ORIGINAL ARTICLE

Memory-guided attention: bilateral hippocampal volume positively predicts implicit contextual learning

Mario A. Rosero[1] · Tobias Winkelmann[1] · Sebastian Pohlack[1] · Juliana Cavalli[1] · Frauke Nees[1] · Herta Flor[1]

Abstract

Several studies have begun to demonstrate that contextual memories constitute an important mechanism to guide our attention. Although there is general consensus that the hippocampus is involved in the encoding of contextual memories, it is controversial whether this structure can support implicit forms of contextual memory. Here, we combine automated segmentation of structural MRI with neurobehavioral assessment of implicit contextual memory-guided attention to test the hypothesis that hippocampal volume would predict the magnitude of implicit contextual learning. Forty healthy subjects underwent 3T magnetic resonance imaging brain scanning with subsequent automatic measurement of the total brain and hippocampal (right and left) volumes. Implicit learning of contextual information was measured using the contextual cueing task. We found that both left and right hippocampal volumes positively predicted the magnitude of implicit contextual learning. Larger hippocampal volume was associated with superior implicit contextual memory performance. This study provides compelling evidence that implicit contextual memory-guided attention is hippocampus-dependent.

Keywords Hippocampal volume · Contextual memory · Implicit memory · Visual search · Memory-guided attention

---

Frauke Nees and Herta Flor joint last authors.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00429-019-01887-9) contains supplementary material, which is available to authorized users.

✉ Herta Flor
herta.flor@zi-mannheim.de

Mario A. Rosero
mrosero671@unab.edu.co

Tobias Winkelmann
tobias.winkelmann@zi-mannheim.de

Sebastian Pohlack
sebastian.pohlack@zi-mannheim.de

Juliana Cavalli
julicavalli2828@gmail.com

Frauke Nees
frauke.nees@zi-mannheim.de

[1]   Department of Cognitive and Clinical Neuroscience, Central
      Institute of Mental Health, Medical Faculty Mannheim,
      Heidelberg University, Square J5, 68159 Mannheim,
      Germany

Introduction

In addition to its traditional role in episodic memory and spatial navigation, a substantial body of research in humans has shown that the hippocampus is also involved in contextual processing. Specifically, it has been reported that the hippocampus is critical for encoding of object-context associations (Henke et al. 1997; Cohen et al. 1999; Giovanello et al. 2003; Staresina and Davachi 2008), to establish associations between objects and their spatial location (Burgess et al. 2002; Ekstrom et al. 2003; Olson et al. 2006; Piekema et al. 2006) and the acquisition of contextual fear conditioning (Alvarez et al. 2008; Lang et al. 2009; Pohlack et al. 2012). Collectively, these studies suggest that one of the most important functions of the hippocampus consist of binding elements with their context to form memories.

While it is generally agreed that encoding of contextual or relational memories depends critically on the hippocampus, the selective role of the hippocampus in conscious expressions of these memories has been a subject of debate (Chun and Phelps 1999; Manns and Squire 2001; Park et al. 2004; Greene et al. 2007; Preston and Gabrieli 2008; Westerberg et al. 2011). Traditional models of hippocampal function emphasize the role of the hippocampus in the conscious

retrieval of past events (Tulving and Schacter 1990; Moscovitch 1992; Squire 2004). According to those theories, the hippocampus exclusively support the conscious recollection of event and facts, while other forms of learning that does not require conscious or deliberative access, depend on different brain systems such as the amygdala, caudate, putamen, globus pallidus and cerebellum (Tulving and Schacter 1990; Moscovitch et al. 2006). However, there is evidence indicating that the hippocampus is also involved in implicit forms of learning (Turk-Browne et al. 2008, 2010; Hannula and Ranganath 2009), including contextual facilitation, suggesting that the hippocampus is not only a brain region in which contextual representations may be formed but that it is also important when this process does not correspond to a conscious experience (Cohen et al. 1997; Konkel and Cohen 2009; Henke 2010; Ranganath 2010; Hannula and Greene 2012).

One important source of evidence for the role of the hippocampus in implicit contextual memory comes from the use of the contextual cueing paradigm developed by Chun and Jiang (1998), which has been shown to be sensitive to hippocampal function. In this paradigm, subjects are encouraged to search a target item (e.g. a letter T) embedded in a spatial array of distractors items (e.g. a set of the letters L). When the target is embedded in a repeated configuration of arrays, subjects spend less time in finding the target compared to a novel configuration of arrays. In the first case, the distractor items configure a context that predicts the location of the target facilitating the visual search. Interestingly, subjects are not able to explicitly recognize memory traces for repeated configurations of arrays. Using this paradigm, Chun and Phelps (1999) observed that subjects with hippocampal damage did not show the contextual facilitation in search times compared to controls subjects. Similar results were reported by Park et al. (2004), who injected the GABA-A agonist midazolam, a benzodiazepine that induces anterograde amnesia, in healthy subjects. In addition, Greene et al. (2007), using functional magnetic resonance imaging (fMRI), found that faster search times for repeated contexts are related to greater activation in the hippocampus. Other studies, however, have suggested that hippocampal activity is correlated with explicit recognition of repeated contexts (Preston and Gabrieli 2008; Westerberg et al. 2011). Indeed, it has been suggested that patients with circumscribed hippocampal damage performed normally in the contextual cueing task (Manns and Squire 2001). The source of this discrepancy remains under debate (Greene et al. 2007; Preston and Gabrieli 2008; Westerberg et al. 2011; Geyer et al. 2012). Taken together, there is increasing evidence that the hippocampus is critically involved in implicit contextual memory-guided attention.

While several fMRI studies have identified associations between implicit contextual learning and hippocampal BOLD activity, there are no studies on structural brain correlates of implicit contextual learning. Here, we use structural MRI to test the hypothesis that hippocampal volume would positively predict contextual cueing performance.

Materials and methods

Participants

Forty healthy subjects (28 males; mean age 27.23, SD 2.12, range 21–32 years) participated in the study. They were recruited in schools for ambulance rescue workers located in Southern Germany as part of a longitudinal study investigating predictors of post-traumatic stress disorder (Pohlack et al. 2011, 2012, 2014; Cacciaglia et al. 2015; Winkelmann et al. 2017). None of the participants had to be excluded due to mental disorders such as major depressive disorder, current or chronic substance abuse, schizophrenia or borderline personality disorder, as assessed with the German version of the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders-IV (Wittchen et al. 1997). The Ethics Committee of the Medical Faculty Mannheim of the University of Heidelberg approved the study, and we obtained written informed consent from all persons before participation.

Stimuli and design

Each experimental session consisted of a 25-min test phase in which participants completed a version of the Contextual Cueing task (Chun and Jiang 1998) implemented and executed in Matlab (Natick, MA, USA). The participants were encouraged to search a target item embedded in a spatial array of distractor items. The target was a T stimulus rotated 90° to the right or to the left. The distractor stimulus was an L shape presented randomly in one of four orientations (0°, 90°, 180°, 270°) with a 10 pixel offset at the line junctions. Each display consisted of 12 items (a single target and 11 distractors) randomly positioned in an invisible 8×6 matrix ($37.2° \times 28.3°$). For repeated display, the target appeared in the same location within an invariant configuration of distractors across blocks. For each new display, the distractor configurations were newly generated in each block. Visual stimuli were presented on a gray background in a 17-inch Viewsonic VG710b LCD monitor. The participants were seated 50 cm in front of the computer monitor.

Each trial consisted of the presentation of a 500 ms fixation cross, a display presentation (for a maximum of 6 s) and a variable duration inter-trial-interval (ITI; range 500–1000 ms). During the display presentation, the participants pressed one of the two buttons ("C" or "M") on a computer keyboard, corresponding to whether the bottom of

the T was pointed to the right or to the left. An example of the trial sequence is shown in Fig. 1. Following one practice block, each subject performed 20 blocks of the search task. Each block contained 24 intermixed trials of 12 repeated and 12 new displays. There were rest periods of 10 s between bocks.

Recognition test

After block 20 of the contextual cueing task, the participants were asked if they noticed that certain configurations of the stimuli were repeated from block to block (Chun and Jiang 1998). Then, an explicit recognition test was carried out to assess awareness of the contextual displays. Importantly, the participants were not informed at the beginning of the experimental session about the recognition test. In this test, the 12 repeated displays used in the experimental session and 12 novel displays were presented in random order (Chun and Jiang 1998). The participants were informed that certain display configurations were repeated during the experiment and were instructed to indicate whether each display presented was "repeated" or "new" by responding with 1 of 2 keys.

MRI acquisition

Magnetic resonance imaging was performed at the Central Institute of Mental Health in Mannheim with a 3T MAG-NETOM Trio whole-body scanner (Siemens Medical Solutions, Erlangen, Germany) equipped with a standard 12-channel head coil. T1-weighted high-resolution images were acquired with a magnetization-prepared rapid gradient echo (MPRAGE) sequence [TR 2300 ms, TE 2.98 ms,

field of view 240×256 mm^2, 160 sagittal slices, voxel size $1.0 \times 1.0 \times 1.1$ mm^3, parallel imaging (GRAPPA) factor 2].

MRI volumetry

The segmentation of the hippocampus, amygdala, caudate, putamen, pallidum, cerebellar cortex, and cortical regions (Desikan et al. 2006) were performed using the Freesurfer 5.0 image analysis suite, which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu/). Technical details of these procedures are described in prior publications (Dale et al. 1999; Fischl et al. 1999; Fischl and Dale 2000). The processing involves motion correction, removal of non-brain tissue using a hybrid watershed/surface deformation procedure, automated Talairach transformation, segmentation of the subcortical white and deep gray matter volumetric structures, intensity normalization, tessellation of the gray/white matter boundary, automated topology correction, and surface deformation following intensity gradients to optimally place the gray/white matter and gray matter/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class. Processing was performed on an 8-core UNIX workstation with the Graphics-Processing Unit option enabled. Freesurfer morphometric procedures have been validated against manual segmentation and VBM8 (Grimm et al. 2015) and demonstrate good test–retest reliability across scanner manufacturers and across field strengths (Han et al. 2006). Finally, right and left hippocampal and amygdalar, caudate, putamen, pallidum, cerebellar cortex, cortical regions, and total gray matter volumes were calculated in cubic centimeters and then normalized to the

Fig. 1 Experimental Paradigm. Each block contained 24 randomly interleaved trials of 12 repeated and 12 new contexts. On each trial, subjects fixated a central cross for 500 ms. After that, a search array was presented for a maximum of 6 s or until a response was made (subjects indicated whether the bottom of the T was pointed to the right or to the left). A variable duration ITI (500–1000 ms) separated subsequent trials
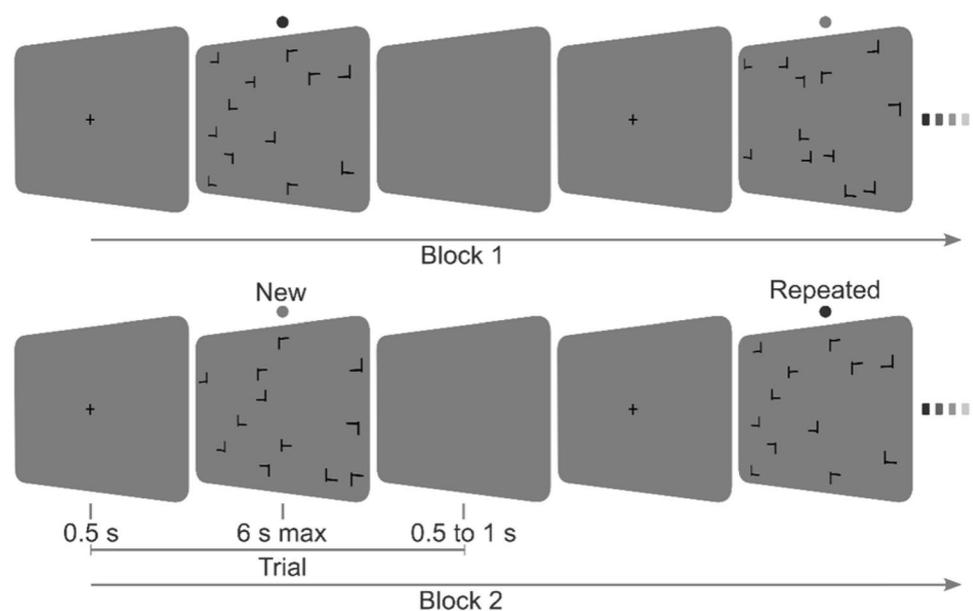
estimated total intracranial volume of each individual, also provided by FreeSurfer.

Statistical analyses

For analysis purposes, search reaction times (RTs) of the 20 blocks were grouped into sets of five yielding four epochs and analyzed using two-way repeated measures ANOVA, based on trials performed correctly within [0.5, 6] s. The independent variables were (1) Context (novel vs. repeated), and (2) Epoch (1 vs. 4). The contextual cueing effect was calculated as the difference in RTs between Old and New arrays collapsed across epochs 3–4 (Chun and Phelps 1999). Differences in the magnitude of contextual cueing effect were evaluated with Student's *t* test. To examine whether participants had explicit recognition of repeated contexts, a paired-samples *t* test on hits and false alarms for the recognition test was conducted (Manginelli et al. 2013). To further address the possibility that explicit recognition of repeated contexts could influence visual search facilitation in the contextual cueing task, the correlations between hit rate and the magnitude of the contextual cueing, corrected hit rate and the magnitude of the contextual cueing effect, and corrected hit rate and left or right hippocampal volumes were calculated (Preston and Gabrieli 2008; Manginelli et al. 2013). To explore relationships between volumetric and behavioral data, linear regression analyses were conducted on the entire sample ($n = 40$), separately for amygdalar, hippocampal, caudate, putamen, pallidum, cerebellar cortex, cortical regions, and total gray matter volumes. For each regression analysis, contextual cueing performance was entered as dependent variable. An additional linear regression analyses was carried out including only those participants who showed a positive (above-zero) contextual cueing effect ($n = 34$). To control for possible influences of demographic variables, partial correlations between volumetric and behavioral data were performed, including age, sex and years of education as confounds. For each of the analyses, the alpha level was set to 0.05. Data are reported as mean ± SD unless otherwise stated. All analyses and statistical tests were performed in Matlab.

Results

Search task

Less than 3% of all trials were omitted from the analyses due to incorrect trials and trials with RT outside of the 0.5–6 s range. Overall accuracy for the new and repeated trials was 99.14 ± 0.9% and 99.34 ± 0.67%, respectively. Accuracy did not differ by array type ($t(39) = 1.67$, $p = 0.102$).

Consistent with previous findings (Chun and Jiang 1998; Manelis and Reder 2012) we found a significant main effect of context (novel vs. repeated), $F(1,39) = 15.41$, $p < 0.001$), indicating that search RTs were faster for repeated than for novel contexts. There was a significant main effect of epoch, $F(1,39) = 169.95$, $p < 0.001$, indicating that search RTs decreased during the task for both types of contexts. In addition, the epoch × context interaction was significant, $F(1,39) = 23.25$, $p < 0.001$, indicating that during the task, search RTs for repeated contexts decreased more than for novel contexts (Fig. 2). The magnitude of contextual cueing was significantly greater than zero (0.125 ± 0.129 s, $t(39) = 6.09$, $p < 0.001$).

Recognition test

Before the explicit recognition test, the participants were asked if they noticed that some displays were repeated during the experiment. None of the participants reported noticing the repeated displays. For the explicit recognition test, the probability that repeated contexts were correctly recognized (hit rate) was 0.32, and this did not differ from the probability that new contexts were misidentified as repeated contexts (false alarm), 0.26, ($t(39) = 1.90$, $p = 0.064$). Furthermore, neither the hit rate nor the corrected hit rate correlated with the magnitude of the contextual cueing effect ($r = 0.04$, $p = 0.760$, $r = -0.01$, $p = 0.934$, respectively). Likewise, the corrected hit rate did not correlate with either left ($r = 0.04$, $p = 0.760$) or right hippocampal volumes. Taken together, there was no clear evidence of explicit recognition of repeated contexts.
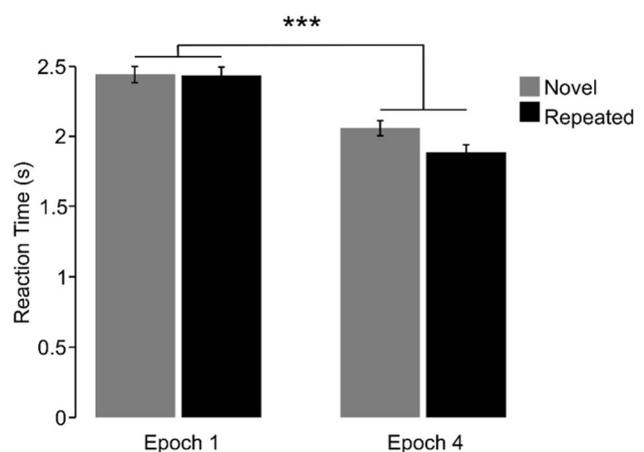
**Fig. 2** Mean correct RTs for novel versus repeated contexts as a function of epoch (Mean ± SEM)

Regression analyses

Linear regression analyses conducted on the entire sample ($n = 40$) revealed that left hippocampal volume significantly predicted contextual cueing performance ($\beta = 0.51$, $t(38) = 3.69$, $p = 0.001$, $r^2 = 0.26$). Right hippocampal volume also significantly predicted contextual cueing performance ($\beta = 0.43$, $t(38) = 2.96$, $p = 0.005$, $r^2 = 0.18$), which is illustrated in Fig. 3. As expected, we found not significant effects of either left ($\beta = 0.30$, $t(38) = 1.97$, $p = 0.056$, $r^2 = 0.09$) or right ($\beta = -0.00$, $t(38) = -0.02$, $p = 0.979$, $r^2 = 0.00$) amygdalar, left ($\beta = -0.07$, $t(38) = -0.47$, $p = 0.639$, $r^2 = 0.01$) or right ($\beta = -0.07$, $t(38) = -0.04$, $p = 0.629$, $r^2 = 0.01$) caudate nucleus, left ($\beta = 0.12$, $t(38) = 0.80$, $p = 0.426$, $r^2 = 0.02$) or right ($\beta = 0.08$, $t(38) = 0.54$, $p = 0.589$, $r^2 = 0.01$) putamen, left ($\beta = 0.03$, $t(38) = 0.20$, $p = 0.842$, $r^2 = 0.00$) or right ($\beta = -0.14$, $t(38) = -0.91$, $p = 0.367$, $r^2 = 0.02$) pallidum, or left ($\beta = 0.29$, $t(38) = 1.88$, $p = 0.068$, $r^2 = 0.09$) or right ($\beta = 0.30$, $t(38) = 1.96$, $p = 0.057$, $r^2 = 0.09$) cerebellar cortex volumes, in predicting contextual cueing performance (Fig. 3). Similar results were obtained including only those participants who exhibited a positive contextual cueing effect ($n = 34$). The results revealed that either left ($\beta = 0.38$, $t(32) = 2.36$, $p = 0.024$, $r^2 = 0.15$) or right ($\beta = 0.41$, $t(32) = 2.60$, $p = 0.014$, $r^2 = 0.17$) hippocampal volumes significantly predicted contextual cueing performance. On the contrary, either left ($\beta = 0.24$, $t(32) = 1.43$, $p = 0.161$, $r^2 = 0.06$) or right ($\beta = 0.07$, $t(32) = 0.40$, $p = 0.691$, $r^2 = 0.00$) amygdalar, left ($\beta = -0.05$, $t(32) = -0.28$, $p = 0.744$, $r^2 = 0.00$) or right ($\beta = -0.02$, $t(32) = -0.14$, $p = 0.888$, $r^2 = 0.00$) caudate nucleus, left ($\beta = 0.18$, $t(32) = 1.04$, $p = 0.305$, $r^2 = 0.03$) or right ($\beta = 0.11$, $t(32) = 0.65$, $p = 0.515$, $r^2 = 0.01$) putamen, left ($\beta = -0.04$, $t(32) = -0.26$, $p = 0.795$, $r^2 = 0.00$) or right ($\beta = -0.16$, $t(32) = -0.95$, $p = 0.384$, $r^2 = 0.03$) pallidum, or left ($\beta = 0.23$, $t(32) = 1.39$, $p = 0.174$, $r^2 = 0.06$) or right ($\beta = 0.25$, $t(32) = 1.48$, $p = 0.149$, $r^2 = 0.06$) cerebellar cortex volumes, did not significantly predict contextual cueing performance.

With regard to the relationship between cortical volumes and contextual cueing performance, linear regression analyses conducted on the entire sample ($n = 40$) revealed that
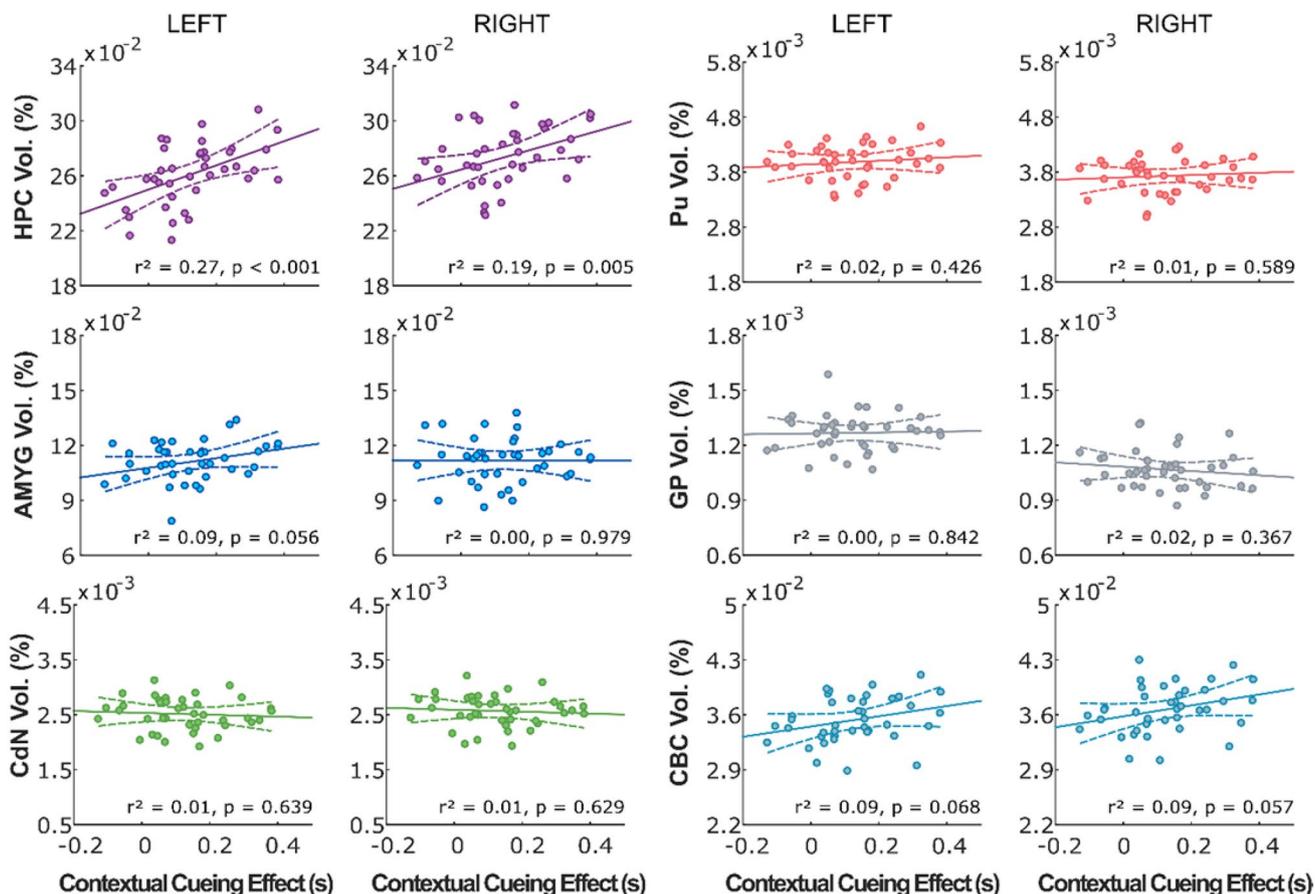
Fig. 3 Hippocampal (HPC) but no amygdalar (AMYG) caudate nucleus (CdN), putamen (Pu), globus pallidum (GP), or cerebellar cortex (CBC) volumes significantly predicted contextual cueing performance. Solid lines represent the line of best fit, and dashed lines represent 95% confidence intervals

both left ($\beta = 0.37$, $t(38) = 2.47$, $p = 0.018$, $r^2 = 0.14$) or right ($\beta = 0.50$, $t(38) = 3.53$, $p = 0.001$, $r^2 = 0.25$) parahippocampal gyrus, left ($\beta = 0.41$, $t(38) = 2.79$, $p = 0.008$, $r^2 = 0.17$) entorhinal cortex, left ($\beta = 0.38$, $t(38) = 2.51$, $p = 0.016$, $r^2 = 0.14$) supramarginal gyrus, or left ($\beta = 0.37$, $t(38) = 2.48$, $p = 0.017$, $r^2 = 0.14$) isthmus of the cingulate cortex volumes, significantly predicted contextual cueing performance, and (Table 1). In contrast, no significant relationships between other cortical regions (Table 1), or total gray matter volumes ($\beta = 0.27$, $t(38) = 1.72$, $p = 0.092$, $r^2 = 0.07$) and contextual

cueing performance were observed. Finally, we conducted linear regression analyses including only those participants who showed a positive contextual cueing effect ($n = 34$). revealed that both left ($\beta = 0.46$, $t(32) = 2.94$, $p = 0.006$, $r^2 = 0.21$) or right ($\beta = 0.40$, $t(32) = 2.48$, $p = 0.018$, $r^2 = 0.16$) parahippocampal gyrus, left ($\beta = 0.38$, $t(32) = 2.51$, $p = 0.016$, $r^2 = 0.14$) supramarginal gyrus, or left ($\beta = 0.41$, $t(32) = 2.54$, $p = 0.016$, $r^2 = 0.17$) isthmus of the cingulate cortex volumes significantly predicted contextual cueing performance (Supplementary Table 1). Conversely,

Table 1 Summary of linear regression analysis results predicting contextual cueing performance from cortical volumes of Desikan parcellations

Cortical regions	Left hemisphere				Right hemisphere			
	β	$t(38)$	P value	r^2	β	$t(38)$	P value	r^2
Temporal lobe								
Entorhinal cortex	0.41	2.79	0.008**	0.17	0.13	0.78	0.437	0.02
Parahippocampal gyrus	0.37	2.47	0.018*	0.14	0.50	3.53	0.001**	0.25
Temporal pole	0.15	0.94	0.353	0.02	0.14	0.89	0.379	0.02
Fusiform gyrus	−0.13	−0.78	0.440	0.02	0.05	0.33	0.746	0.00
Superior temporal gyrus	0.16	1.01	0.321	0.03	0.15	0.96	0.343	0.02
Middle temporal gyrus	−0.01	−0.07	0.944	0.00	0.05	0.30	0.763	0.00
Inferior temporal gyrus	0.22	1.36	0.182	0.05	0.28	1.77	0.085	0.08
Transverse temporal cortex	0.13	0.79	0.437	0.02	0.15	0.95	0.346	0.02
Banks of the superior temporal sulcus	0.16	0.98	0.334	0.02	−0.05	−0.33	0.743	0.00
Frontal lobe								
Superior frontal gyrus	0.12	0.72	0.473	0.01	−0.08	−0.48	0.632	0.01
Rostral middle frontal gyrus	−0.09	−0.53	0.598	0.01	−0.04	−0.22	0.824	0.00
Caudal middle frontal gyrus	−0.07	−0.44	0.662	0.01	−0.09	−0.58	0.568	0.01
Inferior frontal gyrus: pars opercularis	0.02	0.10	0.918	0.00	−0.23	−1.46	0.153	0.05
Inferior frontal gyrus: pars triangularis	0.05	0.29	0.774	0.00	0.02	0.09	0.925	0.00
Inferior frontal gyrus: pars orbitalis	−0.07	−0.42	0.675	0.00	0.18	1.14	0.261	0.03
Lateral orbitofrontal cortex	0.20	1.27	0.211	0.04	0.16	0.98	0.331	0.02
Medial orbitofrontal cortex	0.09	0.53	0.596	0.01	0.10	0.64	0.527	0.01
Frontal pole	0.27	1.72	0.093	0.07	0.18	1.14	0.263	0.03
Precentral gyrus	−0.06	−0.38	0.703	0.00	0.03	0.18	0.858	0.00
Paracentral lobule	−0.03	−0.21	0.835	0.00	−0.19	−1.20	0.238	0.04
Parietal lobe								
Postcentral gyrus	0.15	0.91	0.371	0.02	0.29	1.87	0.069	0.08
Supramarginal gyrus	0.38	2.51	0.016*	0.14	−0.03	−0.16	0.871	0.00
Superior parietal cortex	−0.13	−0.81	0.423	0.02	−0.22	−1.38	0.176	0.05
Inferior parietal cortex	−0.03	−0.17	0.866	0.00	0.14	0.85	0.403	0.02
Precuneus cortex	0.08	0.47	0.639	0.01	0.09	0.57	0.574	0.01
Occipital lobe								
Lingual gyrus	0.19	1.19	0.241	0.04	0.27	1.71	0.095	0.07
Pericalcarine cortex	−0.07	−0.41	0.683	0.00	0.05	0.34	0.739	0.00
Cuneus cortex	−0.01	−0.03	0.972	0.00	0.18	1.13	0.267	0.03
Lateral occipital cortex	0.02	0.14	0.888	0.00	0.01	0.06	0.953	0.00
Rostral anterior cingulate cortex	−0.11	−0.68	0.500	0.01	−0.18	−1.13	0.265	0.03
Caudal anterior cingulate cortex	−0.21	−1.36	0.183	0.05	−0.07	−0.46	0.650	0.01
Posterior cingulate cortex	0.03	0.21	0.838	0.00	−0.05	−0.32	0.751	0.00
Isthmus cingulate cortex	0.37	2.48	0.017*	0.14	0.22	1.42	0.164	0.05

*$P < 0.05$, **$P < 0.01$

no significant relationships between other cortical regions (Supplementary Table 1) and contextual cueing performance were found.

Discussion

Contextual memories are an important mechanism to generate predictions (Bar and Ullman 1996; Hyman et al. 2012), to guide our attention (Chun and Jiang 1998; Auckland et al. 2007; Turk-Browne et al. 2008; Hannula and Ranganath 2009; Goldfarb et al. 2016), to modulate our emotion (Rudy et al. 2004; Brewin et al. 2007; Lang et al. 2009; Acheson et al. 2012; Maren et al. 2013) and ultimately to construct meaning. Since contextual memories play a pivotal role in perception and cognition, there has been an intense interest in understanding the neural mechanisms that support such relational memories. Neuropsychological, electrophysiological, and neuroimaging studies have suggested that the hippocampus is a key structure for contextual memory (Burgess et al. 2002; Ekstrom et al. 2003; Manelis et al. 2011) and that the hippocampus can support implicit forms of contextual memory (Chun and Phelps 1999; Turk-Browne et al. 2008, 2010; Hannula and Ranganath 2009). Here we investigated the role of hippocampal volume in predicting contextual learning in healthy humans. Consistent with our predictions, we found that hippocampal, but not, amygdalar, caudate, putamen, pallidum, or cerebellar cortex volumes predicted the magnitude of contextual learning. Importantly, left and right parahippocampal gyrus left supramarginal gyrus and left isthmus of the cingulate cortex volumes also predicted contextual cueing performance. The results reported here supported convergent evidence that the implicit contextual learning is hippocampus-dependent.

The present data were largely consistent with previous neuropsychological and pharmacological studies on the hippocampus involvement in contextual cueing effect (Chun and Phelps 1999; Park et al. 2004). Our results also complement previous structural MRI findings that shows a specific link between hippocampal volume and contextual memory performance (Rajah et al. 2010; Horner et al. 2012; Pohlack et al. 2012). Similarly, these results also are congruent with previous fMRI and PET studies that has shown increased hippocampal activity during the processing of contextual associations (Henke et al. 1997; Cohen et al. 1999; Greene et al. 2007; Alvarez et al. 2008; Staresina and Davachi 2008; Lang et al. 2009; Manelis and Reder 2012; Giesbrecht et al. 2013; Goldfarb et al. 2016).

In agreement with previous reports, our results indicate that the facilitation for repeated context did not depend on explicit recognition. These results are consistent with previous studies showing that the hippocampus participates in some kinds of implicit learning (Hannula and Ranganath 2009; Turk-Browne et al. 2008, 2010) and support the view that the hippocampus is not only responsible for integrating contextual information, but also that these processes maybe done in the absence of explicit recognition (Cohen et al. 1997; Konkel and Cohen 2009; Reder et al. 2009: Henke 2010; Hannula and Ranganath 2009; Hannula and Greene 2012).

Considered together, these results are consistent with relational memory theory (Eichenbaum et al. 1994), which suggests that the hippocampus is critical for forming associations among items of events. Contrary to the idea that the hippocampus plays a selective role in conscious memory (Squire 2004), an extension of the relational memory theory (Cohen et al. 1997; Ryan and Cohen 2003; Moses and Ryan 2006; Moscovitch 2008) suggests that the hippocampus can support relational memory in the absence of consciousness and that the conscious awareness of encoded and retrieved content is determined by the interaction of the hippocampus with other structures (e.g., prefrontal and parietal regions).

In addition, this study provides evidence that three cortical regions volumes also predicted contextual cueing performance. These areas include the parahippocampal gyrus, the supramarginal gyrus, as well as the isthmus of the cingulate cortex. The involvement of parahippocampal gyrus in implicit contextual memory is consistent with previous observations that parahippocampal cortex responds preferentially to the global spatial configuration of the scenes independent of individual items in the scenes (Epstein and Kanwisher 1998; Epstein and Ward 2010). Likewise, our finding is in agreement with previous reports of parahippocampal cortex engagement in the encoding of spatial contextual information (Bar et al. 2008; Aminoff et al. 2013). Importantly, it has been suggested that the parahippocampal cortex supports the visual encoding of contexts, independently of the fact that this learning is accessible or not accessible to consciousness (Aminoff et al. 2013). Similarly, our results extend previous findings that have implicated the isthmus of the cingulate cortex (retrosplenial cortex) in the processing of contextual associations (Aminoff et al. 2008; Peters et al. 2009; Kveraga et al. 2011), suggesting that the retrosplenial cortex plays a significant role in translating a particular context into a more abstract representation of that context. In addition to the supramarginal gyrus involvement in phonological short-term memory (Buchsbaum and D'Esposito 2009) and long term memory retrieval (Rosen et al. 2017), recent evidence indicates that the ventral posterior parietal cortex (including the supramarginal gyrus) activity also occurs for implicit retrieval (Elman and Shimamura 2011). Taken together, these findings suggest that the hippocampus, parahippocampal cortex, supramarginal gyrus, and the isthmus of the cingulate cortex are part of a brain network that supports both implicit and explicit contextual memory formation and retrieval.

Although the aim of the current study was to examine if hippocampal volume would positively predict contextual cueing performance, the hippocampal system does not tend to work in isolation. Visual search facilitation in repeated contexts could involve reciprocal interactions between medial temporal lobe structures and both dorsal and ventral attentional networks (Hutchinson and Turk-Browne 2012) and the striatum (Goldfarb et al. 2016). Consequently, voluntary control of attention; stimulus–response associations, and exogenous attentional load can interfere with the encoding and expression of implicit memories (Lee et al. 2013; Turk-Browne et al. 2013; Goldfarb et al. 2016). Future research should examine the influence of both dorsal and ventral attentional networks in implicit contextual learning.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical statement The authors state that this manuscript is in accordance with the Authorship statement of ethical standards for manuscripts submitted to Brain Structure and Function.

Ethical approval The Ethics Committee of the Medical Faculty Mannheim of the University of Heidelberg approved the study.

Informed consent We obtained written informed consent from all persons before participation.

References

Acheson DT, Gresack JE, Risbrough VB (2012) Hippocampal dysfunction effects on context memory: possible etiology for posttraumatic stress disorder. Neuropharmacology 62(2):674–685

Alvarez RP, Biggs A, Chen G, Pine DS, Grillon C (2008) Contextual fear conditioning in humans: cortical-hippocampal and amygdala contributions. J Neurosci 28(24):6211–6219

Aminoff E, Schacter DL, Bar M (2008) The cortical underpinnings of context-based memory distortion. J Cogn Neurosci 20:2226–2237

Aminoff E, Kveraga K, Bar M (2013) The role of the parahippocampal cortex in cognition. Trends Cogn Sci 17:379–390

Auckland ME, Cave KR, Donnelly N (2007) Nontarget objects can influence perceptual processes during object recognition. Psychon Bull Rev 14(2):332–337

Bar M, Ullman S (1996) Spatial context in recognition. Perception 25:343–352

Bar M, Aminoff E, Ishai A (2008) Famous faces activate contextual associations in the parahippocampal cortex. Cereb Cortex 18:1233–1238

Brewin CR, Kleiner JS, Vasterling JJ, Field AP (2007) Memory for emotionally neutral information in posttraumatic stress disorder: a meta-analytic investigation. J Abnorm Psychol 116(3):448–463

Buchsbaum B, D'Esposito M (2009) Repetition suppression and reactivation in auditory-verbal short-term recognition memory Cereb. Cortex 19:1474–1485

Burgess N, Maguire EA, O'Keefe J (2002) The human hippocampus and spatial and episodic memory. Neuron 35(4):625–641

Cacciaglia R, Pohlack ST, Flor H, Nees F (2015) Dissociable roles for hippocampal and amygdalar volume in human fear conditioning. Brain Struct Funct 220:2575–2586

Chun MM, Jiang Y (1998) Contextual cueing: implicit learning and memory of visual context guides spatial attention. Cogn Psychol 36(1):28–71

Chun MM, Phelps EA (1999) Memory deficits for implicit contextual information in amnesic subjects with hippocampal damage. Nat Neurosci 2(9):844–847

Cohen NJ, Poldrack R, Eichenbaum H (1997) Memory for items and memory for relations in the procedural/declarative memory framework. Memory 5:131–178

Cohen NJ, Ryan J, Hunt C, Romine L, Wszalek T, Nash C (1999) Hippocampal system and declarative (relational) memory: summarizing the data from functional neuroimaging studies. Hippocampus 9(1):83–98

Dale AM, Fischl B, Sereno MI (1999) Cortical surface-based analysis. I. Segmentation and surface reconstruction. Neuroimage 9(2):179–194

Desikan RS, Segonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, Buckner RL, Dale AM, Maguire RP, Hyman BT, Albert MS, Killiany RJ (2006) An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage 31:968–980

Eichenbaum H, Otto T, Cohen NJ (1994) Two component functions of the hippocampal memory system. Behav Brain Sci 17:449–517

Ekstrom AD, Kahana MJ, Caplan JB, Fields TA, Isham EA, Newman EL, Fried I (2003) Cellular networks underlying human spatial navigation. Nature 425(6954):184–188

Elman JA, Shimamura AP (2011) Task relevance modulates successful retrieval effects during explicit and implicit memory tests. Neuroimage 56:345–353

Epstein R, Kanwisher N (1998) A cortical representation of the local visual environment. Nature 392:598–601

Epstein R, Ward E (2010) How reliable are visual context effects in the parahippocampal place area? Cereb Cortex 20:294–303

Fischl B, Dale AM (2000) Measuring the thickness of the human cerebral cortex from magnetic resonance images. Proc Natl Acad Sci USA 97:11044–11049

Fischl B, Sereno MI, Dale AM (1999) Cortical surface-based analysis. II: inflation, flattening, and a surface-based coordinate system. Neuroimage 9(2):195–207

Geyer T, Baumgartner F, Müller HJ, Pollmann S (2012) Medial temporal lobe-dependent repetition suppression and enhancement due to implicit vs. explicit processing of individual repeated search displays. Front Hum Neurosci 6:272

Giesbrecht B, Sy JL, Guerin SA (2013) Both memory and attention systems contribute to visual search for targets cued by implicitly learned context. Vis Res 85:80–89

Giovanello KS, Verfaellie M, Keane MM (2003) Disproportionate deficit in associative recognition relative to item recognition in global amnesia. Cogn Affect Behav Neurosci 3(3):186–194

Goldfarb EV, Chun MM, Phelps EA (2016) Memory-guided attention: independent contributions of the hippocampus and striatum. Neuron 89:317–324

Greene AJ, Gross WL, Elsinger CL, Rao SM (2007) Hippocampal differentiation without recognition: an fMRI analysis of the contextual cueing task. Learn Mem 14(8):548–553

Grimm O, Pohlack S, Cacciaglia R, Winkelmann T, Plichta MM, Demirakca T, Flor H (2015) Amygdalar and hippocampal volume:

a comparison between manual segmentation, Freesurfer and VBM. J Neurosci Methods 253:254–261

Han X, Jovicich J, Salat D, van der Kouwe A, Quinn B, Czanner S, Busa E, Pacheco J, Albert M, Killiany R, Maguire P, Rosas D, Makris N, Dale A, Dickerson B, Fischl B (2006) Reliability of MRI-derived measurements of human cerebral cortical thickness: the effects of field strength, scanner upgrade and manufacturer. Neuroimage 32:180–194

Hannula DE, Greene AJ (2012) The hippocampus reevaluated in unconscious learning and memory: at a tipping point? Front Hum Neurosci 6(80):1–20

Hannula DE, Ranganath C (2009) The eyes have it: hippocampal activity predicts expression of memory in eye movements. Neuron 63:592–599

Henke K (2010) A model for memory systems based on processing modes rather than consciousness. Nat Rev Neurosci 11(7):523–532

Henke K, Buck A, Weber B, Wieser HG (1997) Human hippocampus establishes associations in memory. Hippocampus 7(3):249–256

Horner AJ, Gadian DG, Fuentemilla L, Jentschke S, Vargha-Khadem F et al (2012) A rapid, hippocampus-dependent, item-memory signal that initiates context memory in humans. Curr Biol 22:2369–2374

Hutchinson JB, Turk-Browne NB (2012) Memory-guided attention: control from multiple memory systems. Trends Cogn Sci 16(12):576–579

Hyman JM, Ma L, Balaguer-Ballester E, Durstewitz D, Seamans JK (2012) Contextual encoding by ensembles of medial prefrontal cortex neurons. Proc Natl Acad Sci 109(13):5086–5091

Konkel A, Cohen NJ (2009) Relational memory and the hippocampus: representations and methods. Front Neurosci 3:166–174

Kveraga K et al (2011) Early onset of neural synchronization in the contextual associations network. Proc Natl Acad Sci USA 108:3389–3394

Lang S, Kroll A, Lipinski SJ, Wessa M, Ridder S, Christmann C et al (2009) Context conditioning and extinction in humans: differential contribution of the hippocampus, amygdala and prefrontal cortex. Eur J Neurosci 29(4):823–832

Lee TG, Blumenfeld RS, D'Esposito M (2013) Disruption of dorsolateral but not ventrolateral prefrontal cortex improves unconscious perceptual memories. J Neurosci 33(32):13233–13237

Manelis A, Reder LM (2012) Procedural learning and associative memory mechanisms contribute to contextual cueing: evidence from fMRI and eye-tracking. Learn Mem 9:527–534

Manelis A, Reder LM, Hanson SJ (2011) Dynamic changes in the medial temporal lobe during incidental learning of object-location associations. Cereb Cortex 22:828–837

Manginelli A, Langer N, Klose D, Pollmann S (2013) Contextual cueing under working memory load: selective interference of viuospatial load with expression of learning. Attent Percept Psychophys 75:1103–1117

Manns JR, Squire LR (2001) Perceptual learning, awareness, and the hippocampus. Hippocampus 11:776–782

Maren S, Phan KL, Liberzon I (2013) The contextual brain: implications for fear conditioning, extinction and psychopathology. Nat Rev Neurosci 14(6):417–428

Moscovitch M (1992) Memory and working-with-memory: a component process model based on modules and central systems. J Cogn Neurosci 4:257–267

Moscovitch M (2008) The hippocampus as a "stupid" domain-specific module: implications for theories of recent and remote memory, and of imagination. Can J Exp Pychol 62:62–79

Moscovitch M, Nadel L, Winocur G, Gilboa A, Rosenbaum RS (2006) The cognitive neuroscience of remote episodic, semantic and spatial memory. Curr Opin Neurobiol 16:179–190

Moses SN, Ryan JD (2006) A comparison and evaluation of the predictions of relational and conjunctive accounts of hippocampal function. Hippocampus 16:43–65

Olson IR, Moore KS, Stark M, Chatterjee A (2006) Visual working memory is impaired when the medial temporal lobe is damaged. J Cogn Neurosci 18:1087–1097

Park H, Quinlan J, Thornton E, Reder LM (2004) The effect of midazolam on visual search: implications for understanding amnesia. Proc Natl Acad Sci USA 101(51):17879–17883

Peters J, Daum I, Gizewski E, Forsting M, Suchan B (2009) Associations evoked during memory encoding recruit the context-network. Hippocampus 19:141–151

Piekema C, Kessels RP, Mars RB, Petersson KM, Fernandez G (2006) The right hippocampus participates in short-term memory maintenance of object-location associations. Neuroimage 33:374–382

Pohlack ST, Nees F, Ruttorf M, Witt SH, Nieratschker V, Rietschel M, Flor H (2011) Risk variant for schizophrenia in the neurogranin gene impacts on hippocampus activation during contextual fear conditioning. Mol Psychiatry 16(11):1072–1073

Pohlack ST, Nees F, Liebscher C, Cacciaglia R, Diener SJ, Ridder S et al (2012) Hippocampal but not amygdalar volume affects contextual fear conditioning in humans. Hum Brain Mapp 33(2):478–488

Pohlack ST, Meyer P, Cacciaglia R, Liebscher C, Ridder S, Flor H (2014) Bigger is better! Hippocampal volume and declarative memory performance in healthy young men. Brain Struct Funct 219(1):255–267

Preston AR, Gabrieli JD (2008) Dissociation between explicit memory and configural memory in the human medial temporal lobe. Cereb Cortex 18:2192–2207

Rajah MN, Kromas M, Han JE, Pruessner JC (2010) Group differences in anterior hippocampal volume and in the retrieval of spatial and temporal context memory in healthy young versus older adults. Neuropsychologia 48:4020–4030

Ranganath C (2010) A unified framework for the functional organization of the medial temporal lobes and the phenomenology of episodic memory. Hippocampus 20(11):1263–1290

Reder LM, Park H, Kieffaber PD (2009) Memory systems do not divide on consciousness: reinterpreting memory in terms of activation and binding. Psychol Bull 135:23–49

Rosen ML, Stern CE, Devaney KJ, Somers DC (2017) Cortical and subcortical contributions to long-term memory-guided visuospatial attention. Cereb Cortex 27:1–13

Rudy JW, Huff NC, Matus-Amat P (2004) Understanding contextual fear conditioning: insights from a two-process model. Neurosci Biobehav Rev 28(7):675–685

Ryan JD, Cohen NJ (2003) Evaluating the neuropsychological dissociation evidence for multiple memory systems. Cogn Affect Behav Neurosci 3:168–185

Squire LR (2004) Memory systems of the brain: a brief history and current perspective. Neurobiol Learn Mem 82:171–177

Staresina BP, Davachi L (2008) Selective and shared contributions of the hippocampus and perirhinal cortex to episodic item and associative encoding. J Cogn Neurosci 20:1478–1489

Tulving E, Schacter DL (1990) Priming and human memory systems. Science 247:301–306

Turk-Browne NB, Scholl BJ, Chun MM, Johnson MK (2008) Neural evidence of statistical learning: efficient detection of visual regularities without awareness. J Cogn Neurosci 21:1934–1945

Turk-Browne NB, Scholl BJ, Johnson MK, Chun MM (2010) Implicit perceptual anticipation triggered by statistical learning. J Neurosci 30:11177–11187

Turk-Browne NB, Golomb JD, Chun MM (2013) Complementary attentional components of successful memory encoding. Neuroimage 66:553–562

Westerberg CE, Miller BB, Reber PJ, Cohen NJ, Paller KA (2011) Neural correlates of contextual cueing are modulated by explicit learning. Neuropsychologia 49:3439–3447

Winkelmann T, Thayer JF, Pohlack S, Nees F, Grimm O, Flor H (2017) Structural brain correlates of heart rate variability in a healthy young adult population. Brain Struct Funct 222(2):1061–1068

Wittchen HU, Wunderlich U, Gruschwitz S, Zaudig M (1997): SKID-I. Strukturiertes Klinisches Interview für DSM-IV. "Structured Clinical Interview for DSM-IV". Hogrefe, Gottingen