Hippocampal Control of Repetition Effects for Associative Stimuli

Nico A.W. Kremers,[1] Lorena Deuker,[1] Thorsten A. Kranz,[1] Carina Oehrn,[1] Juergen Fell,[1] and Nikolai Axmacher[1,2]*

ABSTRACT: Recent findings suggest that repetition effects interact with episodic memory processes that are putatively supported by the hippocampus. Thus, the formation or refinement of episodic memories may be related to a modulating signal from the hippocampus to the neocortex which leads to sparser or more extended stimulus representations (repetition suppression or enhancement), depending on the type of stimulus and the brain site. This framework suggests that hippocampal activity during the initial presentation of a stimulus correlates with the magnitude of repetition effects. Here, we tested this hypothesis in an fMRI study in which associations between faces and buildings were presented twice. BOLD responses showed repetition suppression in fusiform face area (FFA) and parahippocampal place area (PPA), most likely due to a refinement of existing category representations. Hippocampal activity during the first presentations was correlated with the amount of repetition suppression, in particular in the FFA. Repetition enhancement effects were observed on BOLD responses in posterior parietal cortex, possibly related to the formation of new representations of associative stimuli. The magnitude of parietal BOLD repetition effects depended on successful memory formation. These findings suggest that both repetition enhancement and repetition suppression effects are influenced by a modulating signal from the hippocampus. © 2014 Wiley Periodicals, Inc.

KEY WORDS: FFA; PPA; repetition suppression; repetition enhancement; fMRI

INTRODUCTION

When a stimulus is presented repeatedly, responses to that stimulus become faster and more accurate (Tulving and Schacter, 1990). In addition, repeated stimuli are associated with different neuronal representations as compared with novel items (Schacter and Buckner, 1998). These neuronal repetition effects may be in both directions: Either repeated stimuli elicit more pronounced activity as compared with novel stimuli (repetition enhancement), or neural activation is reduced upon repetition (repetition suppression). Several factors have been shown to influence whether repetition suppression or enhancement occurs. First, EEG studies showed that in the posterior parietal cortex,

real-world objects elicit repetition suppression, nonsense objects repetition enhancement (Gruber and Müller, 2002, 2005). Of particular interest were the analyses of induced gamma-band activity (30–100 Hz) reported in these studies, because gamma-band activity is believed to reflect local neural assemblies representing relevant sensory information (e.g., Bertrand and Tallon-Baudry, 2000; Kaiser and Lutzenberger, 2005; Hanslmayr, 2012). Second, in fMRI data from the fusiform gyrus, familiar objects induce repetition suppression, unfamiliar stimuli repetition enhancement (Henson et al., 2000). Third, the direction of repetition effects is affected by other stimulus features, such as visibility (Dolan et al., 1997; George et al., 1999; Turk-Browne et al., 2007) and the amount of repetitions (Müller et al., 2013). In addition to these stimulus dependency of repetition effects, repetition suppression and enhancement effects may occur simultaneously during repetition of the same stimulus in different brain regions (Vannini et al., 2013) or even in different voxels within the same region (de Gardelle et al., 2013).

From a neurophysiologic point of view, the source of the altered response during the second presentation remains unclear: It is still an open question whether the same perceptual network, which represents a stimulus, modifies itself between the first and the second presentation, or whether repetition effects are due to top-down signals from other regions.

The hippocampus is a "hub" region which influences neocortical processing during memory formation (Battaglia et al., 2011; Voss et al., 2011). Recent findings suggest that the hippocampus is also relevant for non-episodic memory processes such as repetition priming, depending on the type of processed information (Degonda et al., 2005; Bakker et al., 2008; Henke, 2010). Indeed, repetition priming and repetition suppression have been shown to correlate with (putatively hippocampus-dependent) episodic memory (Turk-Browne et al., 2006; Gagnepain et al., 2008). Hippocampal effects are most likely to occur when random associations are presented—i.e., associations between items that have not been associated with each other before (Cohen and Eichenbaum, 1995; Henke, 2010).

Here, we test the hypothesis that repetition effects on associative stimuli are related to a modulating signal from the hippocampus (Axmacher et al., 2008).

A similar issue has already been addressed in a recent fMRI study by Vannini et al. (2013). In that study, the authors report repetition suppression in the hippocampus and repetition enhancement in the posterior parietal cortex during repeated presentations of face-name pairs. However, in that study, no attempt was made to directly relate hippocampal activity during initial presentations to the amount of repetition suppression.

We conducted an fMRI experiment to explore the effect which hippocampal BOLD activation during initial stimulus presentation has on repetition effects (1) in category-specific inferior temporal regions and (2) in parieto-occipital visual association cortex. We hypothesized that category-specific regions show repetition suppression because existing category representations become sparser with repetition (Axmacher et al., 2008). In contrast, the parieto-occipital association cortex should exhibit repetition enhancement, related to the formation of new representations for associative stimuli—i.e, of new unified percepts (e.g., Fuster and Bressler, 2012). Furthermore, we hypothesized that during the initial presentation of associations, BOLD activity within the anterior hippocampus (which appears to be more relevant than the posterior hippocampus for encoding of novel information; e.g. Dolan and Fletcher, 1999; Strange et al., 2005; Parsons et al., 2006; Chua et al., 2007) correlates with the magnitude of repetition effects.

Two different measures of hippocampal involvement were analyzed, a direct and an indirect one. In the direct measure, we investigated whether the amplitude of the hippocampal BOLD response during the first presentation was correlated with the magnitude of repetition suppression and repetition enhancement effects. In the indirect measure, we studied whether repetition suppression and repetition enhancement were related with successful formation of episodic associative memories—i.e., whether repetition effects were more pronounced for trials in which associations were afterwards successfully retrieved.

MATERIALS AND METHODS

Participants

Twenty-three (10 females, 13 males) right-handed native German speakers with normal or corrected-to-normal vision participated in the experiment (mean age: 25.1 years, range: 22–33 years). Participants received monetary compensation for their participation. The study was approved by the local ethical committee, and written informed consent was obtained from all subjects.

Experimental Procedure

The experiment consisted of six blocks, each containing an encoding and a retrieval sub-block. Multiple blocks were presented in order to ensure sufficient episodic memory performance. During each encoding sub-block, participants were presented 18 different consecutive stimuli consisting of a male face with neutral emotional expression, superimposed on a building. From these 18 stimuli, 6 were presented only once, and 12 were shown twice (six of them with one other stimulus in between, and 6 with two other stimuli in between). Thus, every encoding sub-block consisted of 30 trials of picture presentation. The order and the combination of the stimuli were randomly chosen for every subject. During each encoding trial, participants were instructed to decide whether the face was consistent with the building or not, which was, of course, a highly subjective task. We chose this instruction as it prompted participants to actively pay attention to the relationship between face and building and promoted a deeper level of processing. Participants were asked to respond as fast as possible. Each stimulus was presented for 3,000 ms, followed by a randomized 3,000 to 5,000 ms interstimulus interval during which a fixation cross was presented.

After each encoding sub-block, participants conducted a self-paced memory test (retrieval sub-block), during which recognition memory for the faces was tested (i.e., item memory for these faces) as well as cued recall of the associated building (i.e., source memory for face-building associations). During each retrieval sub-block, we presented all 18 previously presented faces, randomly intermixed with nine novel faces. Participants first indicated whether they considered the faces to be "old" (presented during encoding) or "new" (not presented during encoding). For faces considered as old, participants were then asked if they remembered the building which was associated with that face ("yes" response) or not ("no" response). If they responded with "yes," a 15 s audio recording period started during which participants described their memory of the associated building as detailed as possible in their own words. No fMRI data were analyzed during retrieval blocks, but behavioural data were analyzed in order to categorize subsequent memory during the encoding subblock. We used this relatively complex procedure to test source memory (i.e., memory for face-building associations) for the following reason: If we had presented a face with several possible associated buildings and asked the participants to indicate the correct one, these buildings would have needed to be chosen from other face-building associations (in order to avoid that the correct one could have been chosen only based on its familiarity and not its association with a particular face). In this case, however, buildings would have been presented multiple times during retrieval, inducing complex recognition and encoding effects during this period. Our procedure allowed for a clean distinction between item memory (recognition of faces) and source memory (description of the correctly associated building).

Audio data was recorded with an MR-compatible microphone (Fibersound Microphone Model FOM1-MR and Fibersound Control Model FOM1-DRx Battery/wall powered; Micro Optics Technologies Fibersound Audio, Middleton, WI) and was later analyzed by two independent experimenters (NAWK and CO), who assigned descriptions of the subjects to buildings presented within the same block. Inter-rater reliability for five randomly chosen participants was very high (94.4%).

For a similar procedure, see Henckens et al. (2009). As a result, each trial from the encoding sub-blocks could be classified as belonging to one of three categories based on subsequent memory:

1. No memory (if a face was afterwards incorrectly labeled as "new")
2. Item memory (if a face was afterwards correctly labeled as "old", but the associated building could not be successfully retrieved)
3. Source memory (if a face was afterwards correctly labeled as "old" and the associated building was successfully retrieved).

Functional localizer

In order to explore repetition effects on BOLD responses in the fusiform face area (FFA) and the parahippocampal place area (PPA), a functional localizer task was conducted immediately after the main experiment. More specifically, the localizer was conducted in a separate session of around 15 min duration after the main experiment had been completed. The localizer was presented in a blocked design with three different categories containing buildings, faces and scrambled pictures. For more information on the design of the functional localizer see Berman et al. (2010). To create individual regions of interest within the FFA, we contrasted faces with buildings (buildings with faces for the PPA, respectively) using Statistical Parametric Mapping software (SPM8, Wellcome Department of Imaging Neuroscience, London, UK) thresholded at $P < 0.001$, no cluster correction. Then, we inclusively masked the results with a structural AAL (Automated Anatomical Labeling) mask of fusiform gyrus and parahippocampal gyrus, respectively (obtained from wfu_pickatlas; Maldjian et al., 2003; Tzourio-Mazoyer et al., 2002). To avoid overlap between anterior HC and PPA, we exclusively masked the PPA mask with the anterior HC mask. The anterior hippocampus mask was anatomically selected based on a structural AAL mask from wfu_pickatlas, which was exclusively masked with a box covering the posterior half of the hippocampus using marsBaR (Brett et al 2002). We focused on the anterior hippocampus because this region appears to be particularly relevant for the encoding of novel information (e.g., Dolan and Fletcher, 1999; Strange et al., 2005; Parsons et al., 2006; Chua et al., 2007). As a control, we also analyzed the posterior hippocampus and posterior PPA. Posterior HC was defined by exclusively masking the hippocampus mask with a (self-constructed) box covering the anterior half of the hippocampus. To analyse posterior PPA, we excluded anterior PPA also using a box before we masked the remaining voxels (inclusively) with the results of the functional localizer in every individual subject.

FMRI Data Acquisition and Processing

FMRI was collected during the entire experiment, including encoding and recall. Recall consisted of both a recognition memory test (for the presented faces) and a cued recall (for the associated building in case the participant indicated that the face was old). However, fMRI data were only analyzed during encoding, because recall was self-paced and may have been contaminated by artifacts due to overt speech. All images were acquired with a Siemens Trio 3T scanner (Siemens, Erlangen, Germany) using a T2*-weighted, echo-planar imaging sequence (number of slices: 40; slice thickness: 2.5 mm; resolution: 3.3 × 3.3 × 2.5 mm; distance factor: 20%; repetition time: 2,800 ms; echo time: 35 ms; field of view: 210 mm). The slices were acquired interleaved in ascending order. Two functional sessions were conducted, first the main experiment (around 1,000 images, depending on the variable length of the retrieval blocks), then the functional localizer (320 images). T1-weighted structural images were also acquired for coregistration purposes (number of slices: 160; slice thickness: 1 mm; distance factor: 50%; repetition time: 1,570 ms; echo time: 3.42 ms; field of view: 256 mm).

During preprocessing, images were first transformed from DICOM to NIfTI format using MRICron (http://www.cabiatl.com/mricro/mricron/dcm2nii.html). Afterwards, data were analyzed using SPM8. Images were corrected for slice acquisition temporal delay before being spatially realigned to correct for motion. Images were then normalized using the parameters derived from the nonlinear normalization of individual gray matter T1 images to the T1 template of the Montreal Neurological Institute (slice thickness: 1 mm) and spatially smoothed using an 8 mm FWHM Gaussian kernel. For statistical analysis, two general linear models (GLM) were specified using the regressors indicated in Table 1. Then, average beta values for the regions of interest were extracted using log-roi-batch v2.0 (http://www.aim-feld.ch/) in MATLAB (The Mathworks, Natick, MA).

For single trial correlation analysis, a GLM with one regressor per trial was generated. Afterwards, these single-trial beta-values were again extracted for each region of interest. A single-trial Spearman's rank correlation analysis was used to determine intra-individual correlations between different brain regions. Then, we calculated a second-level (group) analysis by testing the Fisher-z-transformed individual correlation coefficients against zero. Three subjects had to be excluded from analyses involving FFA and PPA ROIs, because no significant contrast clusters either for FFA or PPA were observable in the functional localizer. For statistical analyses in the three pre-selected ROIs (FFA, PPA, anterior hippocampus), we extracted average beta values and choose a Bonferroni-corrected threshold of $P = 0.05/3 = 0.0167$. For the exploratory whole-brain analyses, we used a FWE-corrected threshold of $P < 0.05$ and an extent threshold of 20 voxels. One additional subject had to be excluded from the subsequent memory single trial correlation analysis as (s)he did not show any trials without subsequent memory.

RESULTS

Behavioural Results

Overall, we found that $29.6 \pm 1.4\%$ of all faces were remembered together with their associated building (source

memory), $40.2 \pm 1.9\%$ were remembered without the associated building (item memory) and $30.2 \pm 1.8\%$ were forgotten. First, we investigated repetition priming in terms of reaction times (RTs) as a function of subsequent memory (Fig. 1B). A two-way ANOVA of RTs with "repetition" (first, second presentation) and "memory" (source memory, item memory, no memory) as repeated measures revealed significant main effects of "repetition" ($F_{(1,22)} = 159.9$; $P < 0.0001$) and "memory" ($F_{(2,44)} = 5.5$; $P = 0.007$) as well as a significant interaction ($F_{(2,44)} = 4.7$; $P = 0.014$). Post hoc t-tests showed that repetition priming effects were significantly more pronounced during encoding of "source memory" stimuli compared with encoding of "item memory" ($t_{22} = 3.07$; $P = 0.006$) and "no memory" stimuli ($t_{22} = 2.49$; $P = 0.021$), while there was no significant difference between "item memory" and "no memory" stimuli ($t_{22} = -0.139$; $P = 0.891$). These results indicate stronger reductions of RTs during (putatively hippocampus-dependent) episodic memory encoding leading to source recollection.

To test whether these effects were indeed due to faster RTs during the second presentation and not due to longer RTs during the initial presentation, we conducted separate one-way ANOVAs of RTs during the first and second presentation. A one-way ANOVA with "subsequent memory" (source memory, item memory, no memory) as repeated measures revealed that subsequent memory had a significant effect on RTs during the second presentation ($F_{(2,22)} = 13.2$; $P < 0.0001$). By contrast, the same ANOVA applied on the RTs during the first presentation did not yield any effect of subsequent memory on RTs during the first presentation ($F_{(2,22)} = 0.6$; $P = 0.54$).

Although repetition effects were highest for "source memory" trials ($t_{22} = 12.11$; $P < 0.0001$), they were also present for trials in which associations were not remembered during retrieval ($t_{22} = 10.08$; $P < 0.0001$) or for which even the identity of the face was forgotten ($t_{22} = 11.15$; $P < 0.0001$). This suggests that repetition effects were not only due to recollection of face-building associations during their second presentations (or recollection of the previous response to these associations). To further exclude this possibility, we tested whether repetition effects also occurred for the minority of trials in which subjects switched their response from the first to the second presentation (i.e., from "face and building fit to each other" to "they don't fit to each other" or vice versa). Indeed, repetition effects were also apparent in these trials (299 ± 172 ms [mean ± s.e.m.] reductions of reaction times; $t_{15} = 2.37$; $P < 0.05$).

FMRI Results (Regions of Interest Analyses)

FMRI data were collected during the entire experiment, but only analyzed during the encoding part, as a function of repetition (i.e., first or second presentation) and subsequent memory (i.e., dependent on behavioural responses during the recall part). First, we analyzed the effect of repeated presentation on BOLD responses in three regions of interest: the anterior hippocampus (HC), the fusiform face area (FFA), and the parahippocampal place area (PPA) (Fig. 2A). As we analyzed three

TABLE 1.

Regressors in General Linear Model

	Regressors	Duration
GLM 1: regressors do not depend on subsequent memory	First presentation	0
	Second presentation	0
	Retrieval blocks	Length of retrieval blocks
	Linear increase across the entire experiment (to model scanner drift)	Experiment
	Mean activation	Experiment
GLM2: regressors depend on subsequent memory	First presentation source memory	0
	Second presentation source memory	0
	First presentation item memory	0
	Second presentation item memory	0
	First presentation no memory	0
	Second presentation no memory	0
	Single trials source memory	0
	Single trials item memory	0
	Single trials no memory	0
	Retrieval blocks	Length of retrieval blocks
	Linear increase across the entire experiment (to model scanner drift)	Experiment
	Mean activation	Experiment

regions of interest (anterior hippocampus, FFA, and PPA), we adjusted our significance values to $P_{\text{corr}} = P \times 3$ for results within these ROIs (i.e., Bonferroni correction). Only results with P_{corr} values below a threshold of 0.05 were considered significant. In all three regions of interest, we observed highly significant effects of repetition suppression, i.e. reductions of beta values during the second as compared with the first presentation (anterior HC: $t_{19} = 6.80$; $P_{\text{corr}} < 0.0001$; FFA: $t_{19} = 6.89$; $P_{\text{corr}} < 0.0001$; PPA: $t_{19} = 7.10$; $P_{\text{corr}} < 0.0001$; Fig. 2B). These effects did not depend on subsequent memory (all $F_{(2,38)} < 0.47$, all $P_{\text{corr}} = 1$). Repetition suppression was significant for trials with

A

A1   A2

B
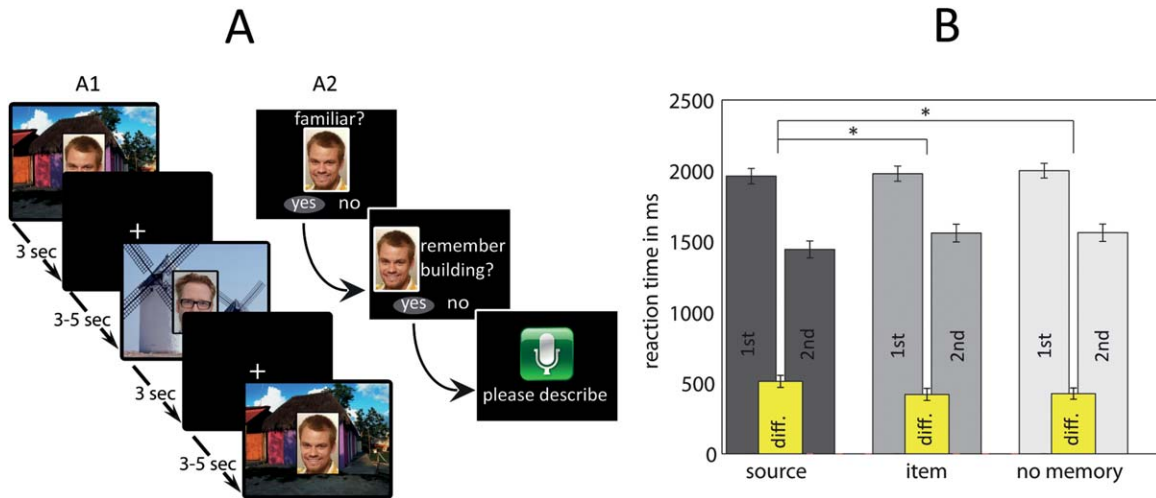
FIGURE 1.   Experimental paradigm and behavioural results. (A) The paradigm included separate blocks for memory encoding (A1) and retrieval (A2). During the encoding phase (A1), participants were instructed to decide whether a face is consistent with a building or not and to respond as quickly as possible by button presses. Some stimuli were presented once, others twice. In the retrieval block (A2), participants first underwent an old/new recognition memory test for the faces. After an "old" response to a face, they were asked to describe the corresponding building in their own words as detailed as possible using an MR-compatible microphone. (B) Reaction times during the encoding phase according to subsequent memory. Bar plots depict mean and S.E.M. of reaction times for all stimuli presented for the first time (1st) and for the second time (2nd). Source memory (face and building correctly remembered), item memory (face recognized as old, but no or incorrect recollection of the associated building), no memory (face not recognized as old). Yellow bars depict repetition priming (1st to 2nd presentation). Repetition effects (diff.) significantly differed between the source memory condition as compared with the two other conditions. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

subsequent source memory, item memory and no memory (all $t_{19} > 2.98$, all $P_{corr} < 0.021$).

Next, we investigated whether hippocampal activity during the first presentation correlated with the amount of repetition suppression in FFA and PPA. In a single-trial correlation analysis, we observed a significant (intraindividual) correlation between BOLD responses in the bilateral anterior HC during first presentation and repetition suppression (i.e., the difference between BOLD responses during first and second presentation) in FFA ($t_{19} = 10.09$; $P_{corr} < 0.0001$; Fig. 2D) and PPA ($t_{19} = 9.13$; $P_{corr} < 0.0001$; Fig. 2E).

As repetition suppression effects are likely to be more pronounced when the activation during the first presentation is already relatively high, we conducted a partial correlation analysis with the activation of FFA/PPA during the first presentation as control variable. In this analysis, the correlation between HC and FFA remained significant ($t_{19} = 3.22$; $P_{corr} = 0.014$), while the correlation between HC and PPA was not significant anymore ($t_{19} = -0.11$; $P_{corr} = 1$) (Fig. 2C). This indicates that the relationship between hippocampal BOLD effects during the first presentation and repetition suppression effects in PPA is mediated by the correlation between hippocampal and PPA BOLD responses during first presentation. Results for correlations between anterior HC and FFA/PPA remained qualitatively unchanged when we added correlations between anterior hippocampus and posterior hippocampus as a second control variable (FFA: $t_{19} = 3.73$; $P_{corr} = 0.013$; PPA: $t_{19} = 1.95$; $P_{corr} = 0.201$).

One might expect that the absence of partial correlations between anterior HC and PPA is due to the direct spatial adjacency of these two regions. To test this, we conducted an additional analysis in which we calculated partial correlations between anterior HC and posterior PPA only. However, no significant result emerged either ($t_{19} = -0.10$; $P_{corr} = 1$).

Finally, we analyzed whether the partial correlations between activity within the anterior HC during the first presentation of trials and suppression effects in FFA and PPA depended on subsequent memory. For the partial correlation between anterior HC and FFA suppression, a one-way ANOVA with "subsequent memory" as repeated measure revealed a highly significant effect ($F_{(2,18)} = 8.625$; $P_{corr} = 0.0027$). Subsequent pair-wise comparisons showed that correlations were significantly greater during "source memory" trials as compared with either "item memory" ($t_{18} = 5.94$; $P_{corr} < 0.0001$) or "no memory" trials ($t_{18} = 2.81$; $P_{corr} = 0.03$), while there was no difference between "item memory" and "no memory" trials ($t_{18} = -0.07$; $P_{corr} = 1$). Partial correlations were significant for "source memory" trials, ($t_{18} = 8.766$; $P_{corr} < 0.0001$), but (after Bonferroni correction) not for the "item memory" trials ($t_{18} = 2.120$; $P_{corr} = 0.144$) and for "no memory" trials ($t_{18} = 1.372$; $P_{corr} = 0.564$).

For the partial correlation between anterior HC and PPA suppression, the corresponding ANOVA revealed a significant effect as well ($F_{(2,18)} = 7.493$; $P_{corr} = 0.006$). Again, subsequent pair-wise comparisons showed that correlations were significantly greater during "source memory" trials as compared with either "item memory" ($t_{18} = 3.18$; $P_{corr} = 0.015$) or "no memory" trials ($t_{18} = 3.42$;
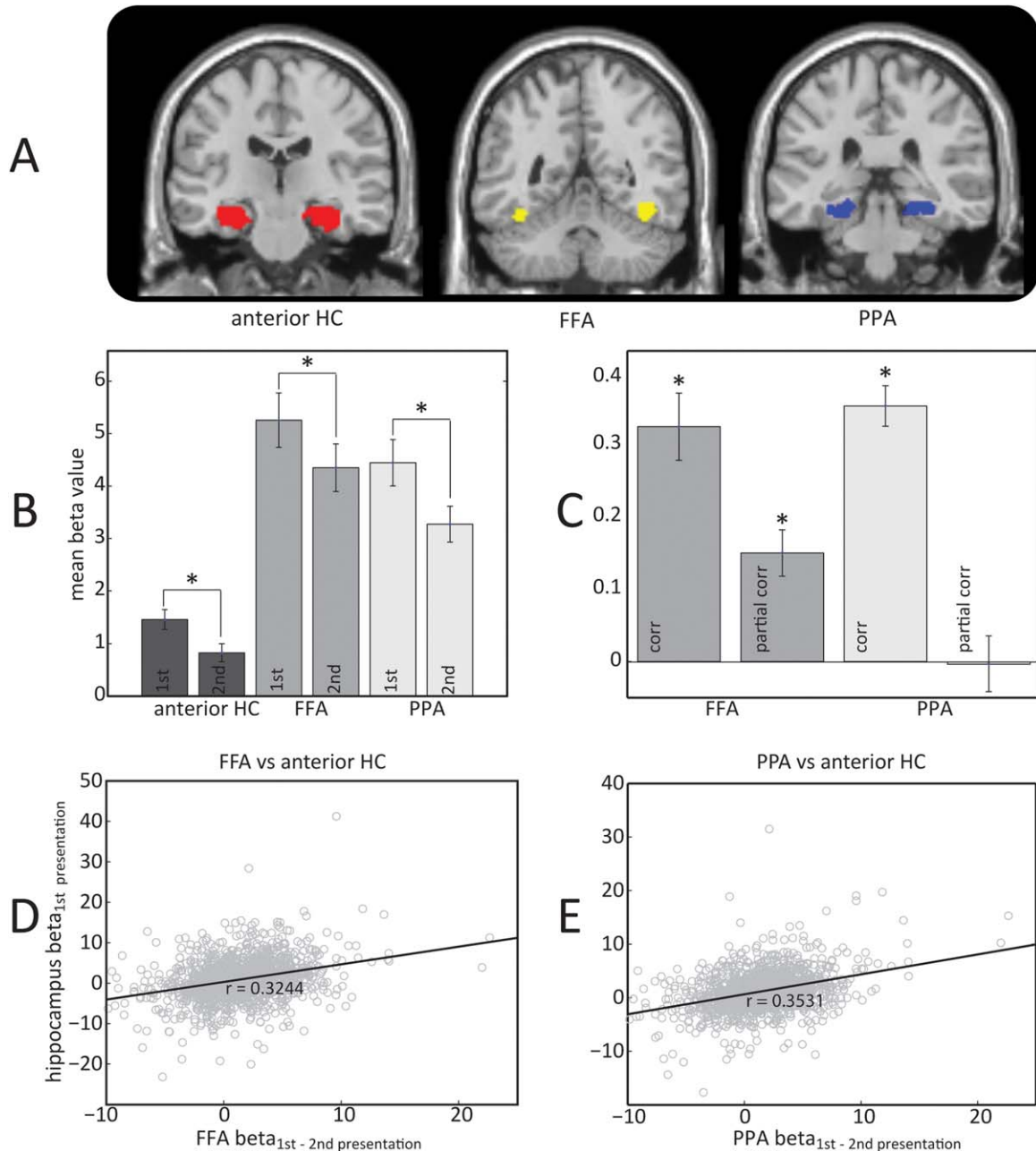
FIGURE 2. fMRI results 1: ROI analysis. (A) Regions of interest. FFA and PPA were individually specified with a functional localizer, anterior hippocampal ROI was selected anatomically. (B) Repetition effects in all 3 regions of interest. Mean percentage BOLD signal change and S.E.M. during first and second presentation in the anterior hippocampus (HC), fusiform face area (FFA) and parahippocampal place area (PPA). Paired *t*-tests revealed significant repetition suppression effects (1st vs. 2nd) in all three regions of interest. (C) Correlation of FFA and PPA repetition effects with anterior hippocampal BOLD response during first presentation. Mean and S.E.M. of correlation coefficients. Only the HC/FFA correlation remains significant when using 1st presentation BOLD activity in FFA as control variable in a partial correlation. (D and E) Scatter plots across all subjects and all trials with mean regression coefficients for FFA (D) and PPA (E). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

$P_{corr} = 0.009$), while there was no difference between "item memory" and "no memory" trials ($t_{18} = 0.39$; $P_{corr} = 1$). Partial correlations were significant for "source memory" trials ($t_{18} = 4.493$; $P_{corr} = 0.0009$), but not for "item memory" ($t_{18} = 0.312$; $P_{corr} = 1$) or "no memory" trials ($t_{18} = 0.252$; $P_{corr} = 1$).
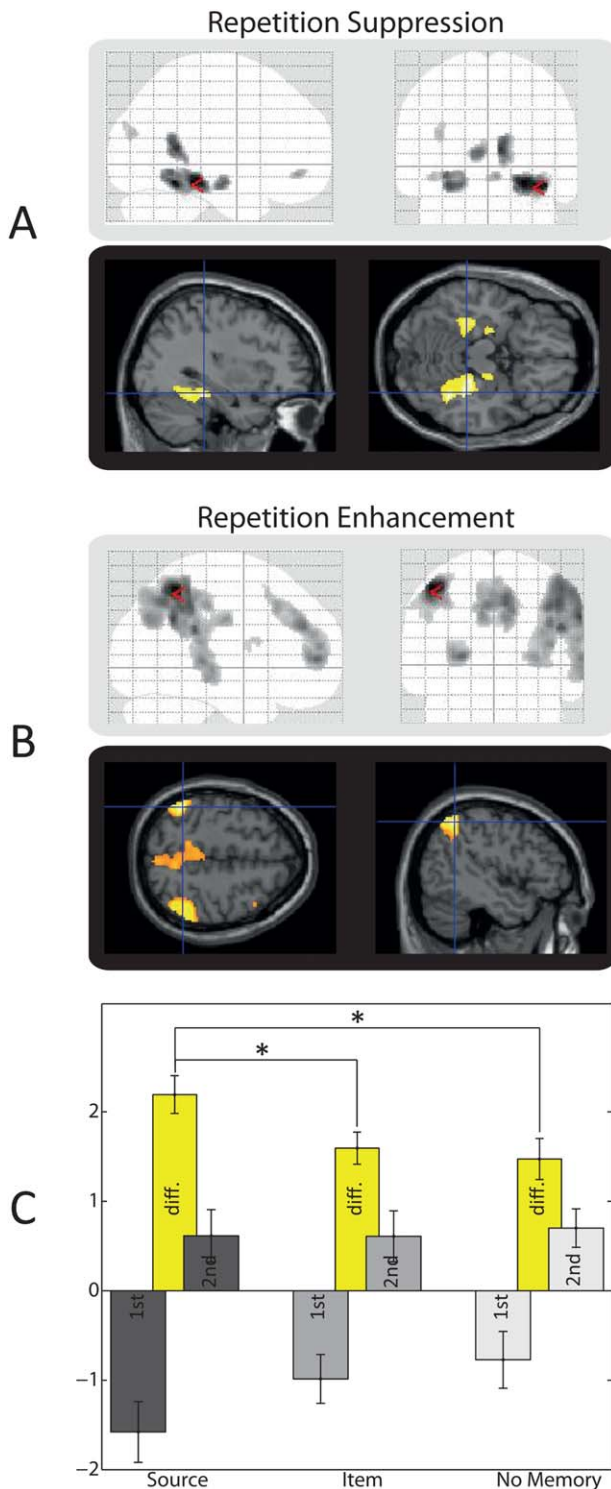
FMRI Results (Whole-Brain Analyses)

Finally, we explored repetition suppression and enhancement effects on BOLD responses in the entire brain (Fig. 3). Repetition suppression effects were most prominent in the hippocampus and parahippocampal cortex extending into fusiform gyrus

(Fig. 3A), consistent with our findings from ROI-based analyses (see Table 2 for an overview of all significant activations at a threshold of $p_{FWE} < 0.05$). When we extracted BOLD values from these regions and averaged across all significant clusters, we did not find any significant effects of subsequent memory: A two-way ANOVA of BOLD responses within the significant suppression clusters with "repetition" (first, second presentation) and "memory" (source memory, item memory, no memory) as repeated measures revealed only a (trivial) main effect of "repetition" ($F_{(2,44)} = 63.0$; $P < 0.001$), but no effect of "memory" ($F_{(2,44)} = 0.1$; $P = 0.920$) and no interaction ($F_{(2,44)} = 2.6$; $P = 0.089$). These results are consistent with our prior findings from ROI-based analyses that repetition suppression effects did not depend on subsequent memory.

Repetition enhancement effects occurred in the inferior and superior parietal lobule as well as in the prefrontal cortex (Fig. 3B; Table 2). These repetition enhancement effects were significantly more pronounced if associations were afterwards remembered ("source memory") as compared with the "item memory" and "no memory" condition: A two-way ANOVA of BOLD responses within the significant enhancement clusters with "repetition" and "memory" as repeated measures revealed a trivial main effect of "repetition" ($F_{(2,44)} = 182.5$; $P < 0.001$), but also a significant "memory" $\times$ "repetition" interaction ($F_{(2,44)} = 3.8$; $P = 0.031$), while the effect of "memory" did not reach significance ($F_{(2,44)} = 2.6$; $P = 0.086$). Repetition effects were significant in all conditions (as indicated by significant parietal clusters in the three individual conditions; see Table 2). However, post-hoc t-tests showed that repetition enhancement effects were significantly more pronounced during "source memory" compared with "item memory" ($t_{22} = -2.12$; $P = 0.045$) and "no memory" trials ($t_{22} = -2.31$; $P = 0.031$), while there was no significant effect between "item memory" and "no memory" trials ($t_{22} = -0.50$; $P = 0.623$). (Notably, these differences cannot be explained by different numbers of trials in the different conditions, because these numbers were highest in the "item memory" condition ($40.2 \pm 1.9\%$) and similarly high during the "source memory" ($29.6 \pm 1.4\%$) and the "no memory" (30.2 ± 1.8) condition.) This result suggests that hippocampal recruitment during initial stimulus presentation (measured indirectly via successful memory formation) is associated with more pronounced repetition enhancement effects in the fronto-parietal association cortex.

DISCUSSION

In an fMRI study, we investigated the hypothesis that hippocampal BOLD activity during presentation of a face-building

FIGURE 3.   fMRI results 2: Whole-brain analysis. (A) Repetition suppression effects. Contrast of BOLD activity during 1st presentations versus 2nd presentations (thresholded at $p_{FWE} < 0.05$) reveals activation in the medial temporal lobe encompassing hippocampus and parahippocampal gyrus. (B) Repetition enhancement effects. Contrast of BOLD activity during 2nd presentations versus 1st presentations ($p_{FWE} < 0.05$) reveals activation in frontoparietal association cortices. (C) Subsequent memory effects within regions showing significant repetition enhancement effects. Repetition enhancement effects (diff.) are significantly more pronounced when associations are successfully recalled ("source memory" condition) compared with activation during the "item memory" and "no memory" condition. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Peak Voxels in Whole-Brain Analyses of fMRI Data

		x	y	z	Cluster size (# voxels)	t-value	Region
Repetition suppression		34	−34	−16	740	10.45	Parahippocampal gyrus
		8	−48	10	193	9.20	Posterior cingulate cortex
		−30	−34	−16	366	8.78	Parahippocampal gyrus
		20	−14	−18	49	8.42	Anterior hippocampus
		−22	−12	−16	35	8.41	Anterior hippocampus
		−8	−50	8	109	8.32	Posterior cingulate cortex
		4	44	−10	45	7.36	Medial prefrontal cortex
		−38	−80	20	47	6.88	Superior occipital gyrus
Repetition enhancement		−46	−52	52	776	14.21	Superior parietal lobule
		62	−54	32	2865	11.36	Angular gyrus
		8	−50	42	2465	10.48	Posterior cingulate cortex
		−26	52	4	379	10.17	Superior frontal gyrus
		40	42	26	1080	9.83	Middle frontal gyrus
		62	8	16	22	6.89	Inferior frontal gyrus
Repetition enhancement	Source memory	44	−46	40	1217	11.42	Inferior parietal lobule
		−10	−72	38	1224	10.61	precuneus
		−48	−50	56	576	10.00	Superior parietal lobule
		40	40	26	384	9.14	Middle frontal gyrus
		−30	58	10	257	8.98	Superior frontal gyrus
		60	−26	−4	55	7.46	Superior temporal gyrus
		6	−28	42	40	7.16	Cingulate gyrus
		58	−28	42	26	7.13	Postcentral gyrus
	Item memory	62	−50	38	533	8.70	Supramarginal gyrus
		56	−26	−8	54	8.19	Middle temporal gyrus
		−46	−52	42	147	7.83	Inferior parietal lobule
		10	−70	28	67	6.98	Precuneus
	No memory	50	−54	46	305	8.15	Inferior parietal lobule
		8	−66	30	106	8.07	Precuneus

Contrasts: repetition suppression (first presentation > second presentation), repetition enhancement (second presentation > first presentation). Voxel-wise threshold of $p_{FWE} < 0.05$, at least 20 contiguous voxels.

association correlates with the magnitude of repetition effects between the first and the second presentation. Hippocampal recruitment was assessed both using neuroimaging (BOLD activity in the hippocampus) and behaviourally (successful source memory encoding). On a neural level, hippocampal BOLD responses during initial presentation correlated with repetition suppression in the FFA. On a behavioural level, successful encoding of new associations (which putatively depends on the hippocampus) was related to stronger reductions in reaction times, more pronounced parieto-occipital BOLD repetition enhancement, and higher anterior hippocampus-FFA as well as anterior hippocampus-PPA partial correlations.

## Repetition Suppression and Enhancement of BOLD Responses

Whole-brain analysis of the fMRI data revealed repetition enhancement effects in fronto-parietal association cortex (Fig. 3B). This is consistent with recent results from Vannini et al. (2013), who observed repetition enhancement BOLD effects in the posterior parietal cortex during repeated presentation of face-name pairs.

In contrast to category-specific visual regions, which support processing of specific stimulus features, the parieto-occipital association cortex is relevant for the integration of these features into unified percepts (e.g., Fuster and Bressler, 2012). It is likely that these regions also support the representation of new face-building associations and are increasingly activated during the formation of these associations. Activation of the parieto-occipital association cortex has not only been investigated during conscious control processes, but it may also reflect implicit improvements of associative tasks (King et al., 2012).

To summarize, different directions of repetition effects were observed in (1) FFA and PPA—category-specific regions where individual item features are represented—and (2) higher order neocortical regions which putatively support the representation of new associations (Fig. 4). In FFA and PPA, repeated presentations of the real-world objects used in our study induced repetition suppression, probably due to a refinement of existing representations of these categories. In contrast, repetition
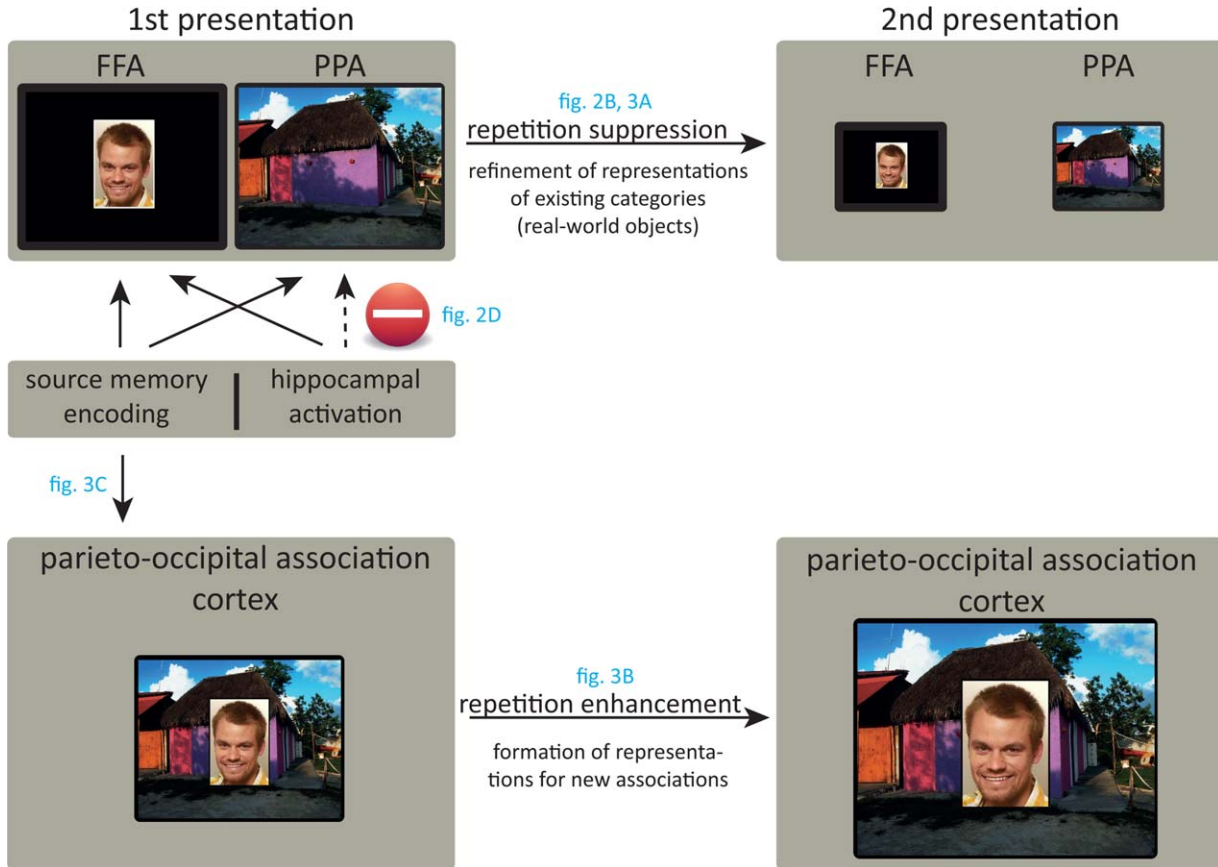
FIGURE 4. Schematic overview of suggested model. Top row: Repetition suppression effects were observed in category-specific regions of the inferior temporal lobe (FFA and PPA) and possibly related to the refinement of representations of existing categories. Bottom row: Repetition enhancement occurred within regions of neocortical association cortex and may be due to the formation of new representations for novel associations. Middle: The magnitude of both effects were related to the recruitment of the hippocampus, measured either via hippocampal activity during first presentation or via successful source memory encoding. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

enhancement effects likely reflect the formation of new networks in higher-order neocortical regions that support representation of novel associations.

Correlation of Hippocampal BOLD Responses and Memory With Repetition Effects

As described in the Introduction, we employed two different measures to assess the relationship between hippocampal involvement and repetition effects, a direct (hippocampal BOLD activity) and an indirect one (successful source memory formation). For the direct measure, we correlated hippocampal BOLD activity during first presentation with repetition suppression of BOLD activity in FFA and PPA (Figs. 2C–E). We observed a robust correlation between HC and FFA, supporting our main hypothesis that repetition suppression effects are related to hippocampal involvement during initial stimulus presentation (Fig. 2C). In contrast, we did not observe any significant partial correlation between hippocampal activity during the first presentation and the magnitude of repetition suppres-

sion effects in the PPA. A possible explanation for the absence of a significant HC-PPA partial correlation (see above, fMRI results) could be the local adjacency of anterior HC and PPA. Although we avoided any spatial overlap between anterior HC and PPA (see Methods for details), fluctuations of single-trial beta values in closely adjacent brain regions tend to be inherently correlated. Alternatively, the absence of HC-PPA partial correlations may be due to the fact that only faces were used as cues, so that participants may have attended faces more carefully than buildings during encoding. Future experiments could address this issue by using both faces and building as test cues.

Concerning the indirect measure, we did not find that repetition suppression effects in FFA and PPA depended on subsequent memory, indicating that these repetition effects are not directly related to source memory formation (of course, for all these correlative analyses no causality can be inferred). In addition, we did not find any relationship between hippocampal repetition suppression and subsequent memory. This contrasts with results from previous studies which showed that medial temporal repetition suppression depended on subsequently memory (e.g., Turk-Browne et al.,

2006; Gagnepain et al., 2008; Xue et al., 2010; Manelis et al., 2013). As described by Manelis and colleagues (2013), the lack of a relationship between hippocampal repetition suppression and subsequent memory may be due to the fact that the hippocampus is relevant for pattern separation, which does not occur if identical stimuli are repeated; thus, in the absence of any changes between two repetitions, hippocampal activity remains elevated during the second presentation.

However, the magnitude of partial correlations between hippocampal activity during the first presentation and repetition suppression in both FFA and PPA depended significantly on memory formation: This partial correlation was only significant for source memory trials, but not for trials without subsequent memory or for trials in which only the face could be remembered. This suggests that repetition suppression in FFA and PPA may actually be related to memory formation, but only if there is a correlation with hippocampal activity during the first presentation. Alternatively, these results could be interpreted as showing that repetition suppression in FFA and PPA is only related to hippocampal activity in the first trial if memory formation occurs (which is putatively supported by additional recruitment of other brain regions).

For the repetition enhancement effects observed in the whole-brain fMRI analysis, the corresponding analyses yielded different results. While the magnitude of repetition enhancement was not correlated with hippocampal activation during first presentation, and there was no interaction of partial correlations with subsequent memory, we did find that the overall magnitude of repetition enhancement effects depended on subsequent memory, and was most pronounced for source memory trials. In other words, the direct measure of hippocampal involvement did not indicate any relevance of the hippocampus for repetition enhancement, while the indirect measure did show such an effect. These results are difficult to interpret at the current stage. They may suggest, though, that repetition enhancement is indirectly related to recruitment of putatively hippocampus-dependent processes of memory formation, but that other brain regions play a crucial role as well.

In this study, we have used both ROI-based and whole-brain analyses because we had only regionally specific hypotheses for the activity in category-specific regions of the inferior temporal lobe and for the anterior hippocampus, but not for other regions. Thus, we used localizer tasks to define ROIs in FFA and PPA, and an anatomical mask for the hippocampus. We have added the results from the whole brain analysis in order to reduce type 2 errors—and indeed found additional effects in parietal regions which are relevant for the interpretation of our results.

CONCLUSION

In a recent review, we have described evidence on the role the hippocampus plays during the modification of stimulus representations during repeated presentations (Axmacher et al.,

2008). In that article, we have focused on the putative inhibitory effect (repetition suppression) related to the refinement of representations of individual items. It should be noted that "inhibition" in this context does not refer to the activity of inhibitory (e.g., GABAergic) neurons, but rather to the process as a result of which representations become sparser, and that measuring BOLD activity cannot differentiate between excitatory and inhibitory neural activity (Logothetis, 2008). In this context, we assume that sparser representations are reflected by decreased BOLD activities. Our current results during repetition of face-building associations suggest a more complex picture: On the one hand, repetition suppression effects were observed on BOLD activity in category-specific regions in the inferior temporal cortex. Importantly, repetition suppression depended on the BOLD response of the hippocampus during the initial presentation and on source memory formation for these associations. These results suggest that there is indeed a modulating influence of the hippocampus on neural representations: hippocampal activity, measured via its BOLD response and via its behavioural effect on memory, renders these representations sparser with repetition. On the other hand, BOLD activity in parieto-occipital regions was significantly enhanced with repetition, and BOLD repetition enhancement effects depended on subsequent memory. Although we did not observe a direct relationship between hippocampal activity during the first presentation and the magnitude of parieto-occipital repetition enhancement, the dependence of repetition enhancement on memory formation may suggest a more indirect impact of the hippocampus on repetition suppression as well. This model is schematically presented in Figure 4.

In the future, it will be desirable to investigate these effects in greater detail. First, it would be important to see whether these effects indeed depend on the use of associative stimuli. Second, it would be interesting to test the influence of the hippocampus on neocortical stimulus representations in a dynamic causal modeling (DCM) analysis with HC, FFA, PPA and parieto-occipital association cortex as volumes of interest. This analysis allows one to analyze effective (directional) connectivity between brain regions and thus to infer causality rather than just correlations. Finally, an analysis of stimulus-specific representations using pattern classification analyses would give us more insight on how these representations change when they are repeated, and on the influence of the hippocampus on these effects. Pattern classification analyses are multivariate approaches to distributed activity patterns (e.g., of BOLD responses) and can be used to differentiate representations of individual items (Haynes and Rees, 2006; Rissman and Wagner, 2012; Deuker et al., 2013).

Taken together, our findings support the hypothesis that hippocampal activity during initial presentation of face-building associations correlates with the amount of neocortical repetition suppression in the FFA, while results are more complex for PPA and parieto-occipital regions (see above). This would be consistent with the idea that during initial presentation of new face-building associations, the hippocampus sends an inhibitory signal to the FFA.

Acknowledgments

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