ohm, 2002); as such, it is likely that some individuals harbor neuronal loss even when volumetric loss is not apparent. Additionally, recent work has suggested that approximately one-fourth or more of controls in this age range have "preclinical AD" (Sperling et al., 2011) and it is possible that this militates against the group difference on task performance due to some of these individuals beginning to develop hippocampal atrophy and/or dysfunction; nonetheless, these individuals would still support the overall relationship between hippocampal volume and the contextual cuing effect. These are important issues in the field currently, and warrant longitudinal studies.

As discussed above, most controversy around the neural bases of contextual cueing has focused on the hippocampus and related structures. However, our findings also speak to

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recent claims that the striatum might also be involved in contextual cueing. These claims are based on the finding that early stage Parkinson's disease patients (van Asselen et al., 2009) and prodromal and early stage Huntington's disease patients, conditions with primary basal ganglia pathology, fail to show contextual cueing (van Asselen et al., 2012). The lack of correlation between caudate nucleus volume and contextual cueing in our study does not support involvement of this region, at least in the population investigated here. More research is needed to clarify this issue.

Another finding from the present study was that, more generally, the data support the notion that older adults may display evidence of intact contextual cueing effects, as the term for age in the regression model was not significant and was not related to performance. The lack of relationship with age, however, should be considered in the context of a relatively restricted range in this sample (61–84 years old). There is currently some debate as to whether contextual cueing is affected in healthy aging. Howard and colleagues compared young and healthy older adults on the standard contextual cueing task using 30 learning blocks, and showed that contextual cueing is spared in healthy aging (Howard et al., 2004). Recently, Smyth and Shanks sought to replicate this finding in a contextual cueing task that used only 16 blocks, and found impaired cueing deficits in older adults (Smyth & Shanks, 2011). Thus, the observed age deficits in their study may have been due to insufficient training for older adults. Furthermore, it is important to note that despite this lack of effect of age per se, the relationship of age with hippocampal atrophy may be what drives any age deficits in contextual cueing reported in the literature. The present study provides support for this by showing that contextual cueing was dependent on hippocampal volume rather than age.

Finally, the significant, linear relationship between hippocampal volume and contextual cueing effect adds to the accumulating evidence that hippocampus is important for cognitive processes that require learning of spatial contexts. This linear relationship may also support the potential of this cognitive measure for detecting pathology within the hippocampus and for monitoring progression, as well as have implications for the nature of the computations performed by this structure, or specific subfields. However, while we expect the hippocampal correlations with contextual cueing are largely driven by AD-related hippocampal changes, it is possible that this relationship is non-specific; in some participants, it could be due to other factors that may be associated with hippocampal volume, such as non-AD related aging effects, variations in hippocampal development, and vascular risk factors. The relationship of contextual cueing with specific causes of hippocampal pathology is worthy of further study.

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